Fisiopatologia, diagnòstic i noves estratègies terapèutiques per a la disfàgia orofaríngia neurògena o associada a l'envelliment

Tesi doctoral presentada per **Laia Rofes i Salsench**
per optar al grau de **Doctor**

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CIBEREHD

Centro de Investigación Biomédica en Red de enfermedades hepáticas y digestivas
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FAN CONSTAR:

Que la memòria titulada "*Fisiopatologia, diagnòstic i noves estratègies terapèutiques per a la disfàgia orofaríngia neurògena o associada a l'envelliment*" presentada per LAIA ROFES i SALSENCH per optar al grau de Doctor, duta a terme al Grup de Recerca CIBERehd de l'Hospital de Mataró, s'ha realitzat sota la nostra direcció, i al considerar-la finalitzada, autoritzem la seva presentació per a ser avaluada pel Tribunal corresponent.

I per a que consti a tals efectes signem la present,

Hospital de Mataró, 15 de maig del 2014

Dr Pere Clavé i Civit	Dr Joan Monés i Xiol	Dr Carlos Guarner Aguilar
Director de la Tesi	Co-Director de la Tesi	Tutor de la Tesi

A mons pares

Retxes de sol atravessen blaus marins,
ses algues tornen verdes i brillen ses estrelles,
que ja s'ha fet de nit i es plàncton s'il·lumina
i canten ses sirenes aproximadament per no existir.
- Joan Miquel Oliver

Agraïments

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Llista de Publicacions

Els capítols que formen el cos d'aquesta Tesi Doctoral han estat publicats o estan pendents de publicació a les següents revistes:

CAPÍTOL 1

Rofes L, Arreola V, Mukherjee R, Clavé P. *Sensitivity and specificity of the Eating Assessment Tool and the Volume-Viscosity Swallow Test for clinical evaluation of oropharyngeal dysphagia.* Under review in Neurogastroenterol Motil (accepted with Major Revision).

CAPÍTOL 2

Rofes L, Arreola V, Romea M, Palomera E, Almirall J, Cabré M, Serra-Prat M, Clavé P. *Pathophysiology of oropharyngeal dysphagia in the frail elderly*. Neurogastroenterol Motil 2010; 22(8): 851-8, e230.

CAPÍTOL 3

Almirall J*, Rofes L*, Serra-Prat M, Icart R, Palomera E, Arreola V, Clavé P. *Oropharyngeal dysphagia is a risk factor for community-acquired pneumonia in the elderly*. Eur Respir J 2013; 41(4): 923-8. *Co-first authors.

CAPÍTOL 4

Rofes L, Arreola V, Mukherjee R, Swanson J, Clavé P. *The effects of a xanthan gum-based thickener on the swallowing function of patients with dysphagia.* Aliment Pharmacol Ther 2014; In press. doi: 10.1111/apt.12696

CAPÍTOL 5

Rofes L, Arreola V, Martin A, Clavé P. *Natural capsaicinoids improve swallow response in older patients with oropharyngeal dysphagia.* Gut 2013; 62(9):1280-7.

CAPÍTULO 6

Rofes L, Arreola V, Martin A, Clavé P. *Effect of oral piperine on the swallow response of patients with oropharyngeal dysphagia.* J Gastroenterol 2013; In press. doi:10.1007/s00535-013-0920-0

CAPÍTOL 7

Rofes L, Arreola V, López I, Martin A, Sebastián M, Ciurana A, Clavé P. *Effect of surface sensory and motor electrical stimulation on chronic poststroke oropharyngeal dysfunction*. Neurogastroenterol Motil 2013; 25(11):888-e701.

Presentacions a congressos i publicacions en forma d'abstract

*Pathophysiology of oropharyngeal dysphagia in the Frail Elderl*y. Rofes L, Arreola V, Romeo M, Palomera E, Cabré M, Serra-Prat M, Clavé P. 2008 Joint International Meeting in Neurogastroenterology and Motility (Lucerne, Switzerland, 6-9 de novembre del 2008). **Neurogastroenterol Motil 2008; 20(Suppl 2):41**

Patofisiologia de la disfàgia orofaríngia en ancians fràgils. Rofes L, Arreola V, Romeo M, Palomera E, Cabré M, Serra-Prat M, Clavé P. XVIII Congrés de la Societat Catalana de Digestologia (Blanes, 29-31 de gener del 2009). **Suplements dels Annals de Medicina 2009; 92(Supl 1):S1-62**

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Pharmacological treatment of oropharyngeal dysphagia through TRPV1 stimulation. Rofes L, Arreola V, Clavé P. 2010 Joint International Meeting in Neurogastroenterology and Motility (Boston, USA, 26-29 d'agost del 2010). **Neurogastroenterol Motil 2010; 22(Suppl 1):3**

L'estimulació de TRPV1 amb capsaicinoids millora la deglució dels pacients amb disfàgia orofaríngia. Rofes L, Arreola V, Clavé P. XX Congrés de la Societat Catalana de Digestologia (Lleida, 27-29 de gener del 2011). **Suplements dels Annals de Medicina 2011; 94(Supl 1):S1-36**

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Piperine improves swallow response of patients with neurogenic dysphagia. Rofes L, Arreola V, Casamitjana F, Enrique A, Clavé P. 2012 Dysphagia Research Society Annual Meeting (Toronto, Canada, 7-10 de març del 2012). **Dysphagia 2012; 27:569-620**

Piperine improves swallow response of patients with neurogenic dysphagia. Rofes L, Alvarez D, Arreola V, Casamitjana F, Enrique A, Clavé P. 2012 Joint International Meeting in Neurogastroenterology and Motility (Bologna, Italy, 6-8 de setembre del 2012). **Neurogastroenterol Motil 2012; 24(Suppl 2):137**

Therapeutic effect of xanthan gum-based thickener on swallowing function in patients with oropharyngeal dysphagia. Rofes L, Arreola V, Mukherjee R, Clavé P. 34th ESPEN Congress on Clinical Nutrition and Metabolism (Barcelona, 8-11 de setembre del 2012). **Clin Nutr 2012; 7(Suppl 1):257**

Diagnostic accuracy of the eating assessment tool and the volume-viscosity swallow test for clinical screening and assessment of oropharyngeal dysphagia. Rofes L, Arreola V, Mukherjee R, Clavé P. 34th ESPEN Congress on Clinical Nutrition and Metabolism (Barcelona, 8-11 de setembre del 2012). **Clin Nutr 2012; 7(Suppl 1):256**

Therapeutic effect of xanthan gum-based thickener on swallowing function in patients with oropharyngeal dysphagia. Rofes L, Arreola V, Mukherjee R, Clavé P. 20th United European Gastroenterology Week (Amsterdam, Netherlands, 20-24 d'octubre del 2012). **Gut 2012; 61(Suppl 3):A429**

Diagnostic accuracy of the eating assessment tool and the volume-viscosity swallow test for clinical screening and assessment of oropharyngeal dysphagia. Rofes L, Arreola V, Mukherjee R, Clavé P. 20th United European Gastroenterology Week (Amsterdam, Netherlands, 20-24 d'octubre del 2012). **Gut 2012; 61(Suppl 3):A17**

L'estimulació elèctrica transcutània millora la seguretat de la deglució en pacients amb disfagia orofaríngia després d'un ictus. Rofes L, Arreola V, López I, Martin A, Sebastián M, Ciurana A, Clavé P. XXII Congrés de la Societat Catalana de Digestologia 2013 (Tarragona, 31 de gener – 2 de febrer del 2013). **Suplements dels Annals de Medicina 2013; 96(Supl 1):S1-43**

Sensory transcutaneous electrical stimulation improves safety of swallow in post-stroke dysphagic patients Rofes L, Arreola V, Lopez I, Martin A, Sebastián M, Ciurana A, Clavé P. 2013 Dysphagia Research Society Annual Meeting. (Seattle, USA, 14-16 de març del 2013). **Dysphagia 2013; 28:610**

Beques

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L'autora vol agraïr el suport econòmic rebut de les diferents entitats.

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Millor Comunicació Oral al XXII Congrés De la Societat Catalana de Digestologia 2013 (Tarragona) pel treball: L'estimulació elèctrica transcutània millora la seguretat de la deglució en pacients amb disfagia orofaríngia després d'un ictus.

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Young Clinician-Scientist Travel Grant a la 20th United European Gastroenterology Week (UEGW 2012, Amsterdam, The Netherlands) pel treball: Diagnostic accuracy of the eating assessment tool and the volume-viscosity swallow test for clinical screening and assessment of oropharyngeal dysphagia.

Young Investigator Award al 2010 Joint International Meeting in Neurogastroenterology and Motility (Boston, USA) pel treball: Pharmacological treatment of oropharyngeal dysphagia through TRPV1 stimulation.

Resumen de la Tesis Doctoral

La disfagia orofaríngea es un trastorno digestivo reconocido por la Organización Mundial de la Salud (OMS) en la *International Classification of Diseases* (ICD-10, código R-13) caracterizado por la dificultad para formar y/o mover el bolo alimentario de la boca al esófago, y que puede ocasionar el paso de alimento a la vía respiratoria. Es un trastorno muy prevalente en pacientes con enfermedades neurológicas y de edad avanzada, que se asocia a graves complicaciones respiratorias y nutricionales con una alta morbi-mortalidad. A pesar de ello, la disfagia orofaríngea continúa siendo un trastorno infradiagnosticado e infratratado. Es importante por lo tanto profundizar en el conocimiento de la fisiopatología de las alteraciones de la deglución y las complicaciones que conllevan, así como mejorar las herramientas diagnósticas y en especial, abrir las puertas a nuevas alternativas de tratamiento, hasta el momento escasas y centradas en mecanismos compensatorios. El primer objetivo de esta Tesis Doctoral ha sido evaluar la validez diagnóstica de una herramienta de cribado (el cuestionario *Eating Assessment Tool-10*, EAT-10) y el método de exploración clínica volumen-viscosidad (MECV-V). Ambos métodos mostraron una alta sensibilidad y especificidad para detectar aquellos pacientes con alteraciones deglutorias. Posteriormente, hemos caracterizado el patrón motor deglutorio de dos fenotipos de ancianos en alto riesgo de padecer disfagia orofaríngea: el anciano frágil y el anciano con neumonía adquirida en la comunidad. Observamos como el factor fisiopatológico crítico que condicionaba la alteración de la seguridad de la deglución en ambos grupos era un retraso en el tiempo de cierre del vestíbulo laríngeo y en el movimiento vertical del hioides, mientras que una débil fuerza de propulsión condiciona la aparición de residuo orofaríngeo. Estas alteraciones son los factores clave en los que se debería focalizar el desarrollo de las nuevas estrategias terapéuticas. Por otro lado, describimos que la disfagia es un factor de riesgo para la neumonía adquirida en la comunidad en el anciano y un factor de mal pronóstico clínico en los dos fenotipos de ancianos, resaltando la relevancia de la patología y la necesidad de intervención. Es en este sentido que hemos evaluado tres grupos de nuevas estrategias terapéuticas: un tratamiento compensador (espesantes de goma xantana); un tratamiento de neuro-estimulación (agonistas de los canales TRP); y un tratamiento de neuro-rehabilitación periférica (estimulación eléctrica transcutánea). Los espesantes de goma xantana mostraron un efecto terapéutico concentración-dependiente en la prevención de penetraciones y aspiraciones, y un mecanismo de acción secuencial: a viscosidad néctar, el aumento de la seguridad de la deglución puede atribuirse a las características intrínsecas del bolo; a viscosidad pudin, el efecto terapéutico fue mayor debido al enlentecimiento de la velocidad del bolo por la orofaringe. Cabe destacar que no aumentó significativamente del residuo orofaríngeo debido al incremento de la viscosidad. Por otro lado, la suplementación del bolo alimentario con el agonista TRPV1 (capsaicina), y el agonista dual TRPV1/A1 (piperina) acortó el tiempo de cierre del vestíbulo laríngeo, reduciendo así la prevalencia de penetraciones. La capsaicina, además, también mejoró la eficacia de la deglución. La estimulación eléctrica transcutánea aplicada a una intensidad de estimulación sensorial, sin producir la contracción muscular, acortó el tiempo de cierre del vestíbulo laríngeo, reduciendo las alteraciones de la seguridad de la deglución; al aplicar una intensidad de estimulación motora, también redujo el residuo orofaríngeo además de mejorar la seguridad de la deglución. Los estudios de esta Tesis Doctoral confirman que es posible diagnosticar y tratar de forma eficaz a los pacientes con disfagia orofaríngea y abren una nueva línea de investigación destinada a cambiar el enfoque de la terapéutica de la disfagia de la compensación a la recuperación de la función.

Summary of the Doctoral Thesis

Oropharyngeal dysphagia is a digestive disorder characterized by the difficulty to form or move the bolus from the mouth to the oesophagus and can cause tracheobronchial aspirations. Oropharyngeal dysphagia is classified by the World Health Organization (WHO) in the International Classification of Diseases (ICD-10, code R-13). It is a highly prevalent disorder in patients with neurological diseases and aging, and is associated with serious complications with high morbidity and mortality. Despite this, oropharyngeal dysphagia remains poorly understood, underdiagnosed and undertreated. It is therefore important to further our knowledge of swallowing disorders and associated complications, improve diagnostic tools and, in particular, open doors to new treatments which are currently limited and mainly focused on compensatory mechanisms. The first objective of this thesis was to establish the diagnostic validity of a screening tool (Eating Assessment Tool -10 questionnaire, EAT- 10) and a method of clinical examination, the Volume - Viscosity Swallow Test (V-VST). Both methods showed high sensitivity and specificity for detecting patients with swallowing impairment. Then we characterized the swallowing pattern of two phenotypes of elderly patients at high risk of deglutition disorders: frail elderly and elderly patients with community-acquired pneumonia. We observed that delayed laryngeal vestibule closure time and vertical hyoid movement were critical factors in determining the alteration of swallowing safety in these patients, while weak bolus propulsion determined the presence of oropharyngeal residue. So, these were the key factors we targeted in the new treatments. Furthermore, we described how oropharyngeal dysphagia was a risk factor for community-acquired pneumonia in the elderly, and an indicator of bad prognosis in both phenotypes of elderly patients, signalling the severity of the pathology and the need for intervention. We thus evaluated three groups of new therapeutic strategies for patients with oropharyngeal dysphagia: compensatory treatment with a xanthan gum thickener; peripheral neuro-stimulation treatment with TRP agonists, and peripheral neuro-rehabilitation treatment with transcutaneous electrical stimulation. Xanthan gum thickeners had a concentration-dependent effect that prevented penetrations and aspirations. The thickener presented a sequential mechanism of action: at nectar viscosity, the increase in the safety of swallow could be attributed to the intrinsic characteristics of the bolus; at pudding viscosity, where the therapeutic effect was maximum, the slower bolus velocity through the oropharynx contributed to the observed effect. Notably, increasing bolus viscosity did not significantly increase oropharyngeal residue. Bolus supplementation with the TRPV1 agonist capsaicin or the dual TRPV1/A1 agonist piperine shortened the laryngeal vestibule closure time, thereby reducing the prevalence of penetrations and aspirations. Capsaicin additionally improved the efficacy of swallow. Finally, transcutaneous electrical stimulation applied at sensory intensity, without causing muscle contraction, shortened the laryngeal vestibule closure time, thus improving the safety of swallow ; at motor intensity, the safety of swallow was also improved and, in addition, oropharyngeal residue was reduced. The studies of this thesis confirm that is possible to diagnose and to treat dysphagic patients efficiently. They open a new line of research that aims to change the approach of dysphagia therapy from compensation to functional recovery.

Abreviaturas

AE efectos adversos (*adverse events*)
AP neumonía por aspiración (*aspiration pneumonia*)
AUC área bajo la curva (*area under curve*)
C cierre *(closure)*
CAP neumonía adquirida en la comunidad (*community acquired pneumonia*)
CI intérvalos de confianza (*confidence intervals*)
COPD enfermedad pulmonar obstructiva crónica (*chronic obstructive pulmonary disease)*
DO disfagia orofaríngea (= **OD**)
DSG *dorsal swallowing group*
EAT-10 *eating assessment tool-10*
EST *extrem spoon thick*
e-stim electroestimulación *(electrostimulation)*
FEES fibroendoscópia de la deglución (*fiberoptic endoscopic evaluation of swallwoing*)
FEP pacientes ancianos frágiles (*frail elderly patients*)
GPJ unión glosopalatina *(glossopalatal junction)*
GPNph rama faríngea del nervio glosofaríngeo (*glossopharyngeal nerve, pharyngeal branch*)
HV voluntarios sanos (*healthy volunteers*)
ICD *International Statistical Classification of Diseases and Related Health Problems*
LV vestíbulo laríngeo *(laryngeal vestibule)*
MECV-V método de exploración clínica volumen viscosidad (**= V-VST**)
MNA *Mini Nutricional Assessment*
MNA-SF *Mini Nutricional Assessment short form*
NMES estimulación eléctrica neuromuscular (*neuromuscular electrical stimulation*)
NPV valor predictivo negativo (*negative predictive value*)
NTS núcleo del tracto solitario (*nucleus tractus solitarii)*
O apertura (*opening*)
OD *oropharyngeal dysphagia* (= **DO**)
PAS escala de penetración-aspiración (*penetration-aspiration scale*)
PEG gastrostomía endoscópica percutánea (*percutaneous endoscopic gastrostomy*)
PPV valor predictivo positivo (*positive predictive value*)
ROC *Receiver Operating Characteristic*
rTMS estimulación magnética transcraneal repetitiva *(repetitive transcraneal magnetic stimulation)*
RTUC *Resource ThickenUp Clear*
SLN nervio superior laríngeo (*superior laryngeal nerve*)
SSQ *Sydney swallowing questionnaire*
tDCS estimulación transcraneal directa (*transcraneal direct current stimulation*)
TMS estimulación magnética transcraneal *(transcraneal magnetic stimulation)*
TOR-BSST *Toronto Bedside Swallowing Screening Test*
TRP *transient receptor potential cation channel*
TRPA1 *transient receptor potential cation channel, subfamily A, member 1*
TRPM8 *transient receptor potential cation channel, subfamily M, member 8*
TRPV1 *transient receptor potential cation channel, subfamily V, member 1*
UES esfínter esofágico superior (*upper esophageal sphincter*)
VFS videofluoroscopia (*videofluoroscopy*)
VPJ unión velofaríngea *(velopharyngeal junction)*
VSG *ventral swallowing group*
V-VST *volume viscosity swallow test* (= **MECV-V**)
WHO Organización Mundial de la Salud *(World Health Organization)*

ÍNDICE

INTRODUCCIÓN

Introducción

1. INTRODUCCIÓN

La deglución es el proceso fisiológico mediante el cual se transportan sólidos y líquidos desde la boca hasta el estómago. Es un proceso rápido y complejo que requiere de la contracción y relajación coordinada de más de 30 pares de músculos de la boca, faringe, laringe y esófago, así como la coordinación entre el sistema digestivo y el sistema respiratorio. Múltiples enfermedades y co-morbilidades pueden alterar esta función fisiológica, conduciendo a la aparición de dificultades o molestias para formar o mover el bolo alimentario de forma segura y eficaz, síntoma que se conoce como disfagia. Dependiendo de su localización, la disfagia puede clasificarse en orofaríngea o esofágica. La disfagia orofaríngea, objetivo de estudio de esta Tesis Doctoral, es un trastorno prevalente en la población anciana y en pacientes con enfermedades neurológicas, que se asocia a graves complicaciones nutricionales y respiratorias, con una alta mortalidad asociada. Está específicamente reconocida por la Organización Mundial de la Salud (WHO) en la *International Statistical Classification of Diseases and Related Health Problems* (ICD-9 y ICD-10) como un trastorno que afecta al sistema digestivo, recibiendo para su diagnóstico los códigos 787.2 y R13.1, respectivamente. A pesar de esto, la disfagia orofaríngea es un trastorno poco conocido, infradiagnosticado e infratratado. Por este motivo, pensamos que es importante profundizar en el conocimiento de las alteraciones de la deglución y las complicaciones que conllevan así como mejorar las herramientas diagnósticas y en especial, abrir las puertas a nuevas alternativas de tratamiento, hasta el momento escasas y centradas en mecanismos compensatorios, para los pacientes con disfagia. Estos aspectos son los que se han pretendido abordar, de forma integrada, durante el desarrollo de esta Tesis Doctoral.

2. ANATOMÍA DEL SISTEMA DEGLUTORIO

2.1 Cavidad oral y lengua

La cavidad oral es la primera porción del tubo digestivo. Interviene en los procesos de masticación, degustación, insalivación, deglución, articulación y resonancia del habla. Es un espacio anatómico dividido en dos partes por los arcos gingivodentarios: una periférica o vestíbulo de la boca y otra central, o cavidad bucal propiamente dicha. Ambas partes se comunican entre sí por los espacios interdentales y el espacio retrodentario, situado entre los últimos molares y la rama ascendente del maxilar inferior. El vestíbulo bucal es el espacio situado entre los labios y las mejillas y los arcos gingivodentarios. Se abre al exterior por medio del orificio bucal que está formado por **los labios superior e inferior cuya unión forman el sello labial**.

La **cavidad bucal** está limitada hacia delante y hacia los lados por los arcos gingivodentarios, por arriba por la bóveda palatina y por abajo por el suelo de la boca. Hacia atrás, se comunica con la faringe por el istmo de las fauces, un orificio circunscrito por el velo del paladar, la úvula, los pilares anteriores del velo y la base de la lengua.

En la **bóveda palatina** se pueden distinguir dos partes: los dos tercios anteriores se denominan paladar duro y el tercio posterior, paladar blando. El paladar duro está formado por tres capas, la capa ósea formada por las apófisis palatinas de los maxilares y las láminas horizontales de los huesos palatinos, la capa mucosa y la capa glandular. El

paladar blando es un tabique músculo-membranoso que prolonga la bóveda palatina hacia atrás y abajo, y separa la nasofaringe de la orofaringe. El borde posterior del paladar blando presenta en su parte media una prolongación de 10 a 15 mm de longitud, la úvula, y a cada lado, dos repliegues curvilíneos, uno anterior y otro posterior, llamados pilares anteriores y posteriores del velo del paladar o arcos palatogloso y palatofaríngeo respectivamente.

El **suelo de la boca** está delimitado por el espacio situado entre la mandíbula y el hueso hioides, y contiene principalmente músculos. Los músculos milohioideos constituyen la pared inferior de este espacio. Sus fibras posteriores se insertan en el hueso hioides y desde aquí se dirigen hacia delante y se insertan en el arco mandibular. Entre la piel y los milohioideos, a cada lado de la línea media se sitúa el vientre anterior del músculo digástrico que va desde la cara interna del mentón hasta el hioides. Durante la deglución, este músculo y el milohioideo traccionan del hioides hacia delante y lo elevan y además abren la boca. Superiormente a los milohioideos, el suelo de la boca está reforzado por el músculo geniohioideo, que se extiende desde la cara interna del mentón hasta el hioides (**Figura 1**).

La **lengua** ocupa la parte media del suelo de la boca. Es un órgano muy móvil formado por músculo estriado recubierto de mucosa. En la lengua se diferencian dos partes principales divididas por un surco en forma de V abierta hacia delante, llamada surco terminal o V lingual: la posterior o faríngea, la raíz, y la anterior o bucal, el cuerpo. La parte faríngea de la lengua, parte fija, ancha y gruesa, constituye la pared anterior de la orofaríngе y se une al paladar blando por los arcos palatoglosos y a la epiglotis, por los pliegues glosoepiglóticos, formando la vallécula. La parte oral de la lengua, el cuerpo, ocupa casi totalmente la cavidad bucal en reposo. La mucosa del dorso de la lengua, la parte superior, está provista de las papilas linguales que contienen receptores para el gusto: las filiformes, delgadas y puntiagudas, son las más abundantes. Entre ellas se encuentran dispersas las papilas fungiformes y delante del surco terminal hay una hilera de 8 a 12 papilas más grandes, llamadas circunvaladas o caliciformes. En ambos bordes laterales de la lengua encontramos las papilas foliadas [1] (**Figura 2**).

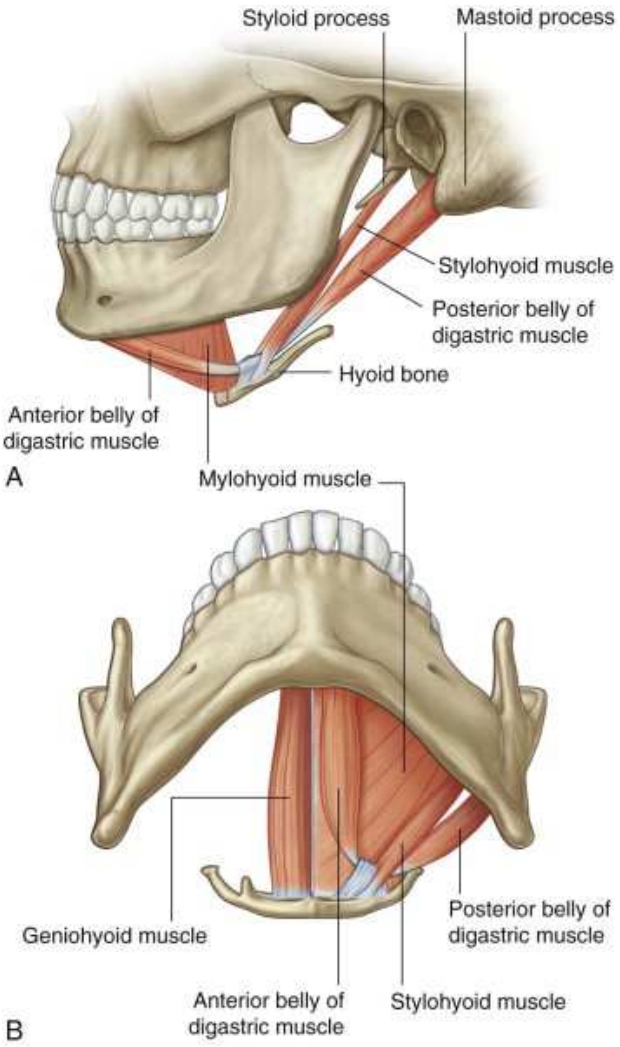

Figura 1: Músculos suprahioideos, vista lateral (A) y vista inferior (B). Reproducido de: Drake RL *et al* (2005) [2].

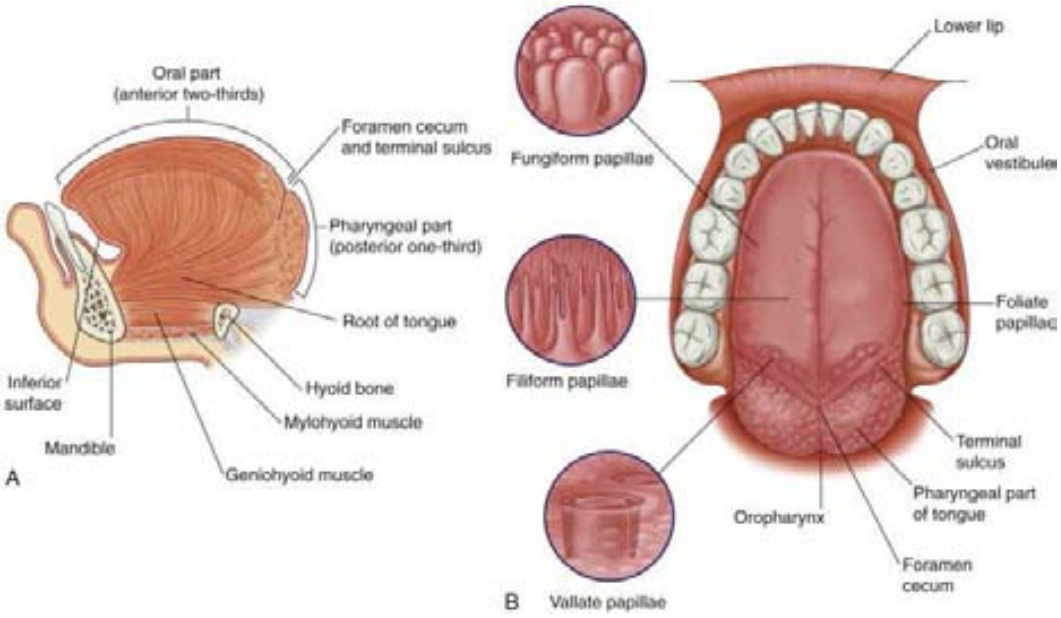

Figura 2: Sección sagital (A) y vista superior (B) de la lengua. Reproducido de: Drake RL *et al* (2005) [2].

2.2 Faringe

La faringe es la segunda porción del tubo digestivo. Es un conducto músculo-membranoso situado detrás de las fosas nasales y de la boca y que termina, por abajo, en la laringe y la tráquea por una parte, y en el esófago por la otra. Es un conducto mixto desde el punto de vista fisiológico, pues forma parte tanto de la vía digestiva como de la vía respiratoria. Basándose en las aberturas que se hallan en la parte anterior de la faringe, este órgano se divide en tres porciones anatómicas craneocaudales: **nasofaringe**, **orofaringe** y **laringofaringe** (**Figura 3**).

La **nasofaringe** desempeña una función puramente respiratoria y fonatoria. Se extiende desde la base del cráneo, por detrás de las fosas nasales (con las que comunica a través de las coanas) hasta el velo del paladar, donde se comunica con la orofaringe por un espacio estrecho, denominado istmo de la faringe. En el proceso de la deglución el velo del paladar se eleva y se pone en contacto con la pared posterior de la faringe formando el **sello velofaríngeo**, que **cerrará la comunicación entre la nasofaringe y la orofaringe y evitará la regurgitación de alimentos a la cavidad nasal**.

La **orofaringe** se extiende desde el istmo faríngeo hasta el plano delimitado por el hueso hioides o punto de inserción de la epiglotis. Se comunica con la cavidad oral por la parte anterior, por medio del istmo de las fauces. Por esta parte de la faringe pasan los alimentos y el aire respiratorio. Los alimentos son conducidos de la boca a la parte inferior de la faringe por los canales alimentarios que encontramos a cada lado del tercio posterior de la lengua.

La **laringofaringe** se extiende desde el hueso hioides hasta el borde inferior del cartílago cricoides, a la altura de la sexta vértebra cervical, donde empieza el esófago. Se localiza detrás de la laringe y tiene forma de embudo, estrechándose en la parte inferior en dirección al esfínter esofágico superior. La pared anterior corresponde al orificio laríngeo. Este orificio, de forma elíptica, tiene los límites formados por los bordes de la epiglotis, los pliegues ariepiglóticos.

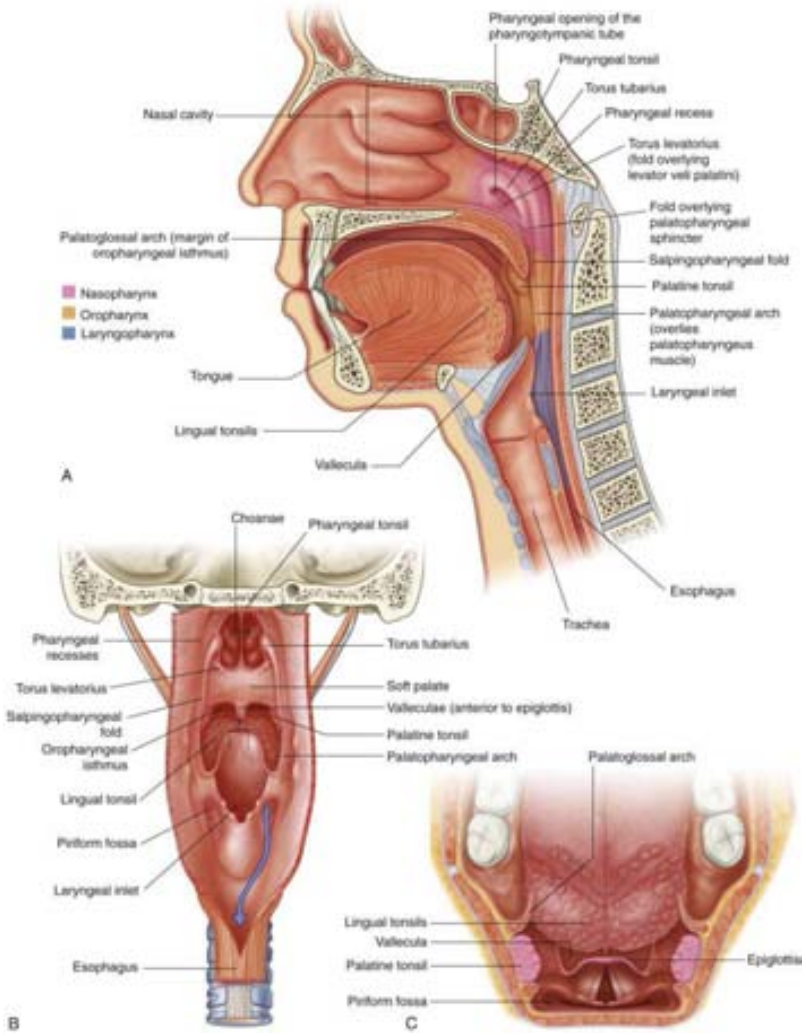

Figura 3: Vista lateral (A), posterior (B) y superior (C) de la faringe. Reproducido de: Drake RL *et al* (2005) [2].

Caudalmente al plano delimitado por dicha abertura, la función de la laringofaringe es exclusivamente el paso de los alimentos. Por debajo del pliegue ariepiglótico se encuentran los **senos piriformes**, continuación de los canales alimentarios, que facilitan el paso del alimento hacia el esófago.

Histológicamente, la faringe está constituida por tres capas: la mucosa o túnica interna, en la cara interior, un armazón fibroso interpuesto entre la túnica muscular y la mucosa, llamado fascia faringobasilar o túnica media y los músculos de la túnica externa. La pared muscular de la faringe está constituida por diez músculos estriados bilaterales: tres músculos constrictores y dos músculos elevadores de cada lado. Los músculos constrictores o intrínsecos (músculo constrictor superior, el medio y el inferior) están formados por fibras transversales y oblicuas y su función es la de estrechar la faringe al paso del bolo alimentario con un movimiento peristáltico (**Figura 4**). Los músculos elevadores o extrínsecos tienen la función de elevar y acortar la faringe durante la deglución y son el palatofaríngeo, el estilofaríngeo y el salpingofaríngeo [3].

2.3 Laringe

La laringe forma parte de la vía aérea y es también el órgano de la fonación. Está situada en la parte mediana y anterior del cuello, debajo del plano del

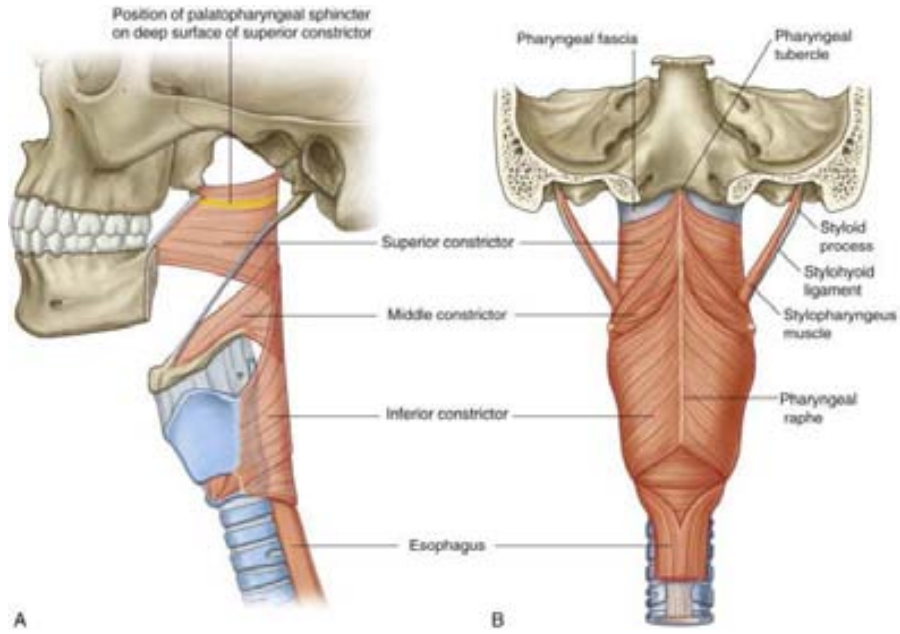

Figura 4: Músculos constrictores de la faringe. Vista lateral (A) y posterior (B). Reproducido de: Drake RL *et al* (2005) [2].

hueso hioides y de la lengua y delante de la faringe, con la cual comunica cranealmente y por encima de la tráquea con la cual comunica caudalmente. La laringe está constituida por un esqueleto cartilaginoso, las articulaciones y ligamentos que unen los cartílagos, los músculos que los movilizan y la mucosa que tapiza el interior del órgano. Los principales cartílagos que forman la laringe son: el **tiroides**, el más voluminoso, es la pieza principal de la laringe; el **cricoides**, situado debajo del tiroides, sobre él se apoya toda la laringe, precede inmediatamente a la tráquea; los **aritenoides** son dos, se sitúan a ambos lados de la línea media y reposan sobre el borde superior del cricoides; la **epiglotis**, de naturaleza elástica y de forma ovalada, se fija al cartílago tiroides por el ligamento tiro-epiglótico de su extremo inferior, y tiene el borde superior libre que se sitúa por detrás de la lengua y del hioides sobresaliendo por encima de éste. La cara anterior o lingual de la epiglotis está tapizada por mucosa lingual que forma **tres pliegues gloso-epiglóticos los cuales delimitan dos fosas, las valléculas**. Durante la deglución, el hueso hioides se mueve hacia arriba y hacia adelante y la epiglotis se dobla posteriormente como resultado de la presión pasiva de la base de la lengua y la contracción activa del músculo ariepiglótico. Mediante este movimiento, **la epiglotis cumple su función principal que es proteger la vía respiratoria y desviar los alimentos y los líquidos de la entrada de la laringe** hacia los senos piriformes y la hipofaringe.

Los músculos de la laringe pueden dividirse entre extrínsecos (aquellos que unen la laringe con los órganos vecinos) e intrínsecos (aquellos que toman sus inserciones en los cartílagos laríngeos asegurando su movilidad). Dentro de los músculos extrínsecos encontramos los elevadores de la laringe: tirohioideo, estilofaríngeo, palatofaríngeo, milohioideo, geniohioideo y estilohioideo; y los depresores de la laringe: esternotirohioideo, esternohioideo y omohioideo. Los músculos intrínsecos pueden dividirse en tres grupos, de acuerdo con sus acciones principales: los cricoaritdenoideos posteriores y laterales y los aritenoides oblicuos y transverso modifican las dimensiones de la glotis. Los cricotiroideos, cricoaritenoideos posteriores, tiroaritenoideos y

vocalis regulan la tensión de los ligamentos vocales. Los aritenoideos oblicuos y los ariepiglóticos actúan facilitando el cierre de la laringe, aduciendo los pliegues ariepiglóticos y aproximando los cartílagos aritenoides a la base de la epiglotis y los tiroepiglóticos facilitan la apertura de la laringe por su acción sobre los pliegues ariepiglóticos.

Internamente se puede dividir la laringe en tres niveles: **el vestíbulo laríngeo** (segmento superior) **conforma la entrada de la laringe** y termina en los pliegues vestibulares o falsas cuerdas vocales y está limitado en su pared anterior por la cara posterior de la epiglotis; el segmento medio lo forma **el ventrículo laríngeo,** limitado en su parte superior por los pliegues vestibulares y en su parte inferior por los pliegues vocales o cuerdas vocales verdaderas. El espacio comprendido entre los pliegues vocales cuando están abiertos es la hendidura glótica; **la cavidad infraglótica** es el segmento inferior de la laringe, limitado arriba por los pliegues vocales y abajo por la tráquea [4] (**Figura 5**).

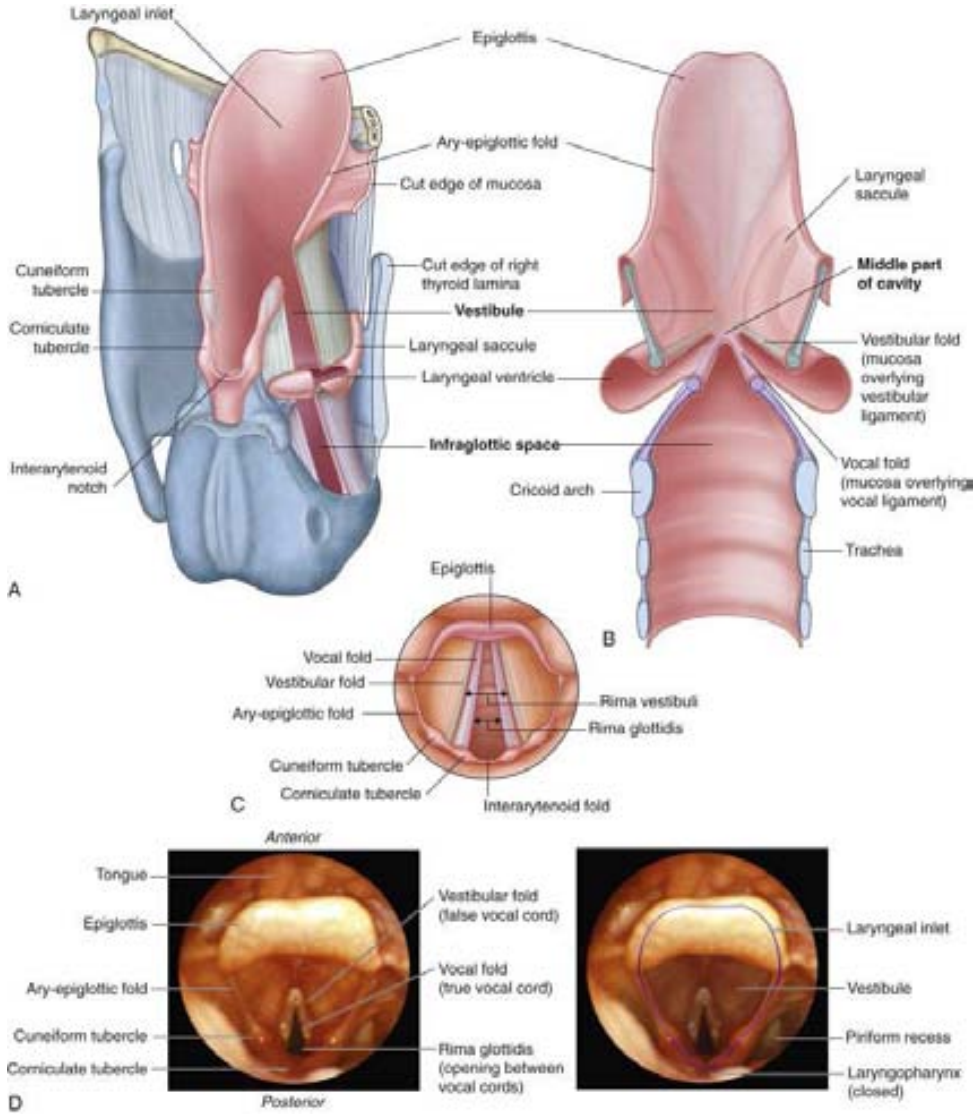

Figura 5: Vista lateral-posterior (A), sección coronal (B) y vista superior (C) de la cavidad laríngea. Vista superior de la laringe obtenida mediante fibro-laringoscopio (D). Reproducido de: Drake RL *et al* (2005) [2].

2.4 Esfínter esofágico superior

El esfínter esofágico superior (UES) es la zona de alta presión del tracto digestivo superior que separa el esófago y la faringe. El UES se encuentra cerrado tónicamente de forma que previene la entrada de aire al tracto digestivo y el reflujo de material del esófago a la faringe. En cambio, el UES se abre en respuesta a una deglución, permitiendo el paso del bolo alimentario al esófago y permite también la salida de material del esófago durante el vómito o los eructos. Se encuentra a la altura de la 5ª-6ª vértebra cervical y mide entre 2 y 4 cm de longitud. Está formado por el músculo cricofaríngeo (componente principal), la parte inferior del músculo constrictor faríngeo y la parte superior del esófago cervical [5;6].

3. FISIOLOGÍA DE LA DEGLUCIÓN

La deglución se divide en cuatro grandes fases, cada una de las cuales (frecuentemente más de una) puede estar afectada y originar un trastorno deglutorio.

3.1 Fase oral preparatoria

Es de control voluntario y su objetivo es la ingesta, masticación y la formación del bolo alimentario. La ingesta del bolo alimentario requiere el descenso de la mandíbula, la apertura de los labios y la depresión de la lengua, acciones que aumentan el volumen de la cavidad oral para acomodar el bolo ingerido. La masticación es un proceso necesario para adecuar el tamaño, la forma y la consistencia del bolo ingerido. Esta acción requiere un complejo y repetitivo movimiento mandibular y el molido de sólidos con los dientes, que son posicionados sobre sus superficies con la ayuda de las mejillas y la lengua. La lengua también ayuda a reducir los sólidos blandos o solubles aplastándolos contra las estructuras óseas que rodean la cavidad oral y mezclándolos con los elementos líquidos del bolo ingerido. La saliva secretada también facilita la disolución y la lubricación del bolo sólido y contribuye al inicio del proceso químico de digestión por medio de la enzima α-amilasa, que cataliza la ruptura del almidón en maltosas, maltotriosas y dextrinas. Una vez el bolo está preparado adecuadamente, es posicionado en un receso de la parte posterior del dorso de la lengua para ser propulsado hacia la orofaringe [7].

3.2 Fase oral propulsora

Es también voluntaria y se caracteriza por la propulsión del bolo alimentario hacia la orofaringe por parte de la lengua. Al inicio de la fase oral propulsora, la parte anterior de la lengua se pone en contacto con el paladar duro ubicando el bolo en la parte posterior de la cavidad oral. A su vez, **la parte posterior de la lengua está en contacto con el paladar blando, formando el sello glosopalatino y evitando la caída prematura del bolo hacia la faringe**. Al iniciar la propulsión, la lengua presiona contra el paladar duro generando una onda de presión en dirección antero-posterior que propulsa el bolo hacia la orofaringe al mismo tiempo que el paladar blando se eleva para abrir el sello glosopalatino y cerrar la nasofaringe. La fase oral se puede considerar finalizada cuando la cola del bolo entra en la orofaringe, momento en el que la parte posterior del dorso de la lengua vuelve a cerrar el sello glosopalatino con el paladar blando para prevenir el escape retrógrado del bolo hacia la cavidad oral [7].

3.3 Fase faríngea

Es involuntaria y comprende el período desde que la cabeza del bolo entra en la cavidad faríngea hasta que la cola del bolo sale del esfínter esofágico superior y este se cierra. Habitualmente

la fase faríngea se produce como continuación de la fase oral, sin embargo, la fase faríngea se puede activar sin necesidad de la fase oral en respuesta a estímulos faríngeos.

La fase faríngea comprende la **respuesta motora oro-faríngea**, la cual se caracteriza por una **serie de acontecimientos que permiten pasar de una configuración respiratoria** (aquella en la cual la nasofaringe, la orofaringe, la laringe y el resto de la vía respiratoria forman un canal continuo por el que circula el flujo de aire) **a una de digestiva** (que comunica la boca, la orofaringe, la laringofaringe y el esófago), **mantener la configuración digestiva durante el tránsito del bolo alimentario por la faringe y finalmente volver a la configuración respiratoria.** El tránsito entre estas configuraciones se produce gracias a la apertura y al cierre coordinado del sello glosopalatino, el sello velo-faríngeo, el vestíbulo laríngeo y el UES [8;9]. Inmediatamente después de la apertura del cierre glosopalatino y por tanto de la entrada del bolo en la orofaringe, el paladar blando se eleva y la pared posterior de la faringe se mueve medialmente para entrar en contacto y formar el sello velo-faríngeo que cierra la nasofaringe para evitar la regurgitación nasal del bolo. Seguidamente, y a medida que el bolo va avanzando por la faringe se producen una serie de acontecimientos destinados a proteger la vía respiratoria: por un lado, se produce la adducción de las cuerdas vocales y de los aritenoides que sellan la vía respiratoria; los aritenoides, además, se mueven hasta contactar la base de la epiglotis y se produce la retroflexión de la epiglotis como consecuencia de la presión pasiva por parte de la base de la lengua y la contracción activa de los músculos ariepiglóticos, que acaba de cerrar el vestíbulo laríngeo y desvía el bolo alimentario fuera de la entrada de la laringe. Por otro lado, los músculos suprahioideos y los músculos longitudinales de la laringe, mueven el hioides y la laringe hacia arriba y anteriormente, de forma que posicionan la entrada de la laringe bajo la base de la lengua, fuera de la zona de paso del bolo alimentario. Esta acción ayuda también al acortamiento y expansión del espacio hipofaríngeo y a la abertura del UES, que a su vez también se eleva unos 2 - 2,5 centímetros, facilitando el paso del bolo hacia el esófago [10] (**Figura 6**).

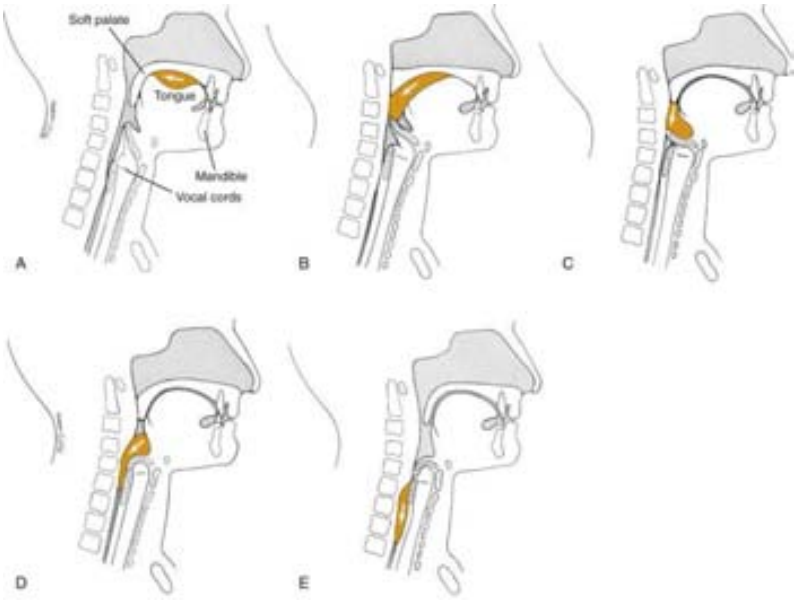

Figura 6: Vistas laterales de la cabeza y el cuello mostrando la progresión del bolo por la cavidad oral y la faringe. Adaptado de: Logemann JA (2010) [11].

La contracción secuencial de los tres músculos constrictores faríngeos se ha postulado como la fuerza motriz que impulsa el bolo hacia el esófago. Sin embargo, la evidencia de que la cabeza del bolo se mueve más rápido que la onda de contracción faríngea sugiere que la energía cinética aplicada al bolo al ser propulsado de la boca a la orofaringe por la lengua es suficiente para llevarlo a través de la faringe, mientras que los constrictores faríngeos podrían tener la principal función de realizar un efecto de barrido y aclaramiento del bolo [12;13]. Se ha evaluado la sincronización de los principales parámetros de la respuesta motora orofaríngea y se ha puesto de manifiesto que en individuos jóvenes y sanos el cierre del vestíbulo laríngeo (tomando como tiempo 0 la apertura del sello glosopalatino) se produce antes de los 160 ms, la apertura del UES se produce antes de los 200 ms y la duración total de la deglución es inferior a 750 ms [8].

3.4 Fase esofágica

Se inicia con la apertura del UES y continúa con la peristalsis esofágica. En la apertura del UES intervienen cuatro mecanismos principales: a) la interrupción del tono vagal sobre el músculo cricofaríngeo, lo que permite la desaparición de la contracción muscular de origen central que lo mantiene cerrado; b) la tracción sobre la cara anterior del esfínter causada por la contracción de la musculatura supra-hioidea; c) la presión sobre el esfínter ejercida por el bolo alimentario, la magnitud de la cual depende de la fuerza de propulsión lingual, y d) la distensibilidad del esfínter que permite su relajación completa, con bajas presiones residuales y escasa resistencia durante el paso del bolo [5].

4. CONTROL NEURAL DE LA DEGLUCIÓN

El control neural de la deglución se puede definir cómo una red multidimensional en la que diferentes niveles del sistema nervioso están involucrados y conectados. Intervienen los receptores periféricos que integran la información sensorial relacionada con las características del bolo, los nervios aferentes que transmiten esta información a los centros deglutorios del bulbo raquídeo y a las regiones corticales y sub-corticales, que integran y modulan la respuesta motora, que es transmitida a los músculos efectores por parte de las motoneuronas de diversos pares craneales (**Figura 8**).

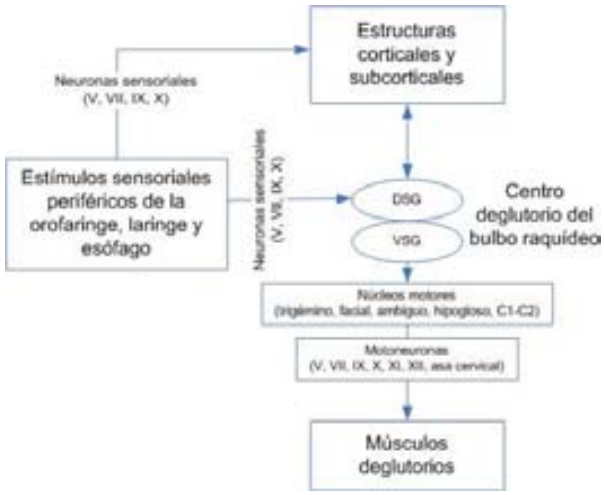

Figura 8: Esquema de la red multidimensional implicada en el control neural de la deglución.

4.1 Estímulo sensorial e innervación aferente

El estímulo sensorial es un elemento crítico en la deglución [14]. El *feedback* sensorial durante la fase oral permite el adecuado posicionamiento de las estructuras orales y la preparación y posicionamiento del bolo para su transporte, así como modula la fuerza, la velocidad y la coordinación de las contracciones musculares.

Facilita también el inicio de la respuesta motora orofaríngea, que no es fija ni refleja como se había postulado históricamente (por lo que no es adecuado usar el término reflejo deglutorio), sino que también depende de este *feedback* sensorial y puede adaptarse a diferentes características del bolo [15]. El sistema sensorial que integra la información del bolo alimentario es complejo y está formado por tres tipos de estímulos fundamentales: el **gusto**, el **olor** y la **quimiosensación**.

La señalización del **gusto** se realiza a través de las papilas gustativas, que pueden distinguir 5 gustos fundamentales: el dulce, el salado, el amargo, el ácido y el umami. Las sales y los ácidos son detectados por canales iónicos (ionotrópicos), localizados en la membrana apical de las células Tipo III de las papilas gustativas, mientras que las sustancias que producen un sabor amargo, dulce o umami (como por ejemplo el glutamato) activan receptores metabotrópicos (acoplados a proteína G) de las células Tipo II de las papilas gustativas. Las células gustativas de los dos tercios anteriores de la lengua se encuentran en las papilas fungiformes, que son inervadas por la rama cuerda del tímpano del nervio facial (VII par craneal), mientras que en el tercio posterior de la lengua, se encuentran en las papilas circunvaladas y foliadas, que están inervadas principalmente por el nervio glosofaríngeo (IX par craneal). Las células gustativas del paladar blando están inervadas por otra rama del nervio lingual, el nervio petroso superficial mayor, y las de la epiglotis y la laringe están inervadas por el nervio superior laríngeo, una rama del nervio vago (X par craneal) [16].

En el proceso de la ingesta, se pueden liberar moléculas volátiles en la parte trasera de la cavidad bucal, que a través de la nasofaringe pueden producir la estimulación retronasal del epitelio olfatorio de la parte superior de la cavidad nasal. Estas moléculas actuando en los receptores de los nervios olfatorios transmitirán la información sensorial al bulbo olfatorio.

Por otro lado, además de los receptores del gusto y del olor, existen estímulos químicos, térmicos y mecánicos que actúan a través de receptores iónicos que se encuentran en las membranas de las neuronas sensoriales primarias y las células epiteliales orofaríngeas, que también son capaces de evocar respuestas sensoriales. A este proceso se la llama **somatosensación**, y en concreto la integración de los estímulos químicos, **quimiosensación**. El **nervio trigémino** (V par craneal) juega un papel fundamental en la quimiosensación, como también el **nervio glosofaríngeo** y el **nervio vago** [17]. Estas fibras, y más en concreto la rama maxilar del trigémino, la rama faríngea del glosofaríngeo y dos ramas del nervio vago, el nervio superior laríngeo y la rama faríngea, inervan las áreas más efectivas para disparar la respuesta motora orofaríngea, como son el arco palatofaríngeo y los pliegues ariepiglóticos [18]. Estas aferencias, que proyectan hacia el centro de la deglución en el tronco cerebral y a estructuras corticales y sub-corticales, expresan las principales dianas moleculares encargadas de integrar los estímulos somatosensoriales, que son la familia de receptores-canales transmembrana *Transient Receptor Potencial Ion Channel* (TRP) [19], y más en concreto los subtipos TRPV1, TRPA1 y TRPM8. Son agonistas de estos canales, actuando como estímulos somatosensoriales, la capsaicina y las temperaturas elevadas (agonistas TRPV1) [20], la piperina (agonista TRPV1 y TRPA1) [21], el mentol (agonista TRPM8) [22;23] y las temperaturas bajas (agonista TRPA1 y TRPM8) [24]. Una de nuestras hipótesis de trabajo es que la suplemetación del bolo alimentario con estos estímulos podría incrementar el *input* sensorial y modular el componenete motor de la respuesta motora orofaríngea.

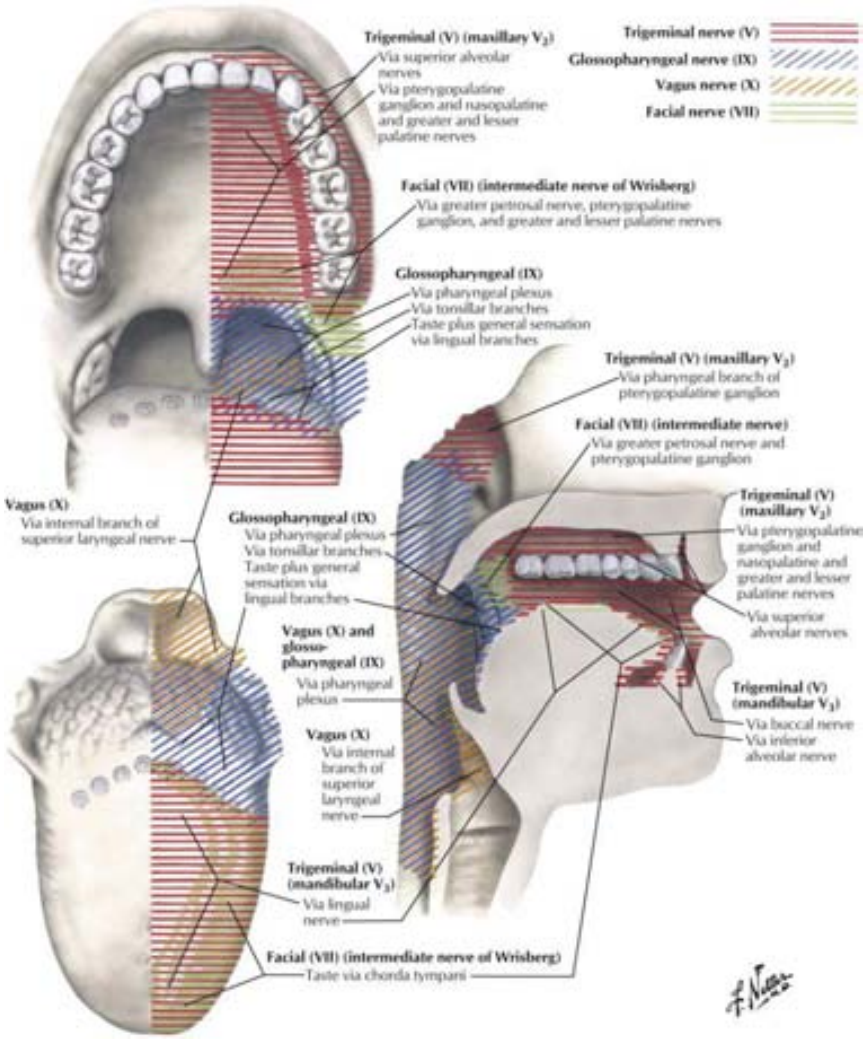

Figura 7: Innervación aferente de la cavidad oral y de la faringe. Adaptado de: Netter FH (2014) [25].

4.2 Sistema nervioso central

4.2.1 Centro deglutorio

El centro deglutorio se encuentra en el **bulbo raquídeo del tronco encefálico**. Consiste en dos hemi-centros, cada uno situado en un lado de la médula, que deben estar bien sincronizados para organizar la contracción coordinada de los músculos bilaterales de la región orofaríngea y del esófago. Está formado por dos grupos de interneuronas: el ***Dorsal Swallowing Group*** (**DSG**), localizado en el Núcleo del Tracto Solitario (NTS) y el ***Ventral Swallowing Group*** (**VSG**), localizado en la cara ventrolateral del bulbo, justo por encima del núcleo ambiguo. La respuesta sináptica de las interneuronas del DSG como consecuencia del estímulo de las neuronas sensoriales, ocurre con una latencia muy corta y estable de 1 a 2 ms, indicando que al menos algunas de estas neuronas están conectadas de forma mono-sináptica con las fibras aferentes. Por otro lado, las interneuronas del VSG requieren de varios pulsos para iniciar la respuesta, la latencia de la cual es visiblemente más larga (7-12 ms) y variable, sugiriendo la existencia de una vía poli-sináptica. Cabe destacar también que se puede iniciar una respuesta en estas neuronas como consecuencia de la estimulación de áreas corticales específicas, con una latencia más corta en las

neuronas del DSG (5-8 ms) que en las del VSG (10-16 ms). Estos resultados sugieren que probablemente las neuronas del VSG son activadas vía neuronas del DSG, siendo las interneuronas del DSG las responsables de integrar la información convergente de la periferia y de las áreas corticales y generar el patrón motor deglutorio cuando se alcanza el umbral de estímulo necesario, mientras que las interneuronas del VSG serían las responsables de distribuir la respuesta a los diferentes núcleos motores [26].

4.2.2 Estructuras corticales y sub-corticales

Aunque el control de la deglución está mediado principalmente por mecanismos bulbares, la corteza cerebral juega un papel fundamental en el inicio voluntario y la regulación de la deglución. Diferentes estudios clínicos, electrofisiológicos y de neuroimagen, han determinado las áreas cerebrales implicadas en el proceso deglutorio. Las regiones que presentan una mayor activación tanto en la deglución voluntaria como en las degluciones de saliva espontáneas son la circunvolución pre-central lateral (que incluye la corteza motora primaria), la circunvolución post-central lateral (que incluye la corteza somatosensorial), la ínsula y la circunvolución frontal inferior - área de Broca- (relacionadas con el procesamiento sensorial del estímulo gustatorio y las sensaciones de la boca y la faringe), la corteza pre-motora, el precúneo -zona media de la corteza parietal superior-, el área motora suplementaria y la circunvolución del cíngulo anterior (relacionadas con la atención y la planificación del movimiento deglutorio), y las circunvoluciones temporales transversal, superior y medial (que parecen estar relacionadas con el procesamiento de los sonidos de la deglución, así como la integración de estímulos gustatorios) [27-29]. Cabe destacar que en individuos sanos **la activación de la red neural implicada en el proceso deglutorio es bilateral aunque presenta una asimetría inter-hemisférica** (independiente de la mano dominante), siendo uno de los hemisferios el que muestra mayor activación y en consecuencia, el dominante para la deglución [27].

Las estructuras sub-corticales implicadas en la función deglutoria incluyen los ganglios basales, la amígdala, el tálamo y el cerebelo, sin embargo, su función específica en el proceso deglutorio no está del todo clara.

4.3 Innervación motora y músculos efectores

Tal y cómo se ha descrito en los puntos anteriores de este capítulo, muchos son los grupos musculares que participan en el proceso deglutorio, tanto en la fase oral como en la fase faríngea. Todos ellos son músculos estriados que usan acetilcolina como neurotransmisor vía receptores nicotínicos en la placa motora. El soma de las motoneuronas que inervan estos músculos se encuentra en los núcleos de la protuberancia del tronco encefálico (trigémino y facial), del bulbo raquídeo (núcleo ambiguo e hipogloso) y de la médula espinal cervical (C1-C2). Los axones de estas neuronas viajan a través de los pares craneales V, VII, IX, X, XI y XII y el asa cervical.

Los músculos del grupo facial (orbicularis orbis y buccinator) están inervados por el VII par craneal. Durante la masticación, su función es sellar la cavidad oral y posicionar la comida sobre las superficies de molido de los dientes. Los músculos masticadores (masetero, temporal, pterigoideo interno y externo) están inervados por la rama mandibular del V par craneal. Su acción es mover la mandíbula durante la masticación, ejerciendo la fuerza suficiente par moler la comida. Los músculos de la lengua, tanto los intrínsecos (longitudinal superior, transverso y vertical) como los extrínsecos

(hiogloso, geniogloso y estilogloso) están inervados por el nervio hipogloso (XII par craneal). Las contracciones de los diferentes músculos linguales permiten la elevación, depresión, protrusión y retracción de la lengua permitiendo por lo tanto, la preparación, formación, posicionamiento y propulsión del bolo alimentario.

Los músculos suprahioideos actúan elevando el hueso hioides y la laringe, mientras que los músculos infrahioideos realizan la acción contraria. Son músculos suprahioideos el digástrico (el vientre anterior inervado por el V par craneal y el vientre posterior inervado por el VII par craneal), el estilohioideo (inervado por el VII par craneal), el geniohioideo (inervado por el XII par craneal) y el milohioideo (inervado por el V par craneal). Los músculos infrahioideos (omohioideo, esternohioideo, tirohioideo y esternotirohioideo) están inervados por el asa cervical. Los músculos del paladar (músculo de la úvula, palatogloso y elevador del velo del paladar) están inervados por el plexo faríngeo (constituido por ramas del IX y X pares craneales y del ganglio cervical superior) mientras que el músculo tensor del velo del paladar lo está por el nervio mandibular (V par craneal). Estos músculos actúan durante la fase oral de la deglución para endurecer el paladar blando, bajar el velo del paladar para evitar la caída prematura del bolo en la faringe o elevar el velo del paladar para abrir el sello glosopalatino. Los músculos de la faringe, tanto los constrictores como los elevadores, están inervados por el plexo faríngeo del nervio vago, a excepción del músculo estilofaríngeo que está inervado por el IX par craneal. Finalmente, todos los músculos intrínsecos de la laringe están inervados por motoneuronas que tienen sus somas localizados en el núcleo ambiguo y los axones viajan a través de la rama inferior laríngea del nervio recurrente laríngeo (X par craneal) [7].

5. DISFAGIA OROFARÍNGEA

5.1 Epidemiología

La disfagia orofaríngea (DO) es un síntoma que se refiere a la dificultad o molestia para formar o mover el bolo alimenticio de la boca al esófago. El término disfagia proviene del griego “dis” que significa “dificultad” y “fagia” que significa “comer”.

A pesar de que a menudo se utilizan como términos sinónimos, debemos diferenciar entre disfagia orofaríngea (síntoma) y disfunción deglutoria, que se refiere a la alteración evidenciada en las pruebas instrumentales.

La DO puede originarse por diferentes causas que se resumen en la **Tabla 1**. El objetivo de estudio de esta Tesis Doctoral son las alteraciones deglutorias que se asocian a patologías neurológicas en individuos adultos y al envejecimiento.

La prevalencia real de DO es difícil de determinar y los estudios publicados difieren significativamente en los datos reportados, dependiendo de diferentes factores, como pueden ser: la patología asociada, el estadio de la enfermedad asociada, el método diagnóstico utilizado, el entorno (hospitalario, residencia, comunidad…) y el país donde se ha desarrollado el estudio, entre otros. En la **Tabla 2** se describe la prevalencia de disfagia descrita en ancianos, pacientes que han sufrido un ictus y pacientes con enfermedades neurodegenerativas, que conforman las principales poblaciones de estudio en la presente Tesis Doctoral.

Tabla 1. Causas de disfagia orofaríngea más frecuentes (Modificado de Cook & Kharilas. Gastroenterology 1999) [30].

Envejecimiento
Neurológicas:
Ictus, esclerosis múltiple, esclerosis lateral amiotrófica, síndrome de Guillain-Barré, enfermedad de Parkinson, demencias, parálisis pseudobulbar, tumores del tronco cerebral, traumatismo craneoencefálico, enfermedad de Huntington, poliomielitis, síndrome postpolio, discinesia tardía, encefalopatías metabólicas.
Musculares y reumatológicas:
Enfermedad mixta del tejido conectivo (síndrome de superposición), dermatomiositis, miastenia gravis, distrofias musculares, distrofia oculofaringea, poliomiositis, sarcoidosis.
Estructurales:
Barra cricofaríngea, divertículo de Zenker, membranas cervicales, tumores orofaríngeos, osteofitos y alteraciones esqueléticas, fisura palatina.
Metabólicas:
Amilodosis, síndrome de Cushing, thyrotoxicosis, enfermedad de Wilson
Infecciosas:
Difteria, botulismo, enfermedad de Lyme, sífilis, mucositis (herpes, citomegalovirus, candidiasis…)
Iatrogénicas:
Efectos secundarios de fármacos (quimioterapia, neurolépticos, antidepresivos…), post-quirúrgicas, radioterapia, corrosivas, intubación prolongada.

Tabla 2. Prevalencia de disfagia orofaríngea (DO). MECV-V, método de exploración clínica volumen viscosidad; UGA, unidad geriátrica de adultos; VFS, videofluoroscopia; FEES, Fibroendoscopia de la deglución.

	Población diana	Método de evaluación	Prevalencia de DO	Referencias
Ancianos	Independientes de la comunidad	Cribado (cuestionarios)	11.4%- 33.7%	Holland 2011 [31] Roy 2007 [32] Bloem 1990 [33] Kawashima 2004 [34] Yang 2013 [35]
		Exploración clínica (MECV-V)	23%	Serra-Prat 2011 [36]
	Hospitalizados- UGA	No especificado/ test del agua/ MECV-V	29.4% -47%	Lee 1999 [37] Cabré 2014 [38]
	Hospitalizados- UGA con neumonía	Test del agua	55%	Cabré 2010 [39]
	Institucionalizados, residentes	Cribado (cuestionarios)	40%	Nogueira 2013 [40]
		Test del agua	38%	
		Cribado + exploración clínica	51%	Lin 2002 [41]
Ictus	Fase aguda	Cribado	37 -45%	Martino 2005 [42]
		Exploración clínica	51 -55%	
		Métodos instrumentales	64% -78%	
	Fase crónica	Exploración clínica	25% -45%	
		Métodos instrumentales	40 -81%	
Neurodegenerativas	Enfermedad de Parkinson	Sintomatología reportada por los pacientes	35%	Kalf 2012 [43]
		Exploración objetiva	82%	
	Demencia	Sintomatología reportada por los cuidadores	19% -30%	Langmore 2007 [44] Ikeda 2002 [45]
		Métodos instrumentales (VFS y FEES)	57% - 84%	Suh 2009 [46] Langmore 2007 [44] Horner 1994 [47]

5.2 Fisiopatología

5.2.1 La disfagia en el paciente anciano

La disfagia en el anciano puede originarse ya sea como consecuencia de cambios en la fisiología deglutoria asociados al envejecimiento, o bien puede ser secundaria a diferentes patologías, mayoritariamente neurológicas, altamente prevalentes en la población anciana. El proceso natural de envejecimiento ocasiona cambios en la anatomía del cuello y de la cabeza, así como en diferentes mecanismos neuronales y musculares, produciéndose una pérdida de la reserva funcional que puede afectar el proceso deglutorio. Cuando estos cambios en el mecanismo deglutorio se producen en ancianos sanos y robustos, y no comprometen la seguridad de la deglución, hablamos de **presbifagia**. No obstante, la diferenciación entre lo que constituye una deglución normal y fisiológica en el anciano y hasta qué punto estos cambios representan disfagia es difícil de establecer.

Se ha determinado que los ancianos sanos presentan cambios fisiológicos tanto en la fase oral como en la fase faríngea de la deglución. Así pues, mientras que las presiones máximas isométricas linguales disminuyen con la edad, las presiones linguales y faríngeas generadas durante la deglución no se ven afectadas [48;49]. Por otro lado, el tiempo necesario para alcanzar el pico de presión también aumenta con la edad, así como se produce una respuesta motora orofaríngea prolongada y retrasada comparada con los individuos jóvenes. Además de la pérdida de función motora, se ha descrito que la capacidad de discriminación sensorial de la faringe y la laringe también disminuye con la edad [50;51]. Todos estos cambios nos indican una pérdida de reserva funcional que si bien en el anciano sano puede ser compensada, cuando estos cambios en el proceso deglutorio se combinan con la presencia de factores adicionales, como pueden ser diferentes co-morbididades y/ o sus tratamientos, pueden poner la población anciana en un alto riesgo de padecer disfagia. Por este motivo podemos pensar que de entre los ancianos, el fenotipo frágil [52], que es especialmente vulnerable y susceptible a la enfermedad, presenta uno de los mayores riesgos de padecer DO aunque se desconocen las características fisiopatológicas de la DO en esta población.

5.2.2 La disfagia después de un ictus

Desde una perspectiva neuroanatómica, la prevalencia de DO en los ictus hemisféricos unilaterales es del 40%; en las lesiones bilaterales, de un 56%; en las lesiones de tronco, de un 67%; y en lesiones combinadas, de hasta en un 85% [53;54]. La asimetría inter-hemisférica en la activación cortical que se presenta en el proceso deglutorio, es la responsable de que después de un ictus hemisférico unilateral, aproximadamente un tercio de los pacientes desarrollen disfagia orofaríngea, consecuencia de la afectación del hemisferio dominante para la deglución [27].

La alteración de la seguridad de la deglución en pacientes con ictus se ha relacionado con un retraso en el tiempo de cierre del vestíbulo laríngeo y de la apertura del UES [8;55]. Un retraso en el cierre del vestíbulo laríngeo, aumenta el intervalo de tiempo en el que potencialmente puede ocurrir una aspiración durante la fase faríngea, y un retraso en la apertura del UES aumenta el volumen de bolo acumulado en la hipofaringe, lo que aumenta el riesgo de rebosar a la vía respiratoria. Se ha hipotetizado que estas alteraciones biomecánicas observadas en los pacientes con DO asociada a ictus pueden estar también relacionadas con el déficit sensorial que presentan en la orofaringe y la laringe [56]. Se ha descrito que el

umbral sensorial de la orofaringe de los pacientes con disfagia secundaria a un ictus es superior al de los pacientes con ictus sin disfagia, evidenciando la relevancia del trastorno sensorial en la fisiopatología de la alteración deglutoria [56].

La disfagia en el ictus también cursa con alteraciones en la eficacia de la deglución, siendo común la observación de residuo orofaríngeo en esta población, consecuencia de una débil fuerza de propulsión del bolo alimentario [55]. Las alteraciones deglutorias en los pacientes con ictus revierten espontáneamente aproximadamente en un 50% de los casos durante las primeras semanas después del episodio, pero persisten en la otra mitad, lo cual deja a esta población en un alto riesgo de complicaciones nutricionales y respiratorias [57]. Se ha descrito que esta recuperación de la función deglutoria después de un ictus hemisférico unilateral, está relacionada con un aumento de la representación motora faríngea en el hemisferio contra-lesional [58].

5.2.3 La disfagia en las enfermedades neurodegenerativas

Los pacientes con enfermedades neurodegenerativas (Parkinson, esclerosis lateral amiotrófica, esclerosis múltiple, etc) representan un grupo heterogéneo de pacientes. En general, de forma similar que en los pacientes con enfermedades neurológicas no progresivas, la alteración de la seguridad de la deglución en pacientes con enfermedades neurodegenerativas se ha relacionado con un retraso en el tiempo de cierre del vestíbulo laríngeo y de apertura del UES y la alteración de la eficacia con una débil fuerza de propulsión del bolo alimentario. No obstante, la prevalencia de alteraciones de la seguridad de la deglución en éste grupo de pacientes es inferior que en los pacientes con enfermedades neurológicas no progresivas, mientras que las alteraciones de la eficacia de la deglución, parecen ser más prevalentes [55].

6. DIAGNÓSTICO

El proceso de diagnóstico del paciente con disfagia debe ser abordado de forma integrada por un equipo multidisciplinar de profesionales que identifique, de forma secuencial a los pacientes en riesgo de disfagia, lleve a cabo evaluaciones clínicas y realice pruebas diagnósticas instrumentales cuando sea necesario.

6.1 Identificación del paciente vulnerable: cribado

El primer paso del abordaje diagnóstico de la disfagia es la identificación del paciente vulnerable, es decir, el paciente con riesgo elevado de padecer DO. La historia clínica del paciente, una exploración física y los resultados de un test de cribado básico, como son el EAT-10 (*Eating Assessment Tool-10*) [59] o el SSQ (*Sydney Swallow Questionnaire*) [60], son necesarios en este proceso.

EAT-10: es un cuestionario de 10 preguntas auto-administrado por el paciente que evalúa la sintomatología, severidad e impacto clínico y social de la disfagia. Cada pregunta puntúa de 0 (ningún problema) a 4 (es un problema serio). De acuerdo con en el límite superior del intervalo de referencia descrito en sujetos sanos, se ha sugerido que una puntuación final en el EAT-10 ≥3 indica anormalidad [59]. El EAT-10 está traducido y validado al español [61] (Ver **Anexo 1**).

SSQ: es un cuestionario de 17 preguntas auto-administrado por el paciente para evaluar la severidad de los síntomas de la disfagia [60]. Cada pregunta se responde en una escala analógica visual horizontal de 100 mm, donde el paciente

marca con una X el punto que él cree que representa su grado de disfunción. Se obtiene la puntuación correspondiente a cada pregunta, midiendo la distancia en mm desde el origen de la escala hasta la X marcada por el paciente.

Se desconoce la precisión diagnóstica de ambos cuestionarios para la detección clínica de la disfagia y tampoco se han realizado estudios específicos para determinar los puntos de corte de cada cuestionario que indica DO. Todo aquel paciente que sea identificado en riesgo de disfagia en esta etapa del proceso, debe ser referido a una exploración deglutoria más exhaustiva.

6.2 Exploración clínica

El objetivo principal de los métodos de exploración clínica para la DO es recoger los datos necesarios para establecer un diagnóstico clínico. Además, debe permitirnos evaluar la fisiopatología de la enfermedad, para identificar los principales signos y síntomas de DO y el mecanismo de disfunción de la deglución, seleccionar aquellos pacientes que deben ser referidos a una exploración instrumental y/o seleccionar el tratamiento más adecuado para los pacientes que no pueden someterse fácilmente a una videofluoroscopia (VFS) o a una fibroendoscopia de la deglución (FEES).

Uno de los métodos de exploración clínica que cumple estos criterios es el **Método de Exploración Clínica Volumen -Viscosidad** (**MECV-V** o **V-VST** de las siglas del inglés *Volume-Viscosity Swallow Test*).

El **MECV-V** fue diseñado por Clavé y Arreola [62] para identificar los principales signos y síntomas clínicos de alteración de la eficacia y de la seguridad de la deglución, permitiendo establecer la viscosidad ideal para ser administrada de forma segura y eficaz a los pacientes en riesgo de aspiraciones. Los signos de alteración de la seguridad de la deglución evaluados son: tos, cambios de voz y desaturación de oxígeno ≥3%. Los signos de alteración de la eficacia de la deglución evaluados son: la eficacia del sello labial, presencia de residuo oral, deglución fraccionada y síntomas de residuo faríngeo. El MECV-V es una prueba de esfuerzo en la cual se administran una serie de bolos de diferentes volúmenes y viscosidades, en orden creciente de dificultad. El test se empieza administrando un bolo de viscosidad néctar a un volumen de 5 mL, continuando con la administración de volúmenes de 10 mL y 20 mL; se continúa con una serie de bolos de líquido a los mismos volúmenes y finalmente con la serie de pudin. Si el paciente presenta signos de alteración de la seguridad de la deglución en algún bolo, la serie se interrumpe y se continúa con pudín o finaliza la exploración (**Figura 8**).

La precisión diagnóstica del MECV-V se ha validado frente al test de referencia videofluoroscopia, usando espesantes de almidón modificado. En la **Tabla 3** se muestran los valores de sensibilidad, especificidad y valores predictivos positivo y negativo de los principales signos de alteración de la seguridad y de la eficacia de la deglución. La precisión diagnóstica del test con espesantes de goma xantana se desconoce.

El **test del agua** es también una de las herramientas históricamente más utilizadas para realizar la exploración clínica de la deglución [63;64]. En su forma más común, consiste en que el paciente debe beber 90 mL de agua de un vaso sin interrupción. Es un test que presenta una alta sensibilidad para detectar aspiraciones (94%-96%) pero una baja especificidad (26%-46%).

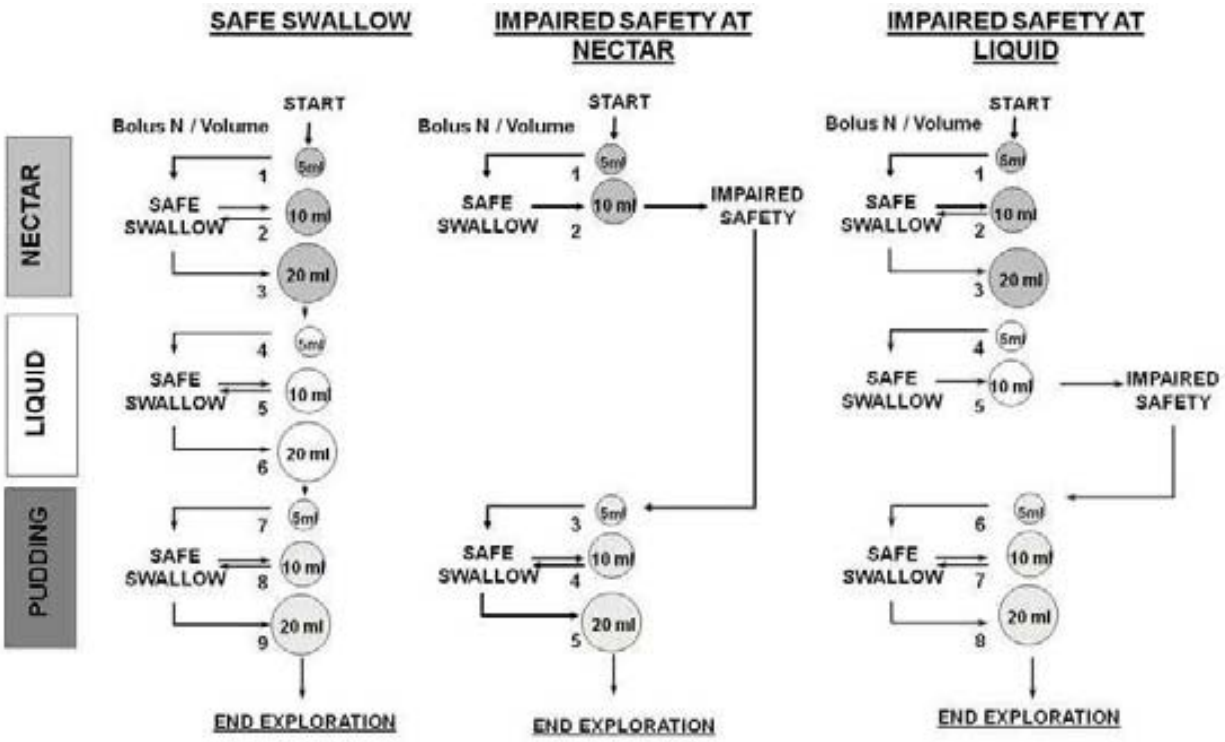

Figura 8. Algoritmo del MECV-V. Izquierda: los pacientes con deglución segura completan toda la exploración. Medio: diagrama representativo de pacientes con alteración de la seguridad de la deglución a 10 mL nectar. Derecha: diagrama representativo de pacientes con alteración de la seguridad a 10 mL líquido. Reproducido de Rofes *et al* (2012) [65].

Tabla 3. Sensibilidad, especificidad y valores predictivos del MECV-V en pacientes con disfagia. Reproducido de Clavé *et al* (2008) [62].

	Sensitivity (%)	*Specificity (%)*	*PPV (%)*	*NPV (%)*
Impaired safety	88.2	64.7	90.9	57.9
Impaired efficacy	100	28.8	28.8	100
Penetration	83.7	64.7	87.2	57.9
Oral Residue	69.2	80.6	39.1	93.5
Pharyngeal Residue	86.4	34.6	75.0	52.9

6.3 Técnicas instrumentales

6.3.1 Videofluoroscopia

La VFS es una técnica radiológica dinámica que consiste en la obtención de una secuencia de imágenes en perfil lateral (y antero-posterior si es necesario) de la cavidad oral, la faringe, la laringe y el esófago cervical de un paciente mientras traga una serie de bolos, de contraste hidrosoluble o sulfato de bario, que pueden presentarse a diferentes volúmenes y viscosidades. Actualmente se considera la técnica de referencia para el estudio de la DO. El análisis imagen por imagen de la secuencia videofluoroscopica permite realizar estudios tan cualitativos (signos de alteración de la fase oral y de la fase faríngea de la deglución) como cuantitativos (cronología de la respuesta motora orofaríngea, cinemática del bolo, movimiento de las estructuras deglutorias como son el hioides y la laringe) de la deglución. Durante la exploración videofluoroscópica se puede también evaluar el efecto de diferentes estrategias terapéuticas. Los principales signos VFS de alteración de la eficacia evaluados son el residuo orofaríngeo, definido como presencia de contraste radiológico en la boca o la faringe (incluyendo vallécula y senos piriformes) una vez terminada la deglución. Los principales signos VFS de alteración de la seguridad de la deglución son la presencia de penetraciones en el vestíbulo laríngeo (el contraste radiológico entra dentro del vestíbulo laríngeo pero no traspasa las cuerdas vocales) y las aspiraciones traqueobronquiales (el contraste radiológico entra en el vestíbulo laríngeo y traspasa las cuerdas vocales). Las alteraciones de la seguridad de la deglución se clasifican de acuerdo con la escala de Penetración-Aspiración (PAS) descrita por Rosenbeck *et al* en 1997 [66] y que tiene en cuenta tanto el nivel de penetración de contraste a la vía respiratoria como la respuesta del paciente. Cuando no hay entrada de material a la vía respiratoria, se asigna una puntuación de 1; las penetraciones se clasifican de 2 a 5: cuando se produce entrada de material al vestíbulo laríngeo pero sin que llegue a contactar cuerdas vocales y no deja residuo en la vía aérea, se asigna una puntuación de 2; cuando se produce entrada de material a la vía respiratoria, no contacta cuerdas vocales pero deja residuo, se asigna una puntuación de 3; cuando se produce entrada de material al vestíbulo laríngeo, contacta cuerdas vocales pero sin rebosarlas y no deja residuo, se asigna una puntuación de 4; cuando se produce entrada de material al vestíbulo laríngeo, contacta cuerdas vocales pero sin rebasarlas y deja residuo, se asigna una puntuación de 5; las aspiraciones se clasifican del 6 al 8: cuando el material rebasa las cuerdas vocales, se produce tos y esta tos es efectiva expulsando el material de la vía aérea, se asigna una puntuación de 6; cuando el material traspasa las cuerdas vocales, se produce tos y esta tos no es efectiva expulsando el material de la vía aérea, se asigna una puntuación de 7; cuando el material traspasa las cuerdas vocales y no se produce tos (aspiración silente), se asigna una puntuación de 8. Cabe destacar que se considera deglución segura cuando obtenemos puntuaciones de 1 o 2, ya que las penetraciones de grado 2 no se consideran patológicas y son comúnmente observadas en voluntarios sanos.

El movimiento del hioides tanto vertical como anterior se puede monitorizar trazando un eje de coordenadas, tomando como origen del eje la esquina anterior -inferior de la vértebra C3 y siendo el eje de ordenadas la línea que conecta las esquinas anterior -inferior de las vértebras C3 y C5 [8].

La velocidad media del bolo alimentario a través de la faringe puede calcularse como el tiempo que pasa des de que la cabeza del bolo traviesa el sello

glosopalatino hasta que llega al UES dividido entre la distancia que los separa; la velocidad final del bolo a nivel del UES se calcula de acuerdo con la ecuación: $v = v_0 + at$, donde v_0 es el valor inicial de velocidad que se considera 0, *a* es la aceleración adquirida por el bolo alimentario a nivel del UES (y calculada según la expresión del movimiento rectilíneo uniformemente acelerado desglosada abajo) y *t* es el tiempo que tarda la cabeza del bolo alimentario en llegar al UES. La fuerza de propulsión del bolo alimentario puede determinarse mediante la segunda ley de Newton, $F = ma$, donde *F* es la fuerza a la que el bolo es propulsado por la lengua, *m* es la masa del bolo administrado en cada caso y *a* es la aceleración adquirida por el bolo alimentario a nivel del UES y obtenida a partir de la expresión del movimiento rectilíneo uniformemente acelerado $s = s_0 + v_0 (t- t_0) + ½ a (t- t_0)^2$ donde *s* es la distancia entre el sello glosopalatino y el UES, *t* es el tiempo que ha tardado el bolo alimenticio en recorrer *s;* s_0 , t_0 y v_0 son los valores iniciales de espacio, tiempo y velocidad respectivamente, que se asume que tienen valor 0.

6.3.2 Fibroendoscopia de la deglución (FEES)

La FEES (del inglés *Fiberoptic endoscopic evaluation of swallowing*) ofrece al profesional de la disfagia una herramienta fiable para investigar la deglución. Se utiliza un fibroscopio flexible conectado a una fuente de luz y un aparato de vídeo para grabar la secuencia de imágenes deglutorias. Es bien tolerado, fácilmente repetible y se puede realizar en la cabecera del paciente. Existen varios protocolos para la FEES en los que, igual que en la VFS, pueden utilizarse diferentes consistencias y volúmenes de bolo, que se administrarán teñidos con colorante alimentario, así como evaluar diferentes estrategias terapéuticas. Sin embargo, existen algunas limitaciones de la técnica, como que no es posible evaluar la fase oral de la deglución así como el hecho que durante la deglución, existe visibilidad restringida debido a que el endoscopio entra en contacto con la base de la lengua, la epiglotis y el propio bolo lo que puede impedir la visualización directa de penetraciones y aspiraciones durante la deglución [67].

6.3.3 Manometria faringoesofágica de alta resolución

La manometría faringoesofágica de alta resolución permite el estudio cuantitativo de las presiones a nivel de la faringe y UES. Los parámetros que se pueden medir con esta técnica son la amplitud de la contracción faríngea, la amplitud de la relajación del UES y la coordinación entre ambos. Resulta de especial utilidad cuando se asocia a la VFS sobre todo para el estudio de las alteraciones de apertura del UES.

La técnica utiliza un catéter que incorpora una serie de sensores de presión de estado sólido posicionados en la faringe, UES y cuerpo esofágico colocados cada 1 ó 2 centímetros, de forma que, por interpolación entre ellos, la presión intraluminal puede llegar a ser mostrada de forma continua en el espacio. Las medidas de presión se muestran en unos mapas topográficos de presión [68].

7. TRATAMIENTO

El tratamiento del paciente con disfagia orofaríngea tiene dos objetivos principales: prevenir las complicaciones que podrían derivarse a consecuencia de la disfunción deglutoria presente, cómo son la malnutrición, la deshidratación y la neumonía aspirativa, y en segundo lugar y siempre que sea posible, revertir la disfunción deglutoria de forma que pueda administrarse una dieta lo menos restrictiva posible. Focalizadas en el primer objetivo

encontramos las medidas higiénico-dietéticas básicas y las estrategias compensatorias. Con el objetivo añadido de revertir la disfunción deglutoria encontramos las estrategias rehabilitadoras, los tratamientos quirúrgicos y las estrategias de neuro-estimulación.

7.1 Medidas higiénico-dietéticas

Las recomendaciones generales para el paciente con dificultades en la deglución consisten en repartir la alimentación en 5 ó 6 comidas diarias, que deben realizarse con el paciente en estado de alerta. Se debe asegurar una postura correcta del paciente, sentado con la espalda recta y la cabeza ligeramente inclinada hacia adelante en el momento de tragar; la comida debe producirse bajo supervisión pero fomentando la autoalimentación, en un ambiente tranquilo y relajado. Se deben evitar alimentos con dobles texturas y de riesgo (alimentos que mezclen líquidos y sólidos, que puedan fundirse, pegajosos, que se desmenucen o fragmenten con facilidad…). Se debe considerar la recomendación de suplementos nutricionales en el caso de riesgo de malnutrición. Es también importante establecer unas recomendaciones de higiene oral mínimas que incluyan cepillado dental diario y el uso de colutorios antisépticos en pacientes con DO ya que la colonización de la cavidad oral por patógenos respiratorios, junto con la presencia de aspiraciones y la fragilidad, son factores de riesgo de neumonía por aspiración (AP) en pacientes ancianos con DO [69].

7.2 Estrategias compensatorias

7.2.1 Adaptación de la dieta

7.2.1.1 Adaptación de los sólidos

Las adaptaciones de la dieta deben personalizarse a la capacidad deglutoria del paciente y deben reevaluarse y reajustarse regularmente. La *British Dietetic Association* y el *Royal College of Speech and Language Therapists* clasifican las modificaciones de la textura de los sólidos en cuatro categorías: textura B, C, D y E [70]. La textura B se refiere a una dieta puré fino, que no puede comerse con tenedor porque no mantiene la consistencia; textura C corresponde a textura de puré espeso o denso que sí que mantiene la consistencia y que por lo tanto, puede ser comido con tenedor; textura D descrita como una dieta picada fina, no triturada, contiene alimentos suaves, tiernos y húmedos que requieren cierta masticación y que puede acompañarse con una salsa cremosa densa; textura E blanda, con alimentos enteros que requieren masticación pero que puede aplastarse con un tenedor e ir acompañados con una salsa cremosa menos espesa. Por otro lado, la *American Dietetic Association* publicó en 2002 la *National Dysphagia Diet* en la que se consideran cuatro posibles tipos de dieta: el nivel 1 corresponde a dieta puré; el nivel 2, consiste es una dieta de fácil masticación con alimentos blandos, troceados, húmedos y de fácil formación del bolo; el nivel 3 es una dieta que permite la administración de alimentos en condiciones normales exceptuando aquellos alimentos más duros, pegajosos o crujientes; y el nivel 4 se considera una dieta normal [71].

En aquellos casos en los que la vía oral no sea segura y no permita cubrir los requerimientos nutricionales necesarios, pero se mantenga la capacidad funcional intestinal, se considerará la alimentación enteral mediante la colocación de sondas nasoentéricas o de enterostomías. El sondaje intragástrico transnasal con sondas nasogástricas es de elección para administrar los nutrientes directamente en el estómago durante períodos de tiempo inferiores a 6 semanas; en cambio, para aquellos pacientes con perspectivas

de soporte nutricional mantenido durante un largo período de tiempo, la mejor opción es la colocación de una gastrostomía endoscópica percutánea (PEG). Ambas estrategias de nutrición permiten la administración de fórmulas de nutrición enteral adaptadas a los requerimientos del paciente [72].

7.2.1.2 Adaptación de los líquidos

Una de las intervenciones compensatorias básicas en hospitales e instituciones sanitarias para aumentar la seguridad de la deglución y evitar aspiraciones es espesar los líquidos. Se ha descrito que el aumento de la viscosidad de los líquidos con espesantes de almidón modificado reduce las penetraciones en el vestíbulo laríngeo y las aspiraciones traqueobronquiales [55;73], con la consiguiente reducción en la incidencia de neumonía por aspiración [74]. Se ha propuesto que ralentizar la velocidad del bolo a través de la faringe es el principal mecanismo de acción de los espesantes para proteger contra las aspiraciones [75]. Sin embargo, en paralelo a su efecto terapéutico, el aumento de la viscosidad del bolo con espesantes de almidón aumenta el residuo orofaríngeo post-deglutorio, especialmente en pacientes con propulsión del bolo deficiente como los pacientes ancianos y los pacientes con enfermedades neurodegenerativas. Esto podría aumentar el riesgo de aspiraciones post-deglutorias. Otra desventaja de los líquidos espesados a base de almidón es que, en general, no son bien aceptados por los pacientes y el grado de cumplimiento de su prescripción es bajo [76].

A pesar del uso generalizado de los espesantes en la práctica clínica, existe una falta de consenso en los descriptores de las viscosidades a nivel internacional. La **Tabla 4** muestra los estándares de viscosidad descritos por diferentes sociedades.

Numerosos estudios manifiestan además la dificultad de preparar mezclas ajustadas a los descriptores establecidos, así como reproducir las texturas usadas en el estudio VFS, lo cual hace que los pacientes reciban frecuentemente una textura inadecuada.

Tabla 4: Comparación de terminologías internacionales para líquidos espesados.

	LÍQUIDO	**NÉCTAR**	**MIEL**	**PUDIN**
AUSTRALIA	Regular	Mildly thick (150 mPa s)	Moderately thick (400 mPa s)	Extremely thick (900 mPa s)
IRLANDA	Regular	Grade 2- Mildly thick (150 mPa s)	Grade 3- Moderately thick (400 mPa s)	Grade 4- Extremely thick (900 mPa s)
UK	Thin	Thickened fluid Stage 1	Thickened fluid Stage 2	Thickened fluid Stage 3
EEUU	Thin (1 -50 mPa s)	Nectar-like (51–350 mPa s)	Honey-like (351–1750 mPa s)	Spoon-thick >1750 mPa s

7.2.2 Estrategias posturales

La adopción de cambios posturales durante la deglución es una estrategia ampliamente usada en el paciente con DO. Permiten modificar la dirección del bolo alimentario, traduciéndose en un mejor transporte y en una reducción de las aspiraciones y del residuo orofaríngeo. Sin embargo, y a pesar de su amplio uso en la práctica clínica, la literatura disponible muestra controversias en los beneficios de estas estrategias [77]. Las estrategias posturales más utilizadas son la flexión anterior del cuello [78;79], flexión posterior del cuello [80] y rotación e inclinación de la cabeza hacia el lado paralizado [81].

7.2.3 Maniobras deglutorias

Las maniobras son estrategias específicas encaminadas a compensar alteraciones fisiológicas durante la deglución con el objetivo de proteger la vía aérea, facilitar el cierre laríngeo y facilitar el paso del bolo hacia el esófago sin dejar residuo. Son maniobras voluntarias que requieren el aprendizaje y la colaboración activa del paciente. Los estudios disponibles hasta la actualidad son limitados, contradictorios y con muestras poblacionales pequeñas [82;83]. Las maniobras más utilizadas son: la deglución supraglótica, la deglución supersupraglótica, la deglución forzada, la maniobra de Mendelsohn y la maniobra de Masako [84].

7.3 Estrategias rehabilitadoras

7.3.1 Praxias neuromusculares

Las praxias neuromusculares consisten en repeticiones de ejercicios orofaciales y de cuello que buscan mejorar la fisiología de la deglución, dirigidos a mejorar la movilidad, el tono muscular, la sensibilidad y la motricidad de los órganos implicados en la deglución (labios, lengua, velo del paladar y musculatura suprahioidea). Una de las praxias más conocidas es la maniobra de Shaker que permite potenciar la musculatura hioidea y consigue un efecto terapéutico por incrementar la apertura anteroposterior del UES, disminuyendo el residuo y las aspiraciones post-deglutorias [85].

7.3.2 Estimulación eléctrica neuro-muscular

La terapia mediante estimulación eléctrica neuromuscular (NMES) ha sido propuesta como tratamiento para la disfagia orofaríngea [86], siendo ampliamente usada en EEUU, pero no muy conocida todavía en Europa. La terapia implica la aplicación de estimulación eléctrica a través de dos electrodos de superficie colocados en el cuello, pudiéndose colocar en diferentes configuraciones. En general, se aplican pulsos eléctricos bifásicos de 300 μs con una frecuencia de 80 Hz y una amplitud de entre 2,5 y 25 mA dependiendo de la tolerancia del paciente. Las sesiones de tratamiento suelen durar unos 60 minutos. VitalStim^{TM} es uno de los dos aparatos para NMES aprobados por la FDA (Junio 2001) para el tratamiento de la disfagia. Los datos presentados en la publicación inicial [86] mostraron en una población de 110 pacientes que presentaban problemas de deglución después de haber sufrido un ictus, el tratamiento con NMES era seguro y efectivo. Desde ese momento, varios han sido los estudios publicados evaluando la terapia de NMES presentando resultados discordantes. En un meta-análisis realizado en 2007 [87] se evaluaron los 7 estudios clínicos realizados hasta el momento con un total de 255 pacientes con disfagia asociada a múltiples etiologías, tratados con NMES [86;88-92] encontrando una pequeña significación estadística en la mejora de la deglución de los pacientes tratados con NMES. Los resultados del meta-análisis deben ser, sin embargo, tratados con cuidado ya que no se incluyen estudios controlados randomizados, sólo

pequeños estudios controlados no randomizados y estudios de serie de casos abiertos. La heterogeneidad de los estudios con respecto a la duración del tratamiento, el número de sesiones realizadas, el emplazamiento de los electrodos y el método de evaluación del resultado terapéutico también debe ser considerado, sugiriendo la necesidad de realizar una investigación más rigurosa en este campo.

7.4 Tratamientos quirúrgicos

En algunas situaciones específicas, el tratamiento quirúrgico está indicado para revertir la disfunción deglutoria. La realización de una miotomía del UES, se ha considerado el tratamiento de elección en pacientes con DO que presentan una alteración en la apertura del esfínter con disminución de la distensibilidad e incremento de la resistencia al flujo y adecuada propulsión lingual y faríngea. También en pacientes con divertículo de Zenker se ha asociado a la normalización de la presión hipofaríngea y la distensibilidad del UES. Los resultados de la intervención son buenos en pacientes sin antecedentes neurológicos y con respuesta motora orofaríngea preservada.

La inyección transcutánea de toxina botulínica (Toxina Botulínica Tipo A) en el UES ha demostrado ser un procedimiento seguro y con buenos resultados (mejoría de la disfagia, disminución de episodios de aspiración) en los pacientes con disfunción del cricofaríngeo asociada a disfagia neurógena [93].

En casos de parálisis de una cuerda vocal, puede ser tratado por medialización del pliegue con métodos de inyección transendoscópica, transoral o percutánea o por medio de una laringoplastia de modo que la cuerda contralateral pueda completar el cierre laríngeo [94].

7.5 Estrategias de neuro-estimulación

En los últimos años, han surgido un conjunto de nuevas estrategias destinadas a mejorar la deglución de los pacientes con DO basadas en la neuro-estimulación y la neuro-rehabilitación. Su objetivo es estimular la plasticidad cortical y restaurar la fisiología deglutoria deteriorada. Se pueden clasificar en las que estimulan directamente la corteza motora faríngea y las vías cortico-bulbares (las técnicas de estimulación cerebral no invasivas) y las que promueven la neuro-plasticidad mediante el aumento del estímulo sensorial orofaríngeo por medios físicos, eléctricos, farmacológicos o químicos.

7.5.1 Estrategias de estimulación sensorial periféricas

7.5.1.1 Estímulos químicos

Acidificación del bolo alimentario: La acidificación del bolo alimentario fue una de las primeras estrategias que se utilizó para estimular la respuesta deglutoria en pacientes con DO asociada a ictus y otras enfermedades neurológicas. Se ha asociado a una reducción en el tiempo de tránsito oral, el tiempo de retraso faríngeo, mejora de la eficacia de la deglución [95] y reducción de la prevalencia de aspiraciones y penetraciones [95;96].

Picante: la adición de ingredientes picantes, tales como la capsaicina (*Capsicum sp*) o la piperina (*Piper nigrum*) al bolo alimentario también han sido probados en pacientes con disfagia para evaluar su efecto terapéutico. La administración aguda de capsaicina (10^{-8} -10^{-6} M) reduce la latencia deglutoria (tiempo que transcurre desde la instilación de 1 mL de agua destilada en la faringe hasta el inicio de la deglución) [97]. Por otra parte, la administración diaria de capsaicina durante un

mes (10^{-6} M) también acortó la latencia deglutoria en pacientes ancianos con disfagia, sobre todo en las personas mayores con alto riesgo de aspiración [98]. Por otro lado, 30 días de estimulación olfativa con aceite de pimienta negra también acortan la latencia deglutoria en un grupo de pacientes con disfagia después de un ictus [99].

Otros estímulos químicos usados en pacientes con DO son los **líquidos carbonatados** [100] y el **mentol** [101], así como combinaciones de diferentes estímulos. Todos estos compuestos ejercen su acción mayoritariamente a través de una familia de receptores-canales trans-membrana, los ***Transient Receptor Potencial Channels*** (**TRP**) [24], que se expresan en las neuronas sensoriales primarias de la orofaringe [19], aumentando el estímulo sensorial a los núcleos centrales de la deglución del tronco cerebral y a la corteza cerebral, lo que, potencialmente, podría promover la reorganización neuronal y facilitar la activación de la respuesta deglutoria.

7.5.1.2 Estímulos eléctricos

Estudios en animales y en humanos han reflejado que la aplicación de estímulos eléctricos en las áreas inervadas por el nervio glosofaríngeo (IX) y el vago (X) facilita la respuesta deglutoria [18;102]. En pacientes con DO post-ictus, la aplicación de tres sesiones de un estímulo eléctrico a nivel intrafarígeo (5Hz durante 10 minutos) ocasiona una reducción del tiempo de tránsito faríngeo y del riesgo de aspiraciones relacionándose con un incremento en la excitabilidad faríngea a nivel cortico-bulbar y de la representación cortical en el hemisferio no dañado por el accidente cerebrovascular. La terapia se ha relacionado con un mejor pronóstico clínico, con una mejora del estado nutricional y reducción de la estancia hospitalaria durante el episodio agudo [103].

La estimulación eléctrica transcutánea mediante estímulos eléctricos de baja intensidad y evitando la contracción muscular durante el tratamiento, también se ha utilizado como una estrategia sensorial [104]. Esta estrategia de estimulación sensorial ha mostrado una mejora significativa en varios parámetros deglutorios, como el tiempo de respuesta deglutoria y la prevalencia de aspiraciones en pacientes con disfagia post-ictus [104], pero no en pacientes con disfagia con la enfermedad de Parkinson [105].

7.5.2 Estrategias de estimulación central

El objetivo de las técnicas de estimulación central es inducir la neuroplasticidad cortical por estimulación directa de la corteza cerebral. Las técnicas de estimulación cerebral no invasivas incluyen la estimulación magnética transcraneal repetitiva (rTMS) y la estimulación transcraneal directa (tDCS), ambas mostrando resultados prometedores en los primeros estudios realizados [106-108]. En el **Anexo 2** se presenta un artículo Editorial en el que se discuten las posibles implicaciones futuras de estos tratamientos en el campo de la disfagia [109].

8. COMPLICACIONES

La disfagia orofaríngea es un factor de mal pronóstico para los pacientes que la padecen: los pacientes ingresados con disfagia presentan hospitalizaciones más largas, mayor número de complicaciones, mayor utilización de recursos y mayor porcentaje de institucionalización después del ingreso [110]. A pesar de que la disfagia es sólo un síntoma, la disfución orofaríngea subyacente que la origina puede conducir a dos grupos de complicaciones de gran relevancia clínica, con una alta mortalidad asociada. El deterioro de la eficacia

de la deglución puede conducir a la malnutrición del paciente debido a que no ingiera los requerimientos nutricionales adecuados, y la alteración de la seguridad de la deglución puede cursar con el desarrollo de infecciones respiratorias recurrentes y neumonía por aspiración.

8.1 Malnutrición

El deterioro de la eficacia de la deglución puede reducir la alimentación oral y llevar a la malnutrición. En una reciente revisión se ha reportado que los pacientes con ictus y disfagia presentan 2.4 veces más de riesgo de desarrollar malnutrición que los que no tienen disfagia [111]. La relación entre DO y malnutrición es también evidente en la población anciana, tanto en la que vive en la comunidad [36], en la hospitalizada [112], como en la institucionalizada [113]. También en enfermedades neurodegenerativas como la de Parkinson, la presencia de DO podría ser un factor asociado al peor estado nutricional de estos pacientes [114].

La malnutrición contribuye al peor pronóstico de la enfermedad ya que empeora el sistema inmune, la función muscular y retrasa la posible recuperación. Una Resolución del Consejo de Europa sobre la alimentación y la nutrición en los hospitales afirma que la malnutrición en los pacientes hospitalizados también conduce a hospitalizaciones prolongadas, disminución en la calidad de vida y costos innecesarios de atención sanitaria, e identifica la disfagia orofaríngea como un importante contribuyente a la malnutrición [115]. Es, por tanto, necesario evaluar el estado nutricional de los pacientes con DO e identificar aquellos pacientes malnutridos o que estén en riesgo de malnutrición para poder realizar las intervenciones pertinentes. La evaluación del estado nutricional y la intervención temprana mejoran el pronóstico de los pacientes. Existen diferentes herramientas para realizar la evaluación y el cribado nutricional en las diferentes poblaciones. El test *Mini Nutricional Assessment* (MNA®) [116] es una herramienta válida para evaluar el estado nutricional de los ancianos. Está integrado por 18 ítems que abarcan la evaluación antropométrica (peso, talla, y pérdida de peso), evaluación general (estilo de vida, medicamentos y movilidad), evaluación de la dieta (número de comidas, alimentos e ingesta de líquidos), autonomía a la hora de comer y auto-percepción de la salud y el estado nutricional. La versión corta del MNA® (*MNA® Short-Form*, MNA®-SF) [117] (ver **Anexo 1**) está formada por las primeras 6 preguntas del test, conserva la precisión y validez de la versión larga y puede ser completada en menos de 5 minutos. Actualmente, el MNA®-SF es la versión preferida del MNA® en la práctica clínica habitual en el ámbito comunitario, hospitalario y en centros de larga estancia, debido a su facilidad de uso y practicidad.

Otras herramientas de cribado nutricional recomendadas por la ESPEN (*The European Society for Clinical Nutrition and Metabolism*) son el MUST para los adultos de la comunidad y el NRS-2002 para los pacientes hospitalizados [118].

8.2 Neumonía por aspiración

El término "neumonía por aspiración," se refiere específicamente al desarrollo de un infiltrado radiográficamente evidente en los pacientes que están en riesgo de aspiración orofaríngea [119]. La aspiración de pequeñas cantidades de secreciones orofaríngeas durante el sueño es un hallazgo común en adultos sanos que generalmente no acaba conduciendo a complicaciones debido a la baja carga de bacterias patógenas en las secreciones faríngeas normales, junto con un transporte ciliar activo, y a un sistema inmune humoral y celular normal (gracias en parte a un buen estado nutricional). Sin embargo, cuando se

aspiran volúmenes importantes durante la deglución, en un paciente con un estado inmunológico alterado, y alta carga microbiana patógena en la orofaringe, consecuencia de una mala higiene oral, puede desarrollarse la neumonía. La neumonía es una de las principales causa de muerte en pacientes que han sufrido un ictus [120;121], siendo la disfagia, y más aún la presencia de aspiraciones, factores de riesgo conocidos para el desarrollo de neumonía en pacientes con ictus [42]. También en pacientes con enfermedades neurodegenerativas como la enfermedad de Parkinson, la neumonía es una de las principales causas de muerte [122] aunque su relación con la disfagia no ha sido específicamente estudiada. En ancianos, la neumonía es también una de las principales causas de morbilidad y mortalidad en los países desarrollados. Se ha descrito que la neumonía por aspiración es un importante mecanismo patogénico para la neumonía en ancianos, tanto la adquirida en la comunidad (CAP) como la adquirida en instituciones sanitarias y que el ratio de neumonías por aspiración versus cualquier otro tipo de neumonía aumenta con la edad [123]. Se ha descrito en estudios previos diferentes factores de riesgo de NAC en el anciano, relacionados con el estilo de vida del paciente como el tabaquismo y el consumo de alcohol, la mala situación funcional y nutricional, la pérdida de peso y el uso de inmunosupresores, con co-morbididades como la insuficiencia cardíaca, la enfermedad renal y la enfermedad pulmonar obstructiva crónica (COPD) y con las exposiciones ambientales al humo del tabaco, gases, vapores y sustancias químicas [124-126]. Sin embargo, el papel de la disfagia orofaríngea como factor de riesgo en el desarrollo de neumonía adquirida en la comunidad en el anciano no ha sido específicamente investigado.

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HIPÓTESIS Y OBJETIVOS

HIPÓTESIS

1. La disfagia orofaríngea (DO) puede ser detectada clínicamente con una alta sensibilidad y especificidad mediante métodos de cribado y de exploración en la cabecera del paciente. El cuestionario EAT-10 y el método de exploración clínica de la deglución volumen-viscosidad (MECV-V) cumplen las características psicométricas necesarias para ser ser usados como métodos de cribado y de evaluación clínica para la DO respectivamente.

2. El estudio mediante videofluoroscopia del patrón deglutorio de los ancianos frágiles y de los ancianos con neumonía adquirida en la comunidad nos puede permitir identificar aquellos eventos fisiopatológicos críticos, que conducen a la alteración de la seguridad y de la eficacia de la deglución en estos fenotipos de pacientes ancianos.

3. La DO es un factor de riesgo para el desarrollo de neumonía adquirida en la comunidad en ancianos, y un factor de mal pronóstico clínico en ancianos frágiles y con neumonía adquirida en la comunidad.

4. El incremento de la viscosidad del bolo mediante espesantes previene las aspiraciones en pacientes con DO sin modificar la respuesta motora orofaríngea; los espesantes de goma xantana presentan un mejor perfil terapéutico que los de almidón.

5. Los receptores TRP pueden ser una nueva diana farmacológica para el tratamiento de la DO. La suplementación del bolo alimentario con agonistas de los receptores TRP aumenta el *input* sensorial hacia los centros deglutorios corticales y sub-corticales, facilitando el cierre del vestíbulo laríngeo, mejorando la respuesta motora orofaríngea y evitando las aspiraciones.

6. La estimulación eléctrica transcutánea es un tratamiento seguro y eficaz para la DO post-ictus. El efecto terapéutico de la estimulación eléctrica transcutánea se debe no solo a su efecto sobre los músculos efectores, sino que la integración sensorial del estímulo eléctrico es también en parte responsable del efecto observado.

OBJETIVOS

1. Determinar las características psicométricas y la validez de un método de cribado (EAT-10) y un método de evaluación clínica (MECV-V) para detectar la presencia de disfagia orofaríngea (DO).

2. Caracterizar la fisopatología de la DO y el patrón deglutorio de dos fenotipos de pacientes ancianos (>70 años) con disfagia orofaríngea: el anciano frágil y el anciano con neumonía adquirida en la comunidad. Determinar si la disfagia orofaríngea es un factor de riesgo de neumonía adquirida en la comunidad en el anciano y su impacto como factor pronóstico en pacientes ancianos frágiles y en ancianos con neumonía adquirida en la comunidad.

3. Evaluar el efecto terapéutico y el mecanismo de acción de tres tipos de estrategias terapéuticas para los pacientes con DO asociada al envejecimiento y a enfermedades neurológicas:

    a) Tratamiento compensador mediante espesantes: derivados del almidón y goma xantana.

    b) Tratamiento de neuro-estimulación farmacológica mediante la adición al bolo alimentario de agonistas de los *Transient Receptor Potential Channels (TRP)*: capsaicina y piperina.

    c) Tratamiento de rehabilitación mediante dos protocolos de estimulación eléctrica transcutánea a intensidad sensorial y motora.

CAPÍTULO 1

Capítulo 1

SENSITIVITY AND SPECIFICITY OF THE EATING ASSESSMENT TOOL AND THE VOLUME-VISCOSITY SWALLOW TEST FOR CLINICAL EVALUATION OF OROPHARYNGEAL DYSPHAGIA

Laia Rofes, Viridiana Arreola, Rajat Mukherjee, Pere Clavé. *Sensitivity and specificity of the Eating Assess¬ment Tool and the Volume-Viscosity Swallow Test for clinical evaluation of oropharyngeal dysphagia*. Under review in Neurogastroenterol Motil (accepted with Major Revision).

Abstract

Background: Oropharyngeal dysphagia (OD) is an underdiagnosed digestive disorder that causes severe nutritional and respiratory complications. Our aim was to determine the accuracy of the Eating Assessment Tool (EAT-10) and the Volume-Viscosity Swallow Test (V-VST) for clinical evaluation of OD.

Methods: We studied 120 patients with swallowing difficulties and 14 healthy subjects. OD was evaluated by the 10-item screening questionnaire EAT-10 and the bedside method V-VST, videofluoroscopy (VFS) being the reference standard. The V-VST is an effort test that uses boluses of different volumes and viscosities to identify clinical signs of impaired efficacy (impaired labial seal, piecemeal deglutition, residue) and impaired safety of swallow (cough, voice changes, oxygen desaturation≥3%). Discriminating ability was assessed by the AUC of the ROC curve and sensitivity and specificity values.

Results: According to VFS, prevalence of OD was 87%, 75.6% with impaired efficacy and 80.9% with impaired safety of swallow including 17.6% aspirations. The EAT-10 showed a ROC AUC of 0.89 for OD with an optimal cut-off at 2 (0.89 sensitivity and 0.82 specificity). The V-VST showed 0.94 sensitivity and 0.88 specificity for OD, 0.79 sensitivity and 0.75 specificity for impaired efficacy, 0.87 sensitivity and 0.81 specificity for impaired safety and 0.91 sensitivity and 0.28 specificity for aspirations.

Conclusions: Clinical methods for screening (EAT-10) and assessment (V-VST) of OD offer excellent psychometric proprieties that allow adequate management of OD. Their universal application among at-risk populations will improve the identification of patients with OD at risk for malnutrition and aspiration pneumonia.

Introduction

Oropharyngeal dysphagia (OD) is a gastrointestinal motility disorder that includes difficulty or inability to form or move the alimentary bolus safely from the mouth to the oesophagus and that can include tracheobronchial aspirations.[1] OD is a highly prevalent condition in 37-78% of patients after a stroke[2] and 23-47.5% of different phenotypes of elderly people.[3;4] It is specifically classified as a digestive condition by the World Health Organization in the International Statistical Classification of Diseases and Related Health Problems ICD-9 and ICD-10.[5] OD is one of the major contributors to malnutrition[6], a highly prevalent condition among hospital patients that leads to extended hospital stays, prolonged rehabilitation, and diminished quality of life.[4] OD can also lead to respiratory infections and aspiration pneumonia with an associated mortality of up to 50%.[7] Despite its high prevalence and severe complications, OD is not always systematically explored and detected, and most patients are not even diagnosed and do not receive any treatment for this condition.

Videofluoroscopy (VFS) is the gold standard to study oral and pharyngeal mechanisms of OD, swallowing dysfunction and aspiration.[1] However, it is not feasible to perform a VFS on every patient at risk for OD as it requires specific equipment not

available in all healthcare facilities. Therefore, the development of clinical methods for easy screening and accurate clinical assessment of OD is necessary. The goal of the screening methods for OD should be quick identification of patients with OD, at risk of aspiration or malnutrition, and who need to be referred for more formal and extensive swallowing assessment. One such screening tool is the Eating Assessment Tool (EAT-10), a 10-item self-administered questionnaire developed to evaluate dysphagia symptoms in persons with a wide variety of causes of dysphagia and in different clinical settings.[8;9] However, these studies were not done against a gold standard and the diagnostic accuracy of the EAT-10 as an OD screening tool has not been established. The goal of the clinical assessment methods for OD should be, in addition to collecting the data necessary to establish a clinical diagnosis, to assess the pathophysiology of the disease, to identify the main signs and symptoms of OD and the mechanism of swallowing dysfunction, and to help to select the most appropriate therapy for those patients (such as elderly patients admitted to nursing homes) who cannot easily undergo VFS. A recent systematic review recommended bedside clinical tests using water or other fluids combined with oximetry, the endpoints being coughing, choking, voice changes and desaturation to identify patients with OD.[10] The volume-viscosity swallow test (V-VST) fulfils these criteria and shows high diagnostic accuracy in identifying clinical signs and symptoms of impaired efficacy and safety of swallow.[11] In addition, the V-VST establishes the ideal viscosity to be safely administered to patients at risk of OD and aspirations. The V-VST was first validated against VFS by using liquids thickened with a starch-based thickener [12], however the diagnostic accuracy of the V-VST using the new generation of thickeners based on xanthan-gum has not been established. It is relevant to do so, as the rheological properties of liquids thickened with xanthan gum differ from those of liquids thickened with starch.[13] The inter-rater reliability of the V-VST also needs to be addressed.

The aim of the present study was to validate the screening method EAT-10 and the clinical bedside assessment method V-VST in the detection of OD.

Materials and Methods

Subjects

A stratified-sampling design was chosen for the study, using the data from previous studies to estimate OD prevalence and sub-population proportions.[12] Based on this sampling method, data were simulated from the data available using re-sampling techniques.[12] Boot-strapped confidence intervals were then obtained for different sample sizes using the beta-binomial model suggested for the primary analysis. A sample size of 134 (120 at-risk patients and 14 healthy volunteers) was chosen to estimate the sensitivities with 10% margin of error (length of the 95% simultaneous confidence intervals would be at most 20%). This ensured that the margin of errors for estimating the specificities was at most 15%. Thus, one hundred twenty patients with a history of swallowing difficulties associated with aging, stroke and neurodegenerative diseases consecutively referred to the Gastrointestinal Physiology Lab of the Hospital de Mataró (Spain) for swallowing evaluation and 14 adult healthy volunteers (>18 years), were prospectively included in the study between June 2010 and June 2011. The study protocol was approved by the Institutional Review Board of the Hospital de Mataró and was conducted according to the principles and rules laid down in the Declaration of Helsinki and its subsequent amendments. Trial registration: NCT01158313.

Design

Oropharyngeal dysphagia was clinically evaluated in all patients and controls by means of a screening questionnaire, the EAT-10[8] and a clinical bedside assessment method, the V-VST.[12] Each test was performed by an independent clinician. The same day, a VFS was also performed on all subjects by a clinician blinded to the results of all clinical evaluations. The results from the VFS are considered as the reference standard for establishing the disease status (presence of OD) and characteristics of swallowing dysfunction (impaired safety and/ or efficacy of deglutition). Following the videofluoroscopic study, a second V-VST was performed by another clinician, blinded to the results of the EAT-10, the first V-VST and the

VFS, to assess its test-retest reliability. In addition, socio-demographic, clinical and nutritional parameters were collected for all participants.

Index tests

1) The Eating Assessment Tool (EAT-10): The 10-item Spanish-language-validated version of the screening questionnaire EAT-10[9] was administered to all patients and healthy volunteers. Patients were instructed to complete the EAT-10 by themselves but could have guidance by relatives or caregivers if needed. The EAT-10 consists of 10 questions about the severity of symptoms of OD and its clinical and social impact, each question scoring from 0 (no problem) to 4 (severe problem). Normative data from previous studies explored the upper limit of reference interval and suggested that a final EAT-10 score ≥3 was abnormal.[8]

2) The Volume-Viscosity Swallow Test (V-VST): The V-VST method was performed as described previously.[14] Briefly, the patients' ability to swallow boluses of different volumes (5, 10 and 20 mL) and viscosities (nectar-like, thin liquid, extreme-spoon thick (EST)) was evaluated following the algorithm in **Figure 1**. Signs of impaired efficacy of swallow, such as impaired labial seal, oral residue, piecemeal deglutition (multiple swallows per bolus) and symptoms of pharyngeal residue (auto-reported by the patient as the feeling of having the bolus stuck in the throat after the deglutition), and signs of impaired safety of swallow such as changes in voice quality (including wet voice), cough and decrease in oxygen saturation ≥3% (measured with a finger pulse-oximeter, Nellcor™ OxiMax™, Philips Medical Systems, Eindhoven, Netherlands) were evaluated for each patient. A patient who presented one or more signs of impaired efficacy and/or safety of swallow was considered as having oropharyngeal dysphagia. All clinical explorations, including oxygen saturation measurements, were filmed with a digital video camera (DVR-PC100E, Mini DV, Sony Corporation, Tokyo, Japan) to allow study traceability.

Reference test

Videofluoroscopy: All patients were imaged for the videofluoroscopic study while seated, in a lateral projection which included the oral cavity, pharynx, larynx, and cervical oesophagus. Videofluoroscopic recordings were obtained by using a Super XT-20 Toshiba Intensifier (Toshiba Medical Systems Europe, Zoetermeer, The Netherlands) and recorded at 25 frames/s using a Panasonic AG DVX-100B video camera (Matsushita Electric Industrial Co, Osaka, Japan). Digitization, analysis and measurements of videofluoroscopic images were made using the software Swallowing Observer (Image and Physiology SL, Barcelona, Spain). The ability of the patients to swallow boluses of different volumes and viscosities was also evaluated following the same strategy as in the clinical assessment by the V-VST (Figure 1). An impairment of the efficacy of swallow was considered when at least one of the following signs was identified during the videofluoroscopic study: impaired labial seal closure, oral residue, pharyngeal residue or piecemeal deglutition; and an impairment of the safety of swallow was considered when a penetration or an aspiration was detected. The penetrations and aspirations were classified according to the penetration-aspiration scale.[15] A patient who presented an impairment of the efficacy and/or the safety of swallow was considered as having oropharyngeal dysphagia.

Bolus viscosities

Three different viscosities (thin liquid, nectar-like and EST) were used during V-VST and VFS according to the viscosity ranges of the National Dysphagia Diet Task Force, which are 1-50 mPas for liquids, 51-350 mPas for nectar-like and >1750 mPas for EST.[16]. For V-VST studies, thin viscosity was obtained by using mineral water at room temperature, nectar-like viscosity by adding 1.2 g of thickener (Resource ThickenUp Clear, Nestlé Health Science, Lausanne, Switzerland) to 100 mL mineral water, and EST viscosity by adding 6 g of thickener to 100 mL mineral water. Solutions were prepared 5 min before the test. According to the study protocol, the specific levels of viscosity obtained were 21 mPa s for thin liquids, 238 mPa s for nectar, and 1840 mPa s for EST.[14] For VFS studies, the X-ray contrast Gastrografin (Bayer Hispania SL, Sant Joan Despí, Spain) was diluted 1:1 in mineral water, both at room temperature, to obtain the thin viscosity.

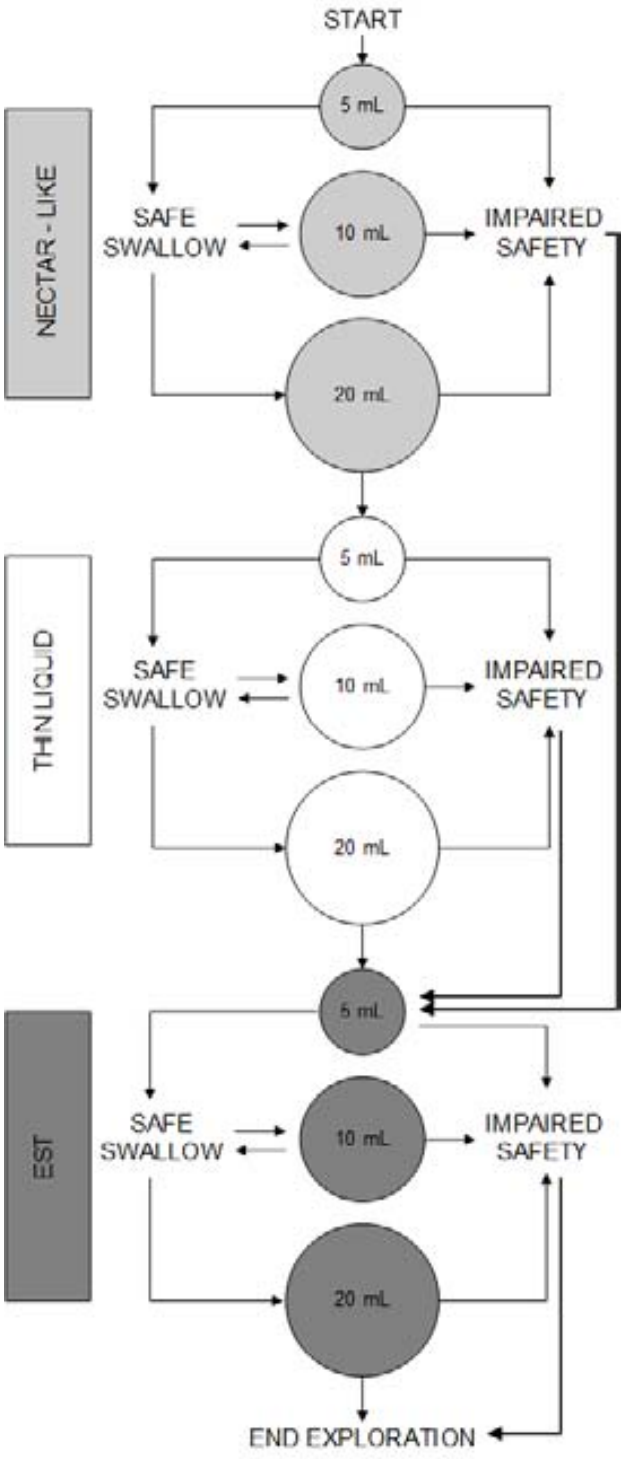

Figure 1. V-VST algorithm. Patients with safe swallow started the exploration with a 5 mL nectar bolus, followed by 10 mL and 20 mL nectar boluses, then performed the thin liquid series with boluses of increasing volume and finally completed the pathway with the three EST boluses to explore efficacy of swallow. If the patient presented signs of impaired safety at nectar or thin liquid viscosities, the series was interrupted and the EST series was assessed. EST, extreme spoon-thick.

Dilution avoids any potential damage to lung tissue in case of aspiration. For thickened solutions, the amount of thickener was adjusted to account for the effect of the X-ray contrast in order to obtain equivalent viscosities to those used in the V-VST. Nectar viscosity was obtained by adding 2.4 g of the thickener to the thin liquid solution containing the X-ray contrast and EST viscosity by adding 5.4 g of the thickener. The solutions for VFS studies were prepared 3 hours prior to the videofluoroscopic examination, in order to obtain stable and equivalent viscosities to those used during the V-VST.[13] Boluses of 5 mL, 10 mL and 20 mL of each viscosity were carefully placed in the anterior part of the mouth with a syringe to ensure accurate measurement of bolus volume during both V-VST and VFS studies.

Post-test probabilities

To assess the probability of presenting OD in the target populations after the test result, positive and negative predictive values (PPV and NPV) of EAT-10 and V-VST were assessed for independently-living and institutionalized elderly people respectively. In our population, pre-test probability (prevalence of OD) for independently-living elderly people is 23%[3] and for institutionalized elderly people, 47.5%.[4]

Data analysis and statistical methods

Quantitative parameters were described by mean±SD and qualitative parameters were described by relative and absolute frequencies. To assess the diagnostic accuracy of the EAT-10 relative to VFS, a receiver operating characteristic (ROC) curve was created plotting sensitivity versus 1-specificity values for each possible cut-off and calculating the area under the curve (AUC). Sensitivity and specificity of the V-VST relative to the videofluoroscopy for dysphagia, impaired safety and impaired efficacy were measured using a conditional likelihood approach and expressed as mean and 95% confidence intervals (CI). The Beta-Binomial model was used to model the three binary outcomes (dysphagia, impaired safety and impaired efficacy) with specific covariates comprising the corresponding videofluoroscopic

result.[17] As the V-VST for each subject was performed twice by independent blinded readers, a subject-specific random-effect term was added to the Beta-Binomial model to obtain a mixed-effect model. PPV and NPV were also assessed, taking the mixed-beta binomial estimates for sensitivities and specificities and the prevalence of the particular impairment. The Bayes' theorem was used to compute the PPV and NPV from estimates of the test's sensitivity and specificity and pre-test probabilities of OD in the target populations. Using the Beta-Binomial model, simultaneous confidence intervals for sensitivity and specificity for several parameters were obtained, accounting for the multiplicity. The inter-rater agreement for V-VST in the diagnosis of dysphagia was estimated by means of the Cohen's Kappa coefficient. Statistical analysis was performed using the stats package in R version 2.15 (www.r-project.org). The package bbmle was used to obtain the maximum likelihood estimates for the beta-binomial parameters.

Results

Subjects

A total of 134 participants were included in the study. Demographic, clinical and nutritional characteristics of the study population are described in **Table 1**. It is worth noting that most patients included in the study presented advanced age (74.4±12.4 years), polymorbidity (Charlson Comorbidity Index 3.04±1.92), high risk of malnutrition (Mini Nutritional Assessment short form, MNA-SF 9.72±2.76) and polymedication (7.77±3.7 drugs/ patient). Patients taking drugs with potential effects on swallow function were: 33.3%, antidepressants; 24.8%, anxiolytics; 16.2%, antiepileptics; 8.5%, sedatives and 4.3%, antipsychotics. One patient presented a serious adverse event during the study with a severe aspiration during the V-VST resulting in tachycardia. The patient was withdrawn from the study and recovered after a few hours. A second subject wished to withdraw before the study end and a third subject could not be analyzed because the VFS images were damaged.

Table 1. Demographic, clinical and nutritional characteristics of the study population. Healthy volunteers (HV); neurodegenerative disease (NDD); Mini Nutritional Assessment short form (MNA-SF)

	HV	Patients	Patients		
			NDD	***Stroke***	***Elderly***
Subjects	14	120	10.8% (13)	55% (66)	34.2% (41)
Sex (men)	57.1% (8)	54.2% (65)	46.2% (6)	56.1% (37)	53.7% (22)
Age (years)	30.5±6.1	74.4±12.4	64.0±19.6	73.5±11.4	79.6±8.2
Charlson Index					
0	100% (14)	10.1% (12)	17.5% (7)	0.0% (0)	38.5% (5)
1-2	0% (0)	31.1% (37)	40.0% (16)	25.8% (17)	30.8% (4)
3-4	0% (0)	37.0% (44)	35.0% (14)	39.4% (26)	30.8% (4)
≥5	0% (0)	21.8% (26)	7.5% (3)	34.8% (23)	0.0% (0)
Nutritional status (MNA-SF)					
Malnourished (0-7)		22.9%(27)	23.1% (3)	25.8% (17)	17.9% (7)
At risk (8-11)		48.3% (57)	38.5% (5)	53.0% (35)	43.6% (17)
Well nourished (12-14)		28.8% (34)	38.5% (5)	21.2% (14)	38.5% (15)

Reference Test Results

Videofluoroscopy. Videofluoroscopic images for analysis were available from 131 subjects. Prevalence of OD according to the VFS study was 87% (114) of the included subjects, 75.6% (99) of them presenting VFS signs of impaired efficacy and 80.9% (106) signs of impaired safety of swallow. Efficacy signs: impaired labial seal closure was observed in 6.1% (8) of subjects, piecemeal deglutition in 68.7% (90), oral residue in 31.3% (41) and pharyngeal residue in 27.5% (36). Safety signs: According to the penetration-aspiration scale,[14] 30.5% (40) of subjects presented score 2 penetrations (material enters the airway, remains above the vocal folds, and is ejected from the airway), 32.1% (42) scores 3-5, (severe penetrations into the laryngeal vestibule not ejected from the airway and/or contacting the vocal folds) and 18.3% (24) scores 6-8 (aspirations into the airway), 62.5% (15) of which were silent (score 8). Increasing bolus viscosity improved the safety of swallow of 80.9% (106) of subjects.

Index Test Results

1) EAT-10: The median EAT-10 score of the subjects included in the study was 9 with 25-75 percentiles of 3-16. The score of healthy subjects was 0, that of patients with swallowing complaints but normal videofluoroscopy results, 3 (1-11.5) and the median score of patients diagnosed with OD was 10 (4-16) (P<0.001). Patients with impaired efficacy of swallow presented a median EAT-10 of 11 with 25-75 percentiles of 5-16 and patients with impaired safety 11 (4-16). Up to 75.9% (101) of the 133 subjects that completed the EAT-10 presented a score above the upper limit of the reference interval (≥3) (**Figure 2**).

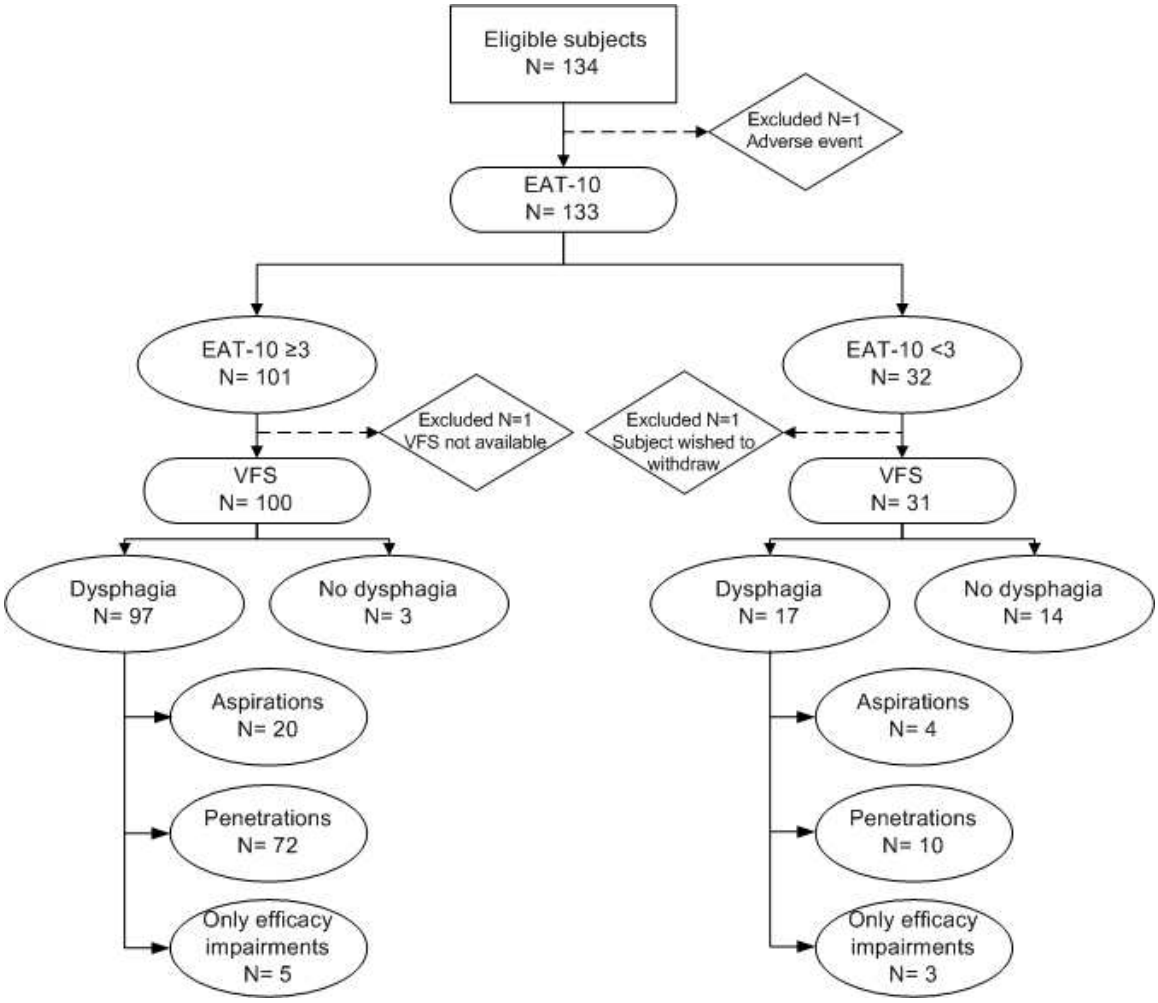

Figure 2. Flow chart of subjects included in the study that underwent the EAT-10. Subjects stratified by presence of oropharyngeal dysphagia according to the VFS study.

2) V-VST: 78.4% (105) of subjects included in the study presented OD according to the V-VST, 58.2% (78) of them presenting signs of impaired efficacy of swallow and 73.1% (98) presenting signs of impaired safety (**Figure 3**). According to the V-VST, increasing bolus viscosity with thickener improved the safety of swallow of 72.4% (97) subjects and the efficacy of swallow of 1 subject.

Accuracy of the EAT-10 and V-VST for detecting OD

1) EAT-10: The AUC of the ROC curve for detecting OD was 0.89 (95% CI=0.802-0.988); for detecting impaired safety, 0.82 (95% CI=0.719-0.928) and for detecting impaired efficacy, 0.79 (95% CI=0.682-0.890). The discriminating ability of the EAT-10 for the normative cut-off value (EAT-10≥3) to detect dysphagia, impaired efficacy, impaired safety of swallow and aspirations is shown in **Table 2**. According to the ROC curve, the optimal cut-off to detect dysphagia [0.895 (95% CI=0.823-0.944) sensitivity and 0.824 (95% CI=0.566-0.962) specificity], impaired safety of swallow [0.915 (95% CI=0.845-0.960) sensitivity and 0.680 (95% CI=0.465-0.850) specificity] and silent aspirations [0.933 (95% CI=0.680-0.998) sensitivity and 0.215 (95% CI =0.145-0.301) specificity] was 2, and to detect impaired efficacy of swallow was 4 [0.859 (95% CI=0.774-0.920) sensitivity and 0.719 (95% CI=0.532-0.862) specificity] (**Figure 4**).

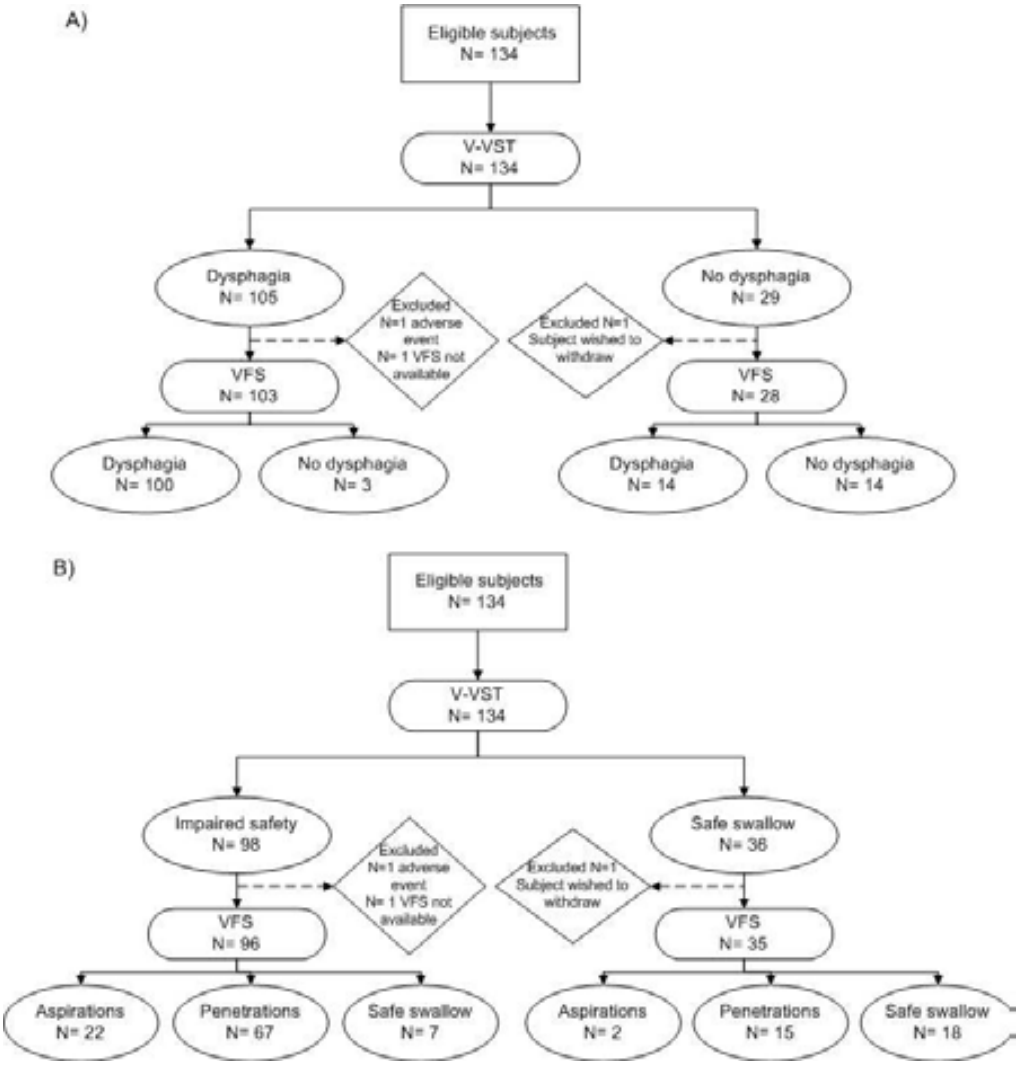

Figure 3. Flow chart of subjects included in the study that underwent the first V-VST. A) Subjects stratified by presence of oropharyngeal dysphagia according to the VFS study; **B)** Subjects stratified by presence of signs of impaired safety of swallow (penetrations, aspirations and safe swallow) according to the VFS study. Note that the test was performed twice, to calculate sensitivity and specificity values of the V-VST, so a subject-specific random-effect term was added to the beta-binomial model to obtain the mixed-effect model.

Table 2. Accuracy of the EAT-10 in detecting dysphagia, impaired efficacy and safety of swallow and aspirations at the normative cutoff 3. CI, simultaneous confidence interval; PPV, positive predictive value; NPV, negative predictive value; OD, oropharyngeal dysphagia.

	EAT-10 ≥3					
	Sensitivity (95% CI)	***Specificity (95% CI)***	***PPV***	***NPV***	***LHR+***	***LHR-***
OD	0.85 (0.77-0.91)	0.82 (0.57-0.96)	0.828	0.847	4.72	0.183
Impaired efficacy	0.88 (0.80-0.94)	0.59 (0.41-0.76)	0.684	0.830	2.15	0.203
Impaired safety	0.87 (0.79-0.93)	0.68 (0.46-0.85)	0.731	0.837	3.13	0.191
Aspirations	0.83 (0.61-0.95)	0.25 (0.17-0.34)	0.525	0.592	1.11	0.680

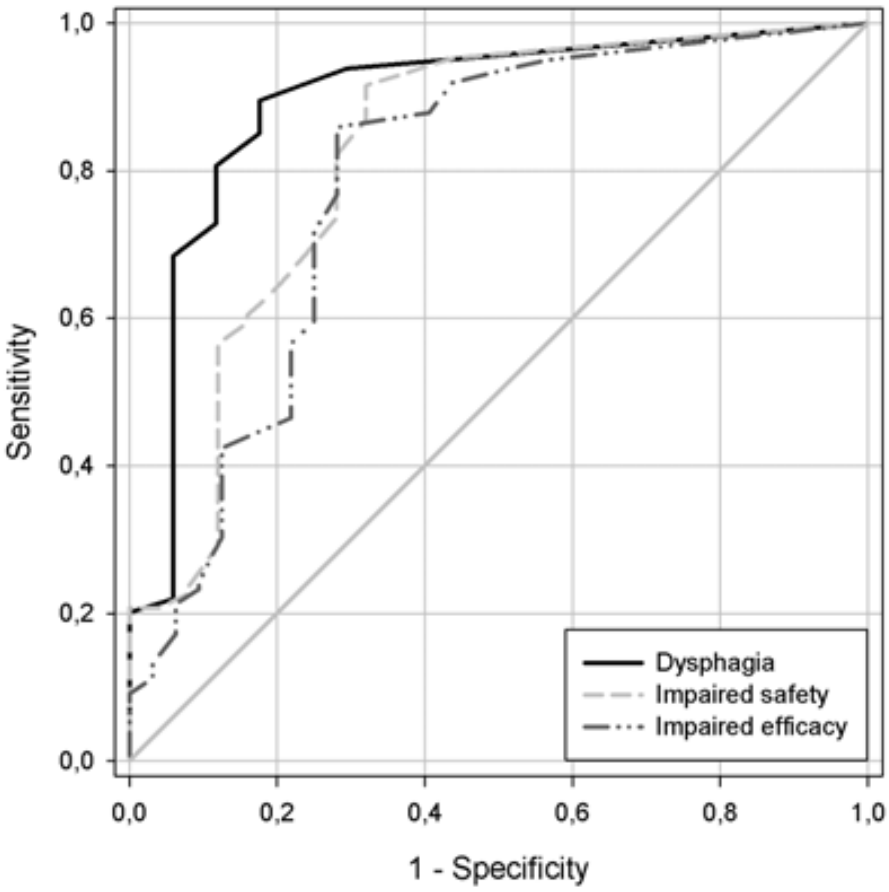

Figure 4. ROC curves of EAT-10 to detect dysphagia, impaired efficacy and impaired safety of swallow with respect to VFS findings.

Table 3. Accuracy of the V-VST to detect dysphagia, impaired efficacy and safety of swallow and aspirations. CI, simultaneous confidence interval; PPV, positive predictive value; NPV, negative predictive value; OD, oropharyngeal dysphagia.

	V-VST					
	Sensitivity (95% CI)	***Specificity (95% CI)***	***PPV***	***NPV***	***LHR+***	***LHR-***
OD	0.94 (0.87-0.98)	0.88 (0.50-0.99)	0.98	0.70	7.83	0.068
Impaired efficacy	0.79 (0.62-0.90)	0.75 (0.45-0.92)	0.93	0.67	3.16	0.280
Impaired safety	0.87 (0.74-0.94)	0.81 (0.48-0.95)	0.93	0.46	4.58	0.160
Aspirations	0.91 (0.78-0.99)	0.28 (0.17-0.34)	0.21	0.94	1.26	0.321

2) V-VST: The discriminating ability of the V-VST (sensitivity, specificity and predictive values) for dysphagia, impaired efficacy and safety of swallow and aspirations is shown in **Table 3**. Interestingly, any sign of impaired safety of swallow in the V-VST predicts the presence of silent aspirations with a sensitivity of 1.00 (95% CI=0.782-1.00) and a specificity of 0.320 (95% CI=0.220-0.394). Moreover, the V-VST showed a sensitivity of 0.821 (95% CI =0.734-0.888) and a specificity of 0.640 (95% CI=0.425-0.820) in detecting patients whose swallow improved with the enhancement of bolus viscosity.

Post-test probabilities

PPV and NPV of OD for EAT-10 in independently living elderly people were 0.603 and 0.963 respectively. For the V-VST in institutionalized elderly people, the PPV and NPV of OD were 0.876 and 0.942 respectively.

Inter-rater correlation for V-VST

The V-VST showed a good inter-rater agreement for detecting dysphagia with a Kappa coefficient of 0.628 (95% CI=0.45-0.78).

Discussion

The main conclusion of this study is that clinical methods for screening (EAT-10) and assessment (V-VST) of OD offer high discriminating ability. We also found that OD was a serious condition characterized by impairment in oropharyngeal function including frequent silent aspirations, and occurred in vulnerable patients at risk of severe nutritional and respiratory complications. Following these results, we recommend the universal application of these methods among older and neurological patients at risk for OD and nutritional or respiratory complications to identify those that could need a more exhaustive evaluation by instrumental techniques.

OD is a prevalent and severe gastrointestinal motility disorder with a very poor prognosis, but the implementation of structured dysphagia programs in hospital settings that systematically evaluate and treat OD reduce the incidence of pneumonia, costs for antibiotics and mortality rates.[18;19] However, despite the high prevalence, morbidity, mortality and costs caused by nutritional and respiratory complications, OD is mostly underdiagnosed and undertreated even in tertiary clinical settings providing specialized care of older adults. The low level of awareness among healthcare professionals and the lack of validated and feasible clinical tools for bedside screening and assessment of OD contribute to this situation. In the present study, we provide validated clinical tools to remedy it.

The studied population presented many co-morbidities, low functionality, impaired nutritional status and high prevalence of OD, most of them

presenting signs of both impaired efficacy and safety of swallow. Prevalence of silent aspirations in the studied population was high (11.4%). This is a serious finding that, taken together with the poor health status and high prevalence of malnutrition, put our population at high risk for severe complications including aspiration pneumonia and death.[7;20]

Screening for OD should be an easy, quick and low cost process able to detect the majority of patients with the disease. At this stage of the diagnostic process, high sensitivity is more desirable than high specificity, as the cost of a more exhaustive swallowing evaluation is preferable to the potentially fatal complications of undetected dysphagia. The 10-item self-administered questionnaire EAT-10 includes questions about dysphagia symptoms in patients with swallowing disorders. In its initial validation study, Belafsky et al found EAT-10 displayed excellent internal consistency, good reproducibility and criterion-based validity and suggested that an EAT-10 score of 3 or higher should be considered abnormal. The score 3 was obtained from the upper limit of reference interval (mean+2SD) of the healthy volunteers score. However, the drawback is that the upper limit found for negative (healthy) subjects overlaps with the lower limit found for positive (diseased) cases, leading to the misclassification of some dysphagic patients as negatives. According to the results of our ROC curve, reducing the cut-off from 3 to 2 increased the sensitivity of the test nearly 5% without affecting the specificity, resulting in fewer false negative cases. To the author's knowledge, the accuracy of only one other questionnaire (the Swallowing Disturbance Questionnaire)[21] has been previously assessed, using FEES as a reference test, and it presented lower sensitivity and specificity values (71.88% and 78.38% respectively) than the EAT-10. In addition, post-test probabilities (PPV and NPV) of EAT-10 for OD in independently-living elderly people were calculated considering the true prevalence of OD in this population (23%)[3], further confirming the low probability of presenting OD after a negative test (EAT-10 <2). Sensitivity and specificity are intrinsic properties of each diagnostic test, independent of disease prevalence. In contrast, PPV and NPV are dependent on disease prevalence and indicate the probability of having the disease following the test, helping the clinician decide how to manage and treat the patient according to the result of the diagnostic test. Following these results we recommend the EAT-10 as a first-line tool for systematic screening of at-risk patients, especially in primary care settings, as it is easy and accurate, facilitating its use to general practitioners and allied healthcare professionals not specifically trained in OD. We believe that patients with an EAT-10 ≥2 should be considered for further clinical bedside assessment.

The clinical bedside tests for swallowing assessment of OD should present good psychometric properties, good reliability, a detailed and easy-to-perform protocol designed to protect patients' safety and able to evaluate the safety and efficacy of swallowing, and a system to detect silent aspirations. The V-VST is an accurate bedside assessment method that was designed for this purpose.[12] The V-VST should be administered by trained healthcare professionals at all medical facilities and can be repeated according to the natural progression of the disease. The test presented high diagnostic sensitivity and high positive predictive value to detect OD, impaired safety and aspirations (including silent aspirations), clearly showing a high discriminating ability. Nevertheless, the specificity for detecting aspirations is low (the test is not able to clearly differentiate between aspirations and penetrations and an instrumental study is needed to discriminate between the two impaired safety signs). However, penetrations scoring 3 or higher in the PAS are also a clinically-significant sign of impaired safety of swallow that puts patients at risk of pneumonia.[22] Therefore, the high positive predictive value of the V-VST for impaired safety (penetrations or aspirations) permits the accurate selection of these patients at risk of respiratory complications and the high negative predictive value for aspiration rules out aspiration in a patient with a negative V-VST (post-test probability of 6%). Moreover, the V-VST characterizes the pathophysiology of the impaired swallow function by identifying impaired safety or efficacy of swallow and also detects patients who improve with thickener treatment. In addition, the V-VST

establishes the ideal viscosity to safely administer to patients at risk of aspirations, adding value to its diagnostic capacity. In a systematic review, Bours and colleagues[10] recommend a water test combined with oximetry using coughing, choking and voice alteration as the endpoints as the best method to clinically assess patients for OD. The water tests are one of the most extended and frequently used tests for dysphagia screening. They present a sensitivity of 51-85% and a specificity of 66-75% to detect aspirations, and a sensitivity of 27-79% and specificity of 63-88% to detect impaired safety of swallow (penetrations or aspirations).[23-26] These parameters are inferior to those offered by the V-VST in the present study. Moreover, the water tests involve the continuous swallow of large amounts of water which may place the patient at risk for aspiration, can miss silent aspirations if oxygen saturation is not monitored [27;28] and do not assess any parameter related to the efficacy of swallow (residue) nor evaluate the ability of patients to swallow different viscosities. Like the V-VST, several tests have been developed using different viscosities and solids to evaluate aspiration and/or penetration. Sensitivity of these tests range from 41% to 100% and specificity from 57% to 82%.[29-31] Although these tests evaluate patients' ability to swallow material of different consistencies, they are not combined with oxygen desaturation, and therefore silent aspirations can be underdiagnosed. Smith et al[32] recommended a water test combined with oxygen saturation followed by bedside swallowing assessment with a variety of quantities and consistencies. This protocol showed a sensitivity of 80% and specificity of 68% for OD, but did not provide a detailed protocol for the swallow test and only acute post-stroke patients were studied. Following these results, we recommend the V-VST for systematic bedside clinical assessment of swallowing function of high risk populations, such as elderly patients admitted to general hospitals, nursing home residents and patients with neurological diseases. The V-VST should be performed by trained healthcare professionals. We would like to emphasize that in this study the viscosities used in the VFS perfectly matched those used in the V-VST and so can be used to prescribe the different levels of thickened liquids for patients with dysphagia.

Differences in ages between the control and patient groups may constitute a limitation of this study because it affects blinding and may influence the researcher's response or diagnosis. Although VFS interpretations were not specifically assessed for reliability in this study, internal controls of our unit found good intra-rater and inter-rater reliability for identification of aspiration and assessment of the Penetration-Aspiration Scale. Similar results were reported in previous studies when the VFS analyses were made by trained clinicians, as they were in our study [33;34].

In conclusion, our study shows that the discriminating ability of both the EAT-10 questionnaire for clinical screening of OD and the V-VST for clinical bedside assessment is very high and both are useful methods for detecting patients at risk for nutritional and respiratory complications who need more exhaustive instrumental evaluation. We recommend their universal application for populations at risk of OD to ensure comprehensive dysphagia care, to avoid the serious nutritional and respiratory complications associated with OD, to reduce the mortality rates and the economic and social burden associated with this disease and to improve quality of life of dysphagic patients.

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CAPÍTULO 2

Capítulo 2

PATHOPHYSIOLOGY OF OROPHARYNGEAL DYSPHAGIA IN THE FRAIL ELDERLY

Laia Rofes, Viridiana Arreola, Maise Romea, Elisabeth Palomera, Jordi Almirall, Mateu Cabré, Mateu Serra-Prat, Pere Clavé. Pathophysiology of oropharyngeal dysphagia in the frail elderly. *Neurogastroenterol Motil* 2010; 22(8): 851-8, e230.

Abstract

Background: Oropharyngeal dysphagia is a major complaint among the elderly. Our aim is to assess the pathophysiology of oropharyngeal dysphagia in frail elderly patients.

Methods: 45 frail elderly patients (FEP, 81.5±1.1 years) with oropharyngeal dysphagia and 12 healthy volunteers (HV, 40±2.4 years) were studied using videofluoroscopy. Each subject's clinical records, signs of safety and efficacy of swallow, timing of swallow response, hyoid motion and tongue bolus propulsion forces were assessed.

Results: HV presented a safe and efficacious swallow, faster laryngeal closure (0.157±0.013 seconds) and upper oesophageal sphincter opening (0.200±0.011 seconds), maximal vertical hyoid motion (0.310±0.048 seconds), and stronger tongue propulsion forces (22.16±2.54 mN) than FEP. In contrast, 63.63% of FEP presented oropharyngeal residue, 57.10%, laryngeal penetration and 17.14%, tracheobronchial aspiration. FEP with impaired swallow safety showed delayed laryngeal vestibule closure (0.476±0.047 seconds), similar bolus propulsion forces, poor functional capacity and higher 1-year mortality rates (51.7% vs 13.3%, p=0.021) than FEP with safe swallow. FEP patients with oropharyngeal residue showed impaired tongue propulsion (9.00±0.10 mN), delayed maximal vertical hyoid motion (0.612±0.071 seconds) and higher (56.0% vs 15.8%, p=0.012) 1-year mortality rates than those with efficient swallow.

Conclusion: Frail elderly patients with oropharyngeal dysphagia presented poor outcome and high mortality rates. Impaired safety of deglutition and aspirations are mainly caused by delayed laryngeal vestibule closure. Impaired efficacy and residue are mainly related to weak tongue bolus propulsion forces and slow hyoid motion. Treatment of dysphagia in frail elderly patients should be targeted to improve these critical events.

Introduction

Oropharyngeal dysphagia is a major complaint among the elderly. Functional oropharyngeal dysphagia affects more than 30% of patients who had a stroke; 52%-82% of those with Parkinson's disease; it affects up to 84% of patients with Alzheimer's disease, and more than 50% of elderly institutionalized patients (1;2). Aging is one of the principal demographic characteristics of developed countries. In the last decade, the population over 65 years of age has increased by 28 % whereas the rest of the population has only grown 0.8% (3). Up to 13.7% independent-living elderly people presented oropharyngeal dysphagia (4), and 16,500,000 US senior citizens will require care for dysphagia by the year 2010 (5). Among the elderly, the frail phenotype is an emerging clinical and research paradigm referring to aged individuals unusually susceptible to disease. Although the definition of frailty is still a matter of discussion and its relationships with aging, disability, and chronic disease have not been settled, it is well recognized that frailty correlates with vulnerability, general susceptibility to disease and poor outcome, including death (6).

Oropharyngeal dysphagia may cause two groups of clinically relevant complications in older people: a) a decrease in the efficacy of deglutition present in up

to 25%-75% patients can lead to malnutrition and/or dehydration and b) a decrease in deglutition safety resulting in choking and tracheobronchial aspiration may result in pneumonia in 50% of cases (3;7). A recent 10-year review found a 93.5% increase in the number of hospitalized elderly patients with a diagnosis of aspiration pneumonia while other types of pneumonia in the elderly decreased (8). We recently found oropharyngeal dysphagia and aspiration is a highly prevalent (55%) clinical finding in elderly patients with pneumonia and is an indicator of pneumonia severity as patients with dysphagia showed lower functional status, higher prevalence of malnutrition, comorbidities, poor prognosis, and higher mortality rates (7). In elderly nursing home residents with oropharyngeal dysphagia, aspiration pneumonia occurs in 50% during the first year with a mortality rate above 45% (9). The pathophysiology of oropharyngeal dysphagia and the alterations of the biomechanics of swallow response and bolus kinematics in the frail elderly are not well understood. Videofluoroscopy (VFS) is the gold standard to study the oral and pharyngeal mechanisms of dysphagia (9). We previously found that slow closure of the laryngeal vestibule and slow opening of the upper oesophageal sphincter are the most characteristic aspiration-related events in neurological patients with oropharygeal dysphagia (10;11). Aspiration may also result from insufficient hyoid and laryngeal elevation, which would fail to protect the airway (11). We found efficacy of deglutition and oropharyngeal residue in neurological patients correlates well with impaired tongue bolus propulsion (10) and pharyngeal residue may lead to post-swallow aspiration (12).

The aim of the present study is to assess the pathophysiology of oropharyngeal dysphagia in frail elderly patients in order to develop more specific therapeutic strategies to avoid nutritional and respiratory complications in this high vulnerable group of older patients.

Materials and Methods

Sample

Healthy volunteers (n=12), showed all parameters in the reference ranges during a general medical examination. Frail elderly patients (n=45): patients over 70 years of age consecutively admitted to the Acute Geriatric Unit with respiratory (38.9%), neurological (13.9%), infectious (13.9%), cardiac (11.1%) or metabolic (11.1%) diseases; 48.8% of them coming from a nursing home. All patients had presented clinical complaints of oropharyngeal dysphagia during a routine clinical test we use for screening for oropharyngeal dysphagia and aspiration (13). A geriatric assessment on the day of admission included: a) demographic data, b) comorbidities with the Charlson Index (14) and presence of geriatric syndromes, c) functional capacity pre-admission (two weeks prior) and on admission, using the Barthel Index (15), d) nutritional status using the Mini Nutritional Assessment (MNA) (16) and e) a clinical test for oropharyngeal dysphagia and aspiration performed by an experienced speech-swallow therapist (7;13). Elderly patients were considered as “frail” if they fulfilled three or more of the following accepted criteria: 1) Unintentional weight loss of >5% of weight, 2) exhaustion (lower energy than usual, or feeling unusually tired or weak in the last month), 3) weakness (low strength with the hand dynamometer <7 kg in women and <14 kg in men), 4) walking slowness (≥7 seconds for 4.5 m), and 5) poor outdoor physical activity (17). After discharge a clinical follow up was performed 30 days after admission and a check up by telephone or visit a year after admission. Protocol studies were approved by the Institutional Review Board of the Hospital de Mataró (Mataró, Spain).

Experimental Design

Subjects were submitted to: a) a symptom inventory to assess the clinical severity of oropharyngeal dysphagia (18) and b) a videofluoroscopic study to assess the signs of safety and efficacy of deglutition and to measure the effect of bolus volume and viscosity, and the physiology of the swallow response (10;13) (Figure 1). VFS studies assessed the effect of increased volumes from 3, to 5, 10, 15 and 20 mL of liquid (20.40±0.23 mPa s), nectar (274.42±13.14 mPa s), and pudding viscosity (3931.23±166.15 mPa s) series according to our previous studies (10;13). Liquid viscosity was obtained by mixing 1:1 mineral water and the X-ray

contrast Gastrografin (Berlimed SA, Madrid, Spain), nectar viscosity by adding 3.5 g of thickener Resource ThickenUp (Nestlé Nutrition, Barcelona, Spain) to liquid solution and pudding viscosity by adding 8 g of the thickener. Bolus density for liquid was 1.19±0.007 g mL^{-1}, nectar, 1.23±0.007 g mL^{-1}, and pudding, 1.27±0.001 g mL^{-1}. Boluses were carefully offered to patients with a syringe (13).

Videofluoroscopic signs

Patients were imaged while seated in a lateral projection which included the oral cavity, pharynx, larynx, and cervical esophagus (11;12) (Figure 1). VFS recordings were obtained by using a Super XT-20 Toshiba Intensifier (Toshiba Medical Systems Europe, Zoetermeer, Netherlands) and images were recorded at 25 frames s^{-1} (Panasonic AG DVX-100B, Matsushita Electric Industrial Co, Ltd, Osaka, Japan). Swallows were analyzed by equipment (Swallowing Observer, Image & Physiology SL, Barcelona, Spain) developed to capture and digitize the swallowing sequences to assess the VFS signs and measure the oropharyngeal swallow response (10;13). Oral and pharyngeal VFS signs of safety and efficacy of deglutition were identified accordingly to accepted definitions (12;14). Penetration was defined as the entrance of swallowed material into the laryngeal vestibule and aspiration as the passage of this material below the vocal cords (11). The severity of aspirations and penetrations was further characterized according to Rosenbek's penetration-aspiration scale and according to whether they were followed by cough (silent aspirations) or not (11;19). Mechanisms of aspiration were classified as pre-deglutitive (before activation of pharyngeal phase), intra-deglutitive or post-deglutitive (11;15).

Oropharyngeal swallow response

Measurements of oropharyngeal swallow response were obtained during 5 mL nectar swallows because all patients swallowed this bolus: a) Oropharyngeal reconfiguration, timing of the opening (O) or closing (C) events at the glossopalatal junction (GPJ), velopharyngeal junction (VPJ), laryngeal vestibule (LV), and upper esophageal sphincter (UES) were measured, GPJ

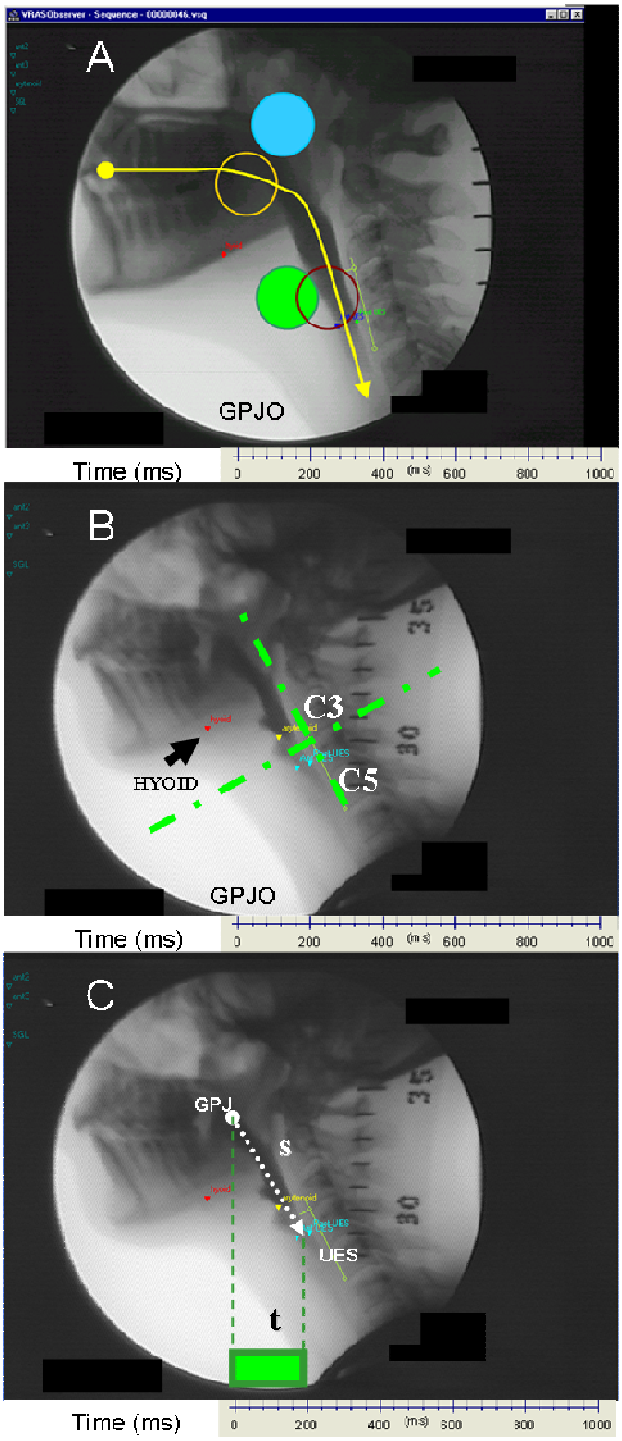

Figure 1 Oropharyngeal swallow response: A) Timing of opening and closing events at glossopalatal junction (GPJ), velopharyngeal junction (VPJ), laryngeal vestibule (LV) and upper esophageal sphincter (UES) were measured and all temporal measurements were referenced to glossopalatal junction opening (GPJO) as time 0. B) To assess extent and timing of hyoid movement, an X-Y coordinate system was used. The anterior-inferior corner of C3 was used as the origin, and the vertical axis was defined by a line connecting the anterior inferior corners of C3 and C5. C) Bolus kinematics. Bolus velocity (mean and maximal) and kinetic energy prior to enter the UESO were determined.

opening being given the time value 0 (11;16); b) hyoid motion (vertical and anterior movement) was determined in a X-Y coordinate system (11); c) anteroposterior diameter of UES opening (mm) (20;21); and d) bolus propulsion force of the tongue was measured by means of Newton's second law of motion and expressed in mN; mean and maximal velocity (m s^{-1}) and kinetic energy (mJ) acquired by the bolus prior to entering the UES (10;13) (**Figure 1**).

Data analysis and statistical methods

Categorical variables were described as percentages. Patients with dysphagia were classified into those with safe deglutition and those with impaired safety (penetration or aspiration) and those with impaired efficacy according to whether they presented oropharyngeal residue (10). Quantitative parameters were described by mean±SEM and comparisons were assessed by the non-parametric Mann-Whitney U test. The effect of increasing bolus volume on safety and efficacy of deglutition was assessed by the non-parametric Cochran Q procedure, testing the null hypothesis that multiple-related prevalence are the same. The effect of increasing bolus viscosity was assessed by the non-parametric McNemar procedure testing the null hypothesis for related samples that multiple responses come from the same population. Hyoid profiles were compared by two-way ANOVA analysis and correlation analysis was assessed by the Spearman correlation coefficient. Statistical significance was accepted if p values were less than 0.05. Statistical analysis was performed by GraphPad Prism 4 (San Diego, CA, USA).

Results

Demographics and clinical inventory scores

Mean age of healthy volunteers was 40.2±2.5 years (6 men and 6 women) and that of frail elderly patients was 81.5±1.2 years (26 men and 19 women). The Charlson comorbidity index score of FEP was 2.2±0.2, chronic pneumopathy (45.9%), diabetes mellitus (29.7%), ischemic cardiopathy (24.3%), hearth failure (24.3%), cerebrovascular disease (21.6%) and dementia (16.2%) being highly prevalent conditions among these frail patients. Mean body mass index of FEP was 25.8±0.9 Kg m^{-2}, and according to the MNA, 16% of FEP presented malnutrition and 48% were at risk of malnutrition. Patients with signs of penetration or aspiration during VFS studies showed poor functional capacity [Barthel Index pre-admission, 62.1±7.7 vs 92.3±3.3 in FEP with safe swallow (p=0.025), and on admission, 31.9±6.3 vs 68.6±6.9 in FEP with safe swallow, (p=0.002)] and increased mortality. One-year mortality was 51.7% among frail elderly patients with impaired safety signs on VFS study and 56.0% in those with impaired efficacy, whereas frail elderly patients with safe (13.3%, p=0.021) or efficient swallow (15.8%, p=0.012) had significantly lower mortality rates. Clinical severity of patients' dysphagia score was significantly higher in FEP with impaired safety (548.9±68.7 points vs 155.8±52.3 in frail patients with safe swallow, p=0.001). Clinical severity scores were also higher for FEP with impaired efficacy and pharyngeal residue (503.2±76.7 points) although these differences did not reach statistical significance when compared with frail patients with efficient swallow (311.2±73.2 points, p=0.098).

Videofluoroscopic signs of oropharyngeal dysphagia

Healthy volunteers: All volunteers presented a safe and efficacious swallow. ***Frail elderly patients:*** The effect of bolus volume and viscosity on the prevalence of VFS signs of impaired safety or efficacy of swallow is summarized in **Figure 2**. The prevalence of FEP with oral residue significantly increased by increasing bolus volume. Pudding viscosity also significantly increased oral residue. Pharyngeal residue was also a common VFS sign as impaired vallecular clearance was observed in up to 42.8% of patients during liquid series, 50% of patients during nectar series and increased to 63.3% of patients at pudding viscosity. Similarly, residue in the pyriform sinus was observed in 19.3% of patients during liquid series, 20% of patients during nectar series and increased to up to 38.5% of patients at pudding viscosity. Pharyngeal residue also significantly increased with bolus volume and pudding viscosity (**Figure 2**). Penetration into the laryngeal vestibule during the

pharyngeal phase was the most prevalent cause of unsafe deglutition and was observed in up to 57.1% of FEP when swallowing liquid boluses and up to 52.8% of patients during nectar series. Increasing bolus viscosity to pudding significantly reduced prevalence of patients with laryngeal penetration to 20.5% (p<0.001). According to Rosenbek's scale, 40% patients with impaired safety showed severe penetrations (levels 3-5). Aspiration into the airway during swallow response was observed in 17.1% of patients during liquid series and 9.1% at nectar viscosity, and reduced to 6.8% with pudding viscosity. Also, 32.5% of patients with impaired safety had silent (level 8) aspirations. Only 4.5% of patients presented aspirations caused by post-deglutitive pharyngeal residue. Up to 53.3% of elderly patients could complete 3-20 mL pudding series safely; a proportion that was reduced to 33.3% during nectar (p=0.004) series and only 17.8% patients could complete the liquid series safely (p<0.001).

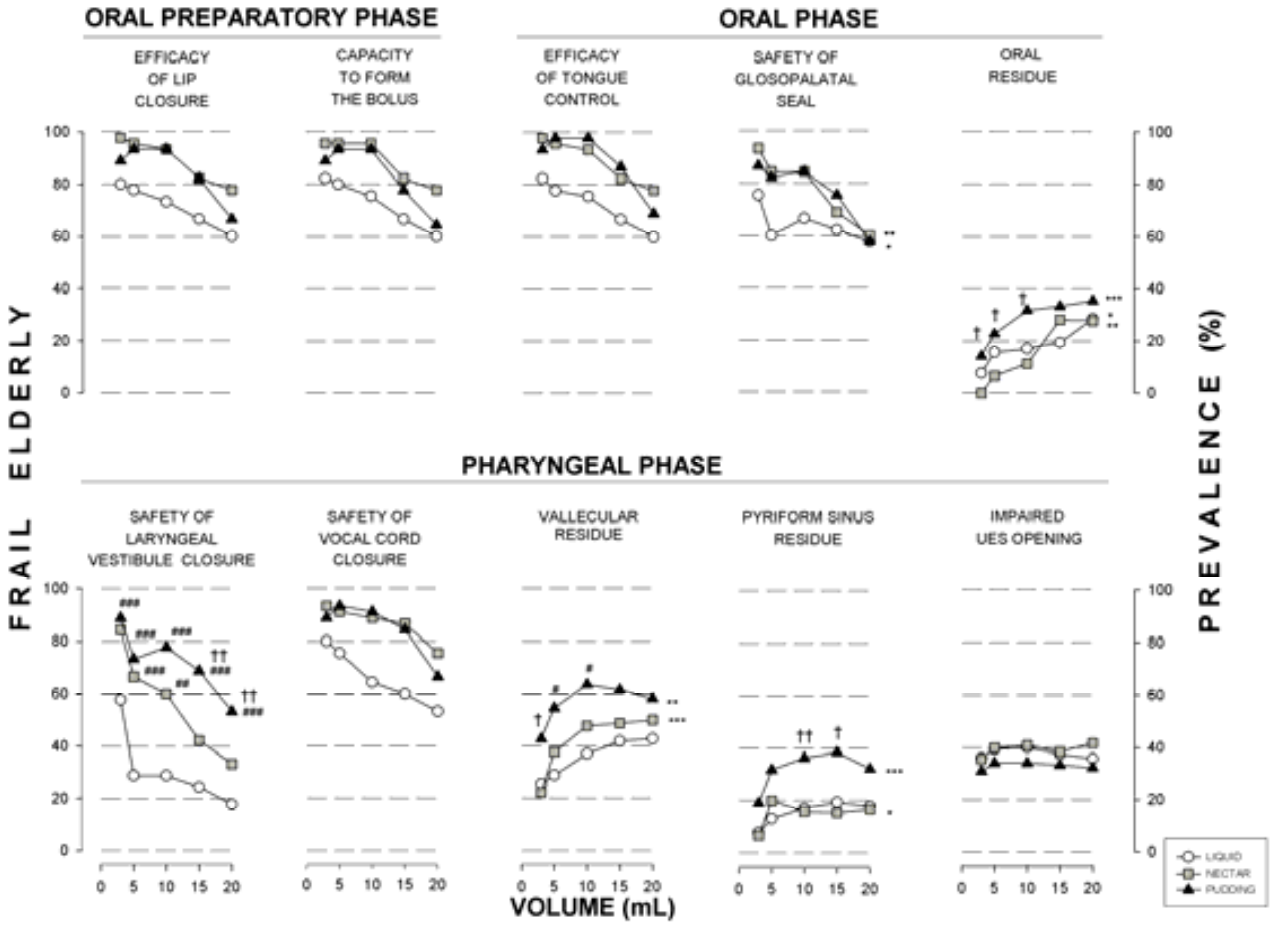

Figure 2 Prevalence of videofluoroscopic signs of safety and efficacy of oral preparatory, oral and pharyngeal phase of swallowing for each bolus volume and viscosity in Frail Elderly Patients with oropharyngeal dysphagia. Safety of laryngeal vestibule and vocal cord closure was expressed as the percentage of patients that could swallow without signs of contrast entering the laryngeal vestibule or traversing the vocal folds for each bolus volume and viscosity. * p<0.05, ** p<0.01, *** p<0.001 effect of increasing bolus volume; # p<0.05, ## p<0.01, ### p<0.001 vs liquid viscosity; † p<0.05, †† p<0.01, ††† p<0.001 vs nectar viscosity.

Oropharyngeal physiology

Healthy volunteers: a) Duration of swallow response (GPJO-LVO) for 5 mL nectar boluses was 0.753±0.023 seconds. Oropharyngeal reconfiguration from a respiratory to a digestive pathway was very fast as time to close the airway entrance (GPJO-LVC) and time to open the UES (GPJO-UESO) was <0.200 seconds (**Figure 3**). b) Maximal extent of vertical hyoid movement was achieved at 0.310±0.048 seconds and maximal anterior hyoid motion occurred at 0.463±0.056 (**Figure 4**). c) UES opening during 5 mL bolus transit was 5.99±0.34 mm. d) Tongue bolus propulsion strength was 22.16±2.54 mN leading to high bolus velocity and kinetic energy (**Figure 5**).

Frail elderly patients: a) Overall duration of swallow response was 0.985**±**0.037 seconds, significantly longer than in HV (p<0.001). The reconfiguration phase to a digestive pathway was also severely delayed in comparison to HV as time to close LV in FEP was 0.392±0.040 seconds (p<0.001), and time to UES opening was 0.384**±**0.032 seconds (p<0.001 vs HV). Time to LVC in frail elderly patients with penetration or aspiration was significantly longer than that of elderly patients with safe swallow (**Figure 3**). Time to LVC and UESO was also significantly delayed in FEP with impaired efficacy when compared with patients without residue (**Figure 3**). b) The profile of vertical hyoid motion of FEP differed from healthy volunteers (p=0.001, **Figure 4A**) as maximal vertical hyoid motion was significantly delayed (0.480±0.055 seconds, p=0.022) in FEP. Among FEP, patients with impaired safety reached the maximal vertical extension later than patients with safe swallow, although these differences did not reach statistical significance in our study (**Figure 4A**); and time to maximal hyoid vertical movement was significantly prolonged in FEP with impaired efficacy, when compared with patients without residue (**Figure 4A**). In contrast, the profile of anterior hyoid motion of FEP was similar to that observed in HV (**Figure 4B**) and FEP achieved the maximal anterior extension in similar time (0.557±0.040 seconds, ns). Anterior hyoid movement was also similar among FEP with impaired safety or efficacy of swallow (**Figure 4B**).

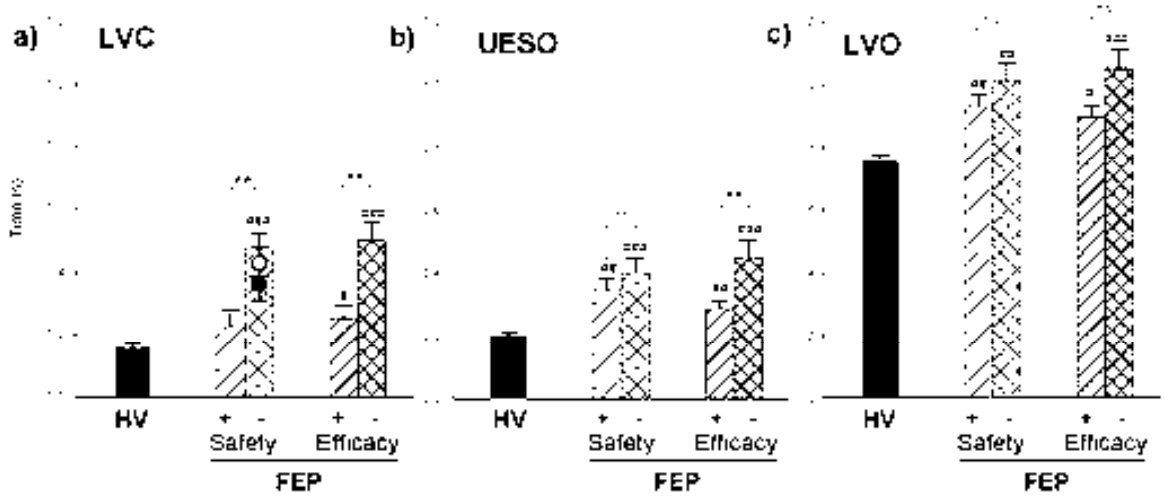

Figure 3 Timing of main events of the oropharyngeal swallow response during 5 mL-nectar swallows in healthy volunteers (HV) and frail elderly patients (FEP) with dysphagia. Patients were stratified according the safety and efficacy of swallow. a) LVC: Laryngeal vestibule closure; b) UESO: Upper esophageal sphincter opening; c) LVO: Laryngeal vestibule opening; Safety + = safe swallow; Safety - = penetration or aspiration; Efficacy + = no oropharyngeal residue; Efficacy -: oropharyngeal residue. Open and full circles show aspiration and penetration times respectively. In HV and patients with safe swallow LVC preceded UES opening but this response was severely impaired in elderly patients with aspirations or penetrations, in whom LVC was delayed until after UESO. * p<0.05, ** p<0.01, *** p<0.001, # p<0.05 vs HV, ## p<0.01 vs HV, ### p<0.001 vs HV, ns: non significant.

c) The extent of the upper esophageal sphincter opening in FEP was 5.40±0.22 mm, also similar to that of HV (p=0.286). d) Frail elderly patients presented weak tongue propulsion strength (8.99±1.09 mN, p<0.001 vs HV), leading to slow bolus velocity (0.409±0.027 m/s, p<0.001) and weak kinetic energy (0.577±0.072 mJ, p<0.001). FEP with safe swallow presented similar bolus propulsion strength and similar mean and maximum bolus velocity and kinetic energy than elderly patients with penetration or aspirations (**Figure 5**). In contrast, patients with oropharyngeal residue presented weaker bolus propulsion forces and slower bolus velocity than elderly patients without oropharyngeal residue (**Figure 5**).

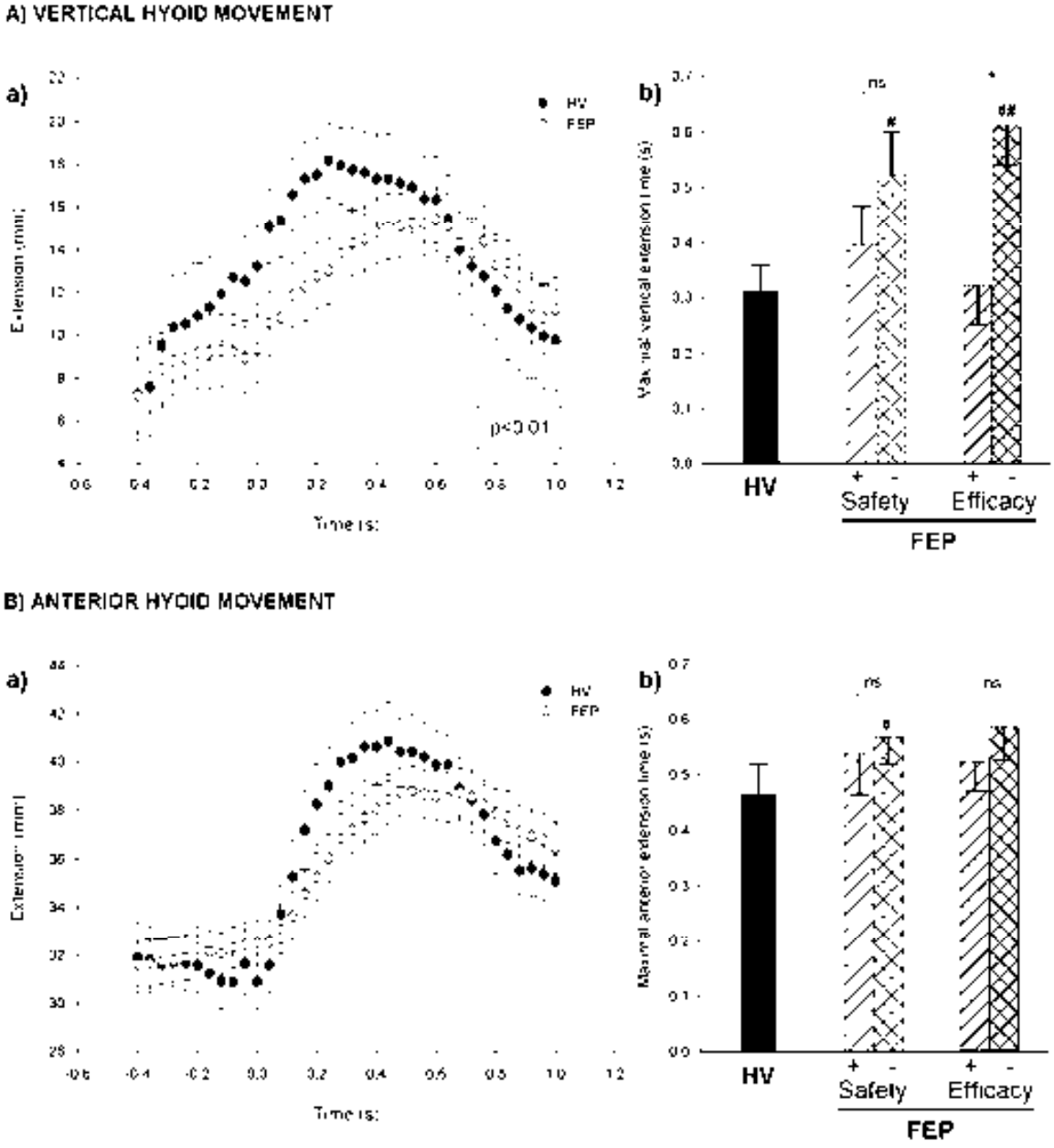

Figure 4 Vertical and anterior hyoid movement: a) Profiles of vertical (A) and anterior (B) hyoid movement in healthy volunteers (HV) and frail elderly patients (FEP) with dysphagia compared by two-way ANOVA analysis. b) Time of maximal vertical (A) and anterior (B) extent of hyoid in HV and FEP with dysphagia stratified according the safety and efficacy of swallow. * p<0.05, # p<0.05 vs HV, ## p<0.01 vs HV, ns: non significant.

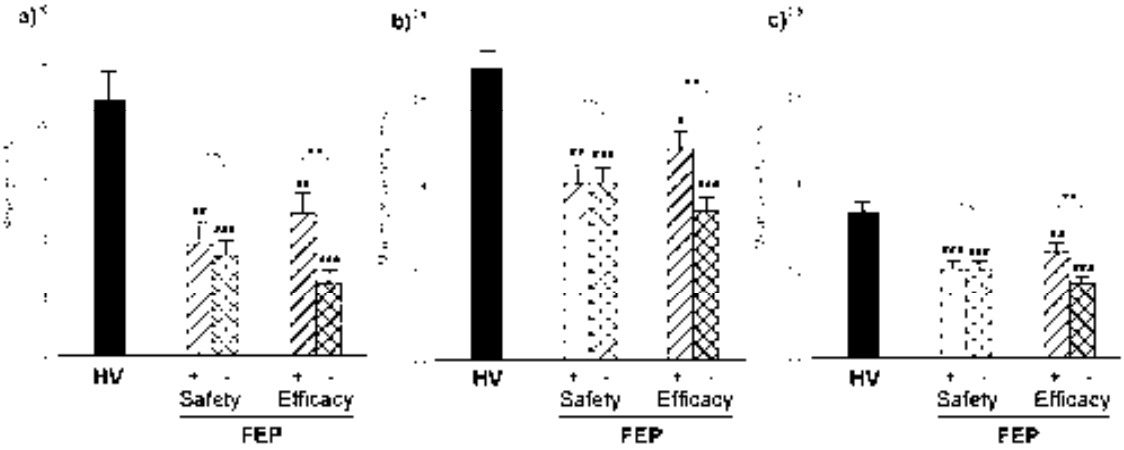

Figure 5 Bolus strength and maximal and mean bolus velocity in healthy volunteers and elderly patients classified according to safety and efficacy of swallowing. HV: healthy volunteers; FEP: Frail elderly patients; Safety + = safe swallow; Safety - = penetration or aspiration; Efficacy + = no oropharyngeal residue; Efficacy -: oropharyngeal residue. * p<0.05, ** p<0.01, *** p<0.001, # p<0.05 vs HV, ## p<0.01 vs HV, ### p<0.001 vs HV, ns: non significant.

Discussion

Our study shows that frail elderly patients admitted to a General Hospital for an acute disease showing clinical complaints of oropharyngeal dysphagia present severe videofluoroscopic signs of impaired safety and efficacy of swallow and are at high risk of respiratory complications and/or malnutrition and show poor survival. Oropharygeal dysphagia is associated to delayed and prolonged swallow response, weak tongue thrust and impaired hyoid motion. Aspirations and penetrations into the airways are specifically related to delayed laryngeal vestibule closure. Impaired efficacy is mainly characterized by oropharyngeal residue caused by weak tongue bolus propulsion forces and slow vertical hyoid motion. We found enhancing bolus viscosity greatly increased safety of oral and pharyngeal phases of swallowing in FEP; in contrast, increasing bolus volume severely impaired efficacy of deglutition in these patients. These results agree with our previous studies (10;13) and we believe oropharyngeal dysphagia should be recognized as a major geriatric syndrome and treatment should be targeted to improve these critical physiological events.

Oropharyngeal dysphagia is a severe clinical symptom in elderly patients. We used a validated index based on mechanical dysfunction (18) and found that symptomatic severity of dysphagia in FEP was similar to dysphagia associated with neurodegenerative diseases and more severe than dysphagia caused by a stroke (10). In contrast, oropharyngeal dysphagia is underestimated as a cause of symptoms and nutritional and respiratory complications in the elderly. Frailty is a biologic syndrome of decreased resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes including institutionalization, hospitalization, and death (6). Patients included in the present study fulfil the criteria of a validated and standardized phenotype of frailty in older adults with predictive validity for these adverse outcomes (17). Once oropharyngeal dysphagia was diagnosed in these frail elderly patients, our goal was to evaluate: a) *swallowing efficacy,* to ensure patients' ability to ingest all the calories and water he or she needs, and b) *swallowing safety,* to avoid respiratory complications. By VFS, we found serious swallowing and cough reflex disorders in this group of FEP as more than half presented penetrations of ingested material into the laryngeal vestibule or aspirations beyond the vocal folds during the swallow response, many of them being silent due to simultaneous impairment of cough reflex (22). In addition, VFS signs of inefficient swallow showing impaired bolus control or weak tongue propulsion and leading to oropharyngeal residue were observed in up to two thirds of our FEP. Again, the

prevalence and severity of VFS signs of impaired safety or efficacy of swallow exceeded those we found in patients with oropharyngeal dysphagia secondary to stroke and neurodegenerative diseases (10). Two thirds of our patients were at risk of malnutrition and the 1-year survival of our patients with impaired safety or efficacy of swallow was very poor. Aspiration pneumonia and malnutrition are two well-recognized complications of oropharyngeal dysphagia in the elderly (23). In a previous study, we found a 55% prevalence of clinical signs of aspiration in elderly patients with pneumonia, dysphagia being a marker of disease severity and poor prognosis and an independent factor strongly associated with 1-year mortality (7). However, dysphagia with oropharyngeal aspiration is rarely considered a risk factor in elderly patients with community-acquired pneumonia (14;15) or in elderly patients with malnutrition (16).

The swallow response includes the arrangement of oropharyngeal structures from a respiratory to a digestive pathway, the transfer of the bolus from the mouth to the oesophagus, and the recuperation of the respiratory configuration (16). Transference of the bolus is mainly caused by the squeezing action of the tongue against the palate providing driving forces to propel swallowed material (24), and the pharyngeal contraction by the pharyngeal constrictor muscles facilitates pharyngeal clearance (25). We found the swallow response was severely impaired in FEP. First, overall duration of swallow response was significantly prolonged. Impaired safety is mainly associated with the delayed LVC. LVC occurs by anterior tilting of the arytenoid cartilages against the base of the epiglottis and by the descent of the epiglottis as a result of a hyolaryngeal elevation (11). Time to LVC is the time interval during which the potential aspiration occurs and is the key abnormality of oropharyngeal swallow response leading to unsafe deglutition in our elderly patients, in agreement with our previous studies (10;13) and an early study by Kahrilas that found that interval from GPJO-LVC leads to unsafe deglutition in neurological patients (9). Other studies have also shown that the strongest predictor of aspiration was the delay to hyoid elevation, as delayed hyoid movement contributes to delayed laryngeal closure (10). Vertical hyoid movement is mainly the result of suprahyoid and thyrohyoid muscle contraction and we found that FEP have a poor and delayed vertical hyoid movement; in contrast the anterior hyoid motion was similar to that of HV. UES opening is caused by interruption of vagally-mediated contraction of cricopharyngeus muscle, anterior hyoid movement (11), and intrabolus pressure caused by tongue thrust (25;26). Our study shows that delayed UES opening is associated with residue in FEP. A recent study has also shown failed UES opening causes residue and postswallow aspiration in elderly patients with neurogenic dysphagia (21). However, in the present study, most aspirations occured during swallow response and are mainly associated with delayed LVC, suggesting that postswallow residue is not a main cause of impaired safety of swallow in FEP. Finally, low bolus propulsion forces leading to slower bolus velocity caused oropharyngeal residue in FEP. In contrast, aspirations and safety of deglutition were not related to tongue strength, showing specific and independent mechanisms for impaired safety and efficacy of swallow in FEP.

Impaired swallow response in the frail elderly might be caused by neurogenic and myogenic factors. Studies in healthy people over 80 years of age found normal aging delays and prolonged swallow response and increased oropharyngeal residue (27-29). Delayed swallow response has been attributed to impaired function of peripheral afferents to the swallowing centre and slow synaptic conduction in the central nervous system caused by high prevalence of neurological and neurodegenerative diseases in the frail elderly as well as the neurodegenerative process related to ageing (30). Drugs with detrimental effects on consciousness or swallow response can also contribute to delayed swallow response (7). On the other hand, weak muscular tongue strength caused by sarcopenia is the major contributor to impaired bolus propulsion (5). All these pathophysiological factors causing dysphagia in the frail elderly can be potentially treated: a) stimulation of TRPV1 receptors located in afferent sensory fibres from the larynx (superior laryngeal nerve) or the pharynx (pharyngeal branch of the glossopharyngeal nerve) by acid, thermal stimulation or specific TRPV1 agonists might speed the neural swallow responses (31-35); b) rehabilitation by lingual resistance exercises is an effective treatment for patients with lingual

weakness and dysphagia due to frailty (36); and c) the classical suprahyoid exercise program (Shaker manoeuvre) improves hyoid motion and UES opening (21) and electrical stimulation of suprahyoid muscles also showed hyoid and laryngeal elevation can be improved (37). Finally, increasing bolus viscosity in our study improved VFS signs of safety and efficacy of swallow in elderly patients (10). Taken together, all these observations suggest that oropharyngeal dysphagia in the frail elderly can be treated by using these individual or combined therapeutic strategies. There is a big discrepancy between the high prevalence, morbidity, mortality and costs caused by nutritional and respiratory complications of oropharyngeal dysphagia in frail elderly and the low level of resources dedicated to assess and treat dysphagia in these patients. In the present study we have explored the specific pathophysiology of dysphagia in FEP patients suggesting potential therapeutic options. We believe oropharyngeal dysphagia fulfils most criteria to be recognized as a major geriatric syndrome as its prevalence is very high in geriatric people, it results in multiple diseases, risk factors and precipitating diseases in frail older patients and represents a specific target for therapeutic interventions (4;38).

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CAPÍTULO 3

Capítulo 3

OROPHARYNGEAL DYSPHAGIA IS A RISK FACTOR FOR COMMUNITY-ACQUIRED PNEUMONIA IN THE ELDERLY

Jordi Almirall*, Laia Rofes*, Mateu Serra-Prat, Roser Icart, Elisabet Palomera, Viridiana Arreola, Pere Clavé. *Oropharyngeal dysphagia is a risk factor for community-acquired pneumonia in the elderly*. Eur Respir J 2013; 41(4): 923-8. *Co-first authors.

Abstract

Objective: To explore whether oropharyngeal dysphagia is a risk factor for community-acquired pneumonia in the elderly and to assess the physiology of deglutition of patients with pneumonia.

Methods: Case-control study: 36 elderly patients (>70 years) hospitalized with pneumonia were matched by age and sex with two independently-living controls. All subjects were given the volume-viscosity swallow test to identify signs of oropharyngeal dysphagia. Pathophysiological study: All cases and 10 healthy elderly were examined with videofluoroscopy.

Results: Case-control study: Prevalence of oropharyngeal dysphagia was 91.7% in cases and 40.3% in controls ($p<0.001$). Adjusting for functionality and co-morbidities, dysphagia showed an independent effect on pneumonia (OR=11.9, 95% CI:3.03-46.9). Pathophysiological study: Among cases, 16.7% showed safe swallow, 30.6% high penetrations, 36.1% severe penetrations and 16.7% silent aspirations during videofluoroscopy, while in the healthy elderly these percentages were 80.0%, 20.0%, 0% and 0%, respectively ($p<0.001$). A delay in the laryngeal vestibule closure (0.414±0.029s vs 0.200±0.059s, $p<0.01$) was the main mechanism of impaired airway protection.

Conclusions: In elderly subjects, oropharyngeal dysphagia is strongly associated with community-acquired pneumonia independently of functionality and co-morbidities. Elderly patients with pneumonia presented a severe impairment of swallow and airway protection mechanisms. We recommend universal screening of dysphagia in older persons with pneumonia.

Introduction

Community-acquired pneumonia (CAP) is a common disease and a frequent cause of hospitalization and death among the elderly[1]. According to population-based studies, the annual incidence rate of CAP in adults varies between 2.6 and 13.4 per 1,000 inhabitants, somewhat higher in elderly people[2;3]. Studies found old age as a relevant risk factor for the acquisition of pneumonia[4]. Other associated factors that predispose to CAP in the elderly include: lifestyle and patient characteristics such as smoking, alcohol use, poor functional and nutritional status, weight loss and use of immunosuppressants; co-morbidities such as heart diseases, renal diseases and chronic obstructive pulmonary disease; and environmental exposure such as secondhand smoke, gases, fumes and chemicals[5-7].

We recently found oropharyngeal dysphagia was also a highly prevalent clinical finding in up to 23% of independently living older (>70 y) persons, 0.74% of them presenting signs of aspiration during swallow[8]. In these patients with oropharyngeal dysphagia, a decrease in the efficacy of deglutition was associated with development of malnutrition and a decrease in the safety was associated with high prevalence of respiratory infections during follow up[9]. Oropharyngeal dysphagia has been identified as a serious risk factor for developing aspiration pneumonia in frail older people[10]. The pathogenesis of aspiration pneumonia in immunocompetent adults has been attributed to pharyngeal colonization of respiratory pathogens

and subsequent inhalation of infectious particles[11]. Oropharyngeal dysphagia has also been proposed as an independent risk factor associated with CAP in the elderly[6;12;13] but this has not yet been proved. Moreover, the pathogenic mechanism that leads to oropharyngeal dysphagia in the frail elderly and in neurological patients has been identified in recent years[14;15]. In contrast, the pathophysiology of impaired swallow response of elderly people with pneumonia has not yet been studied.

The present study has two main objectives: i) to provide further evidence of the association between oropharyngeal dysphagia and CAP in the elderly and ii) to assess the pathophysiology of oropharyngeal dysphagia in elderly subjects with CAP.

Materials and Methods

Case-control study

An observational case-control study was designed. The study protocol was approved by the Ethics Committee of Consorci Sanitari del Maresme (Mataró, Spain). Cases were defined as subjects ≥70 years with confirmed CAP that required hospitalization in the Hospital of Mataró from February 2008 to February 2010 and were consecutively included in the study as long as videofluoroscopic examination was available. We have described the criteria for the diagnosis of CAP previously[2]. Patients from nursing homes or those that had been discharged from hospital 7 or fewer days before the onset of symptoms were excluded. For each case, two matched (by sex and age) controls without CAP were randomly selected from the list of independently-living older subjects assigned to the Cirera-Molins Primary Care Centre in Mataró (Spain). All cases and controls were explored by the volume-viscosity swallow test (see the on-line supplementary material) to assess the clinical signs for oropharyngeal dysphagia and impaired efficacy and safety of swallow. Co-morbidities and pre-admission functional capacity were also registered for all participants.

Pathophysiological study

a) Clinical characteristics of pneumonia and concomitant medications were collected in all cases. Vaccination history, number of previous pneumonias, fever, days of clinical symptoms, lobes affected, severity of CAP[16], Intensive Care Unit admissions and hospital death were recorded. To determine the etiology of pneumonia, blood cultures (n=30) and urine antigen tests for *S. pneumoniae* (n=30) and *L. pneumophila* (n=33) were performed. Whenever possible, respiratory samples were also obtained: sputum (n=9), tracheal aspirate (n=1) and pleural fluid (n=2). A sublingual smear (n=29) was also obtained to assess the oral flora. b) 10 healthy elderly persons (≥70 years) and all patients with CAP were studied by videofluoroscopy during the admission. Details on the videofluorscopic procedures are provided in the online supplementary material. Digitization and analysis of videofluoroscopic images were made using the software Swallowing Observer (Image and Physiology SL, Barcelona, Spain). Laryngeal vestibule penetrations and tracheobronchial aspirations were classified according to a validated scale[17] and oropharyngeal residue was also identified. Timing of the oropharyngeal swallow response, hyoid bone movement and bolus velocity ($m\ s^{-1}$) were also measured[14]. c) CAP patients were followed through the electronic clinical records of the hospital of Mataró for one year or contacted by telephone one year after discharge in order to register death or readmissions caused by lower respiratory tract infections. If telephone contact could not be made, patients' family doctors were contacted.

Statistical analysis

Categorical variables were described as percentages and compared by the Chi-square test or the Fisher exact test when appropriate. Quantitative variables were described as mean±SEM and compared by the Mann–Whitney U-test. As a measure of association between oropharyngeal dysphagia, impaired efficacy and safety of swallow and pneumonia, estimations of the relative risk through odds ratios (OR) and 95% confidence intervals (CI) were calculated. The effect of oropharyngeal dysphagia and impaired safety

and efficacy of swallow on the risk of the development of CAP was adjusted by co-morbidities and pre-admission functional capacity in a multivariate model using logistic regression. Survival curves according to safety of swallow were compared using a Log rank test. Statistical significance was accepted if P values were less than 0.05. Statistical analysis was performed using SPSS 15.0 (SPSS Inc., Chicago, USA).

Results

Case-control study

45 cases with CAP were screened during the study period and 9 cases were excluded because patients were discharged before the videofluoroscopic examination was available. 36 cases with CAP (81.22±0.77 years, 24 men) were finally included in the study and matched with 72 controls (81.21±0.53 years, 48 men). The univariate analysis showed that the prevalence of oropharyngeal dysphagia and clinical signs of impaired efficacy and safety of swallow were higher in cases than in controls (**Table 1**). Cases also presented lower functional capacity than controls according to the Barthel Index (67.1 vs 97.4, p<0.001) and higher prevalence of chronic bronchitis/chronic obstructive pulmonary disease (COPD) and chronic heart failure. A multivariate logistic regression analysis showed an independent effect of oropharyngeal dysphagia related to the development of CAP when adjusting for suboptimal Barthel Index scores (<100), chronic bronchitis/COPD and chronic heart failure (**Table 2**).

Table 1. Univariate analysis of risk factors associated with pneumonia in the elderly. Data presented as number of cases (percentage). COPD indicates chronic obstructive pulmonary disease; OR, Odds Ratio; CI, confidence interval.

	Cases (N=36)	*Controls (N=72)*	*P value*	*OR*	*95% CI*
Barthel Index (<100)	25 (69.4%)	18 (25.0%)	<0.001	6.82	2.81-16.6
COPD/Chronic bronchitis	18 (50%)	20 (27.8%)	0.023	2.60	1.13-5.98
Chronic heart failure	16 (44.4%)	15 (21.1%)	0.012	2.99	1.25-7.13
Benzodiazepine use	10 (27.8%)	16 (22.2 %)	0.254	1.34	0.54-3.37
Oropharyngeal dysphagia	33 (91.7%)	29 (40.3%)	<0.001	16.3	4.57-58.2
Safety impairment	22 (61.1%)	18 (25.0%)	<0.001	4.71	2.00-11.1
Efficacy impairment	30 (83.3%)	24 (33.3%)	<0.001	10.0	3.66-27.3

Table 2. Multivariate logistic regression analysis of risk factors associated with pneumonia in the elderly. COPD indicates chronic obstructive pulmonary disease; OR, Odds Ratio; CI, confidence interval.

	P value	*OR*	*95% CI*
Barthel Index (<100)	0.001	6.93	2.13 -22.5
COPD/Chronic bronchitis	0.032	3.80	1.12 -12.9
Chronic heart failure	0.184	2.19	0.69 -6.95
Oropharyngeal dysphagia	<0.001	11.9	3.03 -46.9

Pathophysiological study

a) General characteristics and etiology of pneumonia. General features of patients with pneumonia are described in **Table 3**. Most of them were treated with corticosteroids (55.6%) and beta(2)-agonists (55.6%); 15 (41.7%) received proton-pump inhibitors; 13, diuretics (36.1%) and 12, ACE inhibitors (33.3%). Patients that received SNC-acting drugs were: 10, (27.8%) benzodiazepines; 6, (16.7%) antidepressants; 3, (8.3%) neuroleptics and 3, (8.3%) antiparkinsonians. The aetiological diagnosis of pneumonia was achieved in 20 patients (55.6%). Streptococcus pneumoniae was found in 17 (47.2%), of whom 9 (52.9%) presented impaired safety of swallow and 8 (47.1%) presented safe swallow. Pseudomonas aeruginosa (2.8%), Klebsiella penumoniae (2.8%) and a co-infection of Pseudomonas aeruginosa and Klebsiella penumoniae (2.8%) were also found as etiologic agents in patients with impaired safety of swallow. On the other hand, normal oral flora was found in 69.0% of oral smears. Candida albicans (8.3%), Pseudomonas aeruginosa (8.3%), Klebsiella penumoniae (2.8%) and Streptococcus agalactiae (2.8%) were the pathogens isolated from patients' oral cavity.

Table 3. Clinical characteristics of patients. Data presented as number of cases (percentage), except *mean (SD). RUL, right upper lobe; RLL, right lower lobe; ML, middle lobe; LUL, left upper lobe; LLL, left lower lobe; PSI, pneumonia severity index; ICU, intensive care unit.

		N=36
Influenza vaccination		20 (55.6%)
Pneumococcal vaccination		5 (13.9%)
Number of previous pneumonias:	**0**	25 (69.4%)
	1	8 (22.2%)
	≥2	3 (8.3%)
Body temperature <37º		11 (30.6%)
Days of clinical symptoms*		3.9 (3.6)
Lung location:	**RUL**	14 (38.9%)
	RLL	11 (30.6%)
	ML	3 (8.3%)
	LUL	3 (8.3%)
	LLL	11 (30.6%)
Number of affected lobes ≥2		6 (16.7%)
PSI:	**I**	0
	II	0
	III	8 (22.2%)
	IV	21 (58.3%)
	V	7 (19.4%)
CRB-65*		2.0 (0.9)
ICU admission		7 (19.4%)
Hospital death		3 (9.7%)

b) Videofluoroscopic study. Efficacious swallows without any residue during all series of the videofluoroscopic study were observed in 60% of healthy elderly persons (75.80±0.97 years, 70% men) and in 41.67% of elderly patients with CAP (p=0.066) (**Figure 1**). Safe swallows (score 1 on the penetration-aspiration scale) were observed in 80% of healthy elderly persons, and high penetrations into the laryngeal vestibule (score 2) in 20%. In contrast, 16.7% of elderly patients with CAP showed safe swallow (p<0.001), 30.6% presented high penetrations, 36.1% severe penetrations into the laryngeal vestibule (not ejected from the airways and/or contacting the vocal folds, scores 3-5) and 16.7% silent aspirations (score 8) (**Figure 1**). General prevalence of oropharyngeal dysphagia among CAP patients according to the videofluoroscopic study was 75.0%. In healthy elderly, total duration of swallow response (time from glossopalatal junction opening to laryngeal vestibule opening) for 5 mL nectar boluses was 0.888±0.042 s, the interval for oropharyngeal reconfiguration from a respiratory to a digestive pathway (time to laryngeal vestibule closure) was 0.240±0.039, and timing of upper esophageal sphincter opening was 0.276±0.039 s. Elderly patients with CAP showed similar duration of swallow response (1.00±0.042 s, p=0.241) and time to upper esophageal sphincter opening (0.333±0.025 s, p=0.178) as healthy elderly persons, but a significant delay in laryngeal vestibule closure (0.414±0.029 s, p=0.002). When comparing elderly patients with CAP according to the safety of swallow, patients with safe swallow (scores 1-2 on the penetration-aspiration scale) showed a significantly shorter laryngeal vestibule closure time than patients with impaired safety of swallow (scores 3-8) (**Figure 2**). In contrast, no differences were found in the timing of upper esophageal sphincter opening (0.287±0.024 s and 0.375±0.040 s respectively, p=0.144) or the total duration of swallow response (0.948±0.039 s and 1.05±0.071 s respectively, p=0.437). Regarding hyoid bone movement, healthy elderly persons achieved maximal vertical extension in 0.314±0.041 s and maximal anterior extension in 0.349±0.058 s. Elderly patients with CAP reached maximal vertical and anterior extension significantly later (0.437±0.039 s and 0.549±0.040 s, p<0.05). CAP patients with impaired safety of swallow also

achieved maximal vertical extension later than CAP patients with safe swallow (**Figure 3**). Maximal vertical and anterior hyoid displacement was similar among groups (data not shown). Finally, the maximal velocity acquired by the bolus at the upper esophageal sphincter was very similar between healthy elderly (0.481±0.073 m s^{-1}) and elderly patients with CAP (0.482±0.035 m s^{-1}, p=0.946) and was not affected by impairment in the safety of swallow.

c) 1-year follow up. CAP patients with impaired safety of swallow showed decreased survival rates compared to patients with safe swallow 1 year after admission (Figure 4). Up to 50.00% of CAP patients with safe swallow and 71.43% with impaired safety of swallow (p=0.201) were readmitted during the follow up with lower respiratory tract infections.

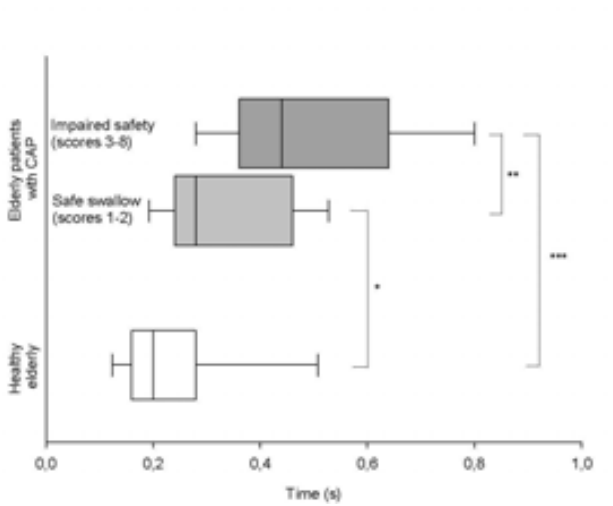
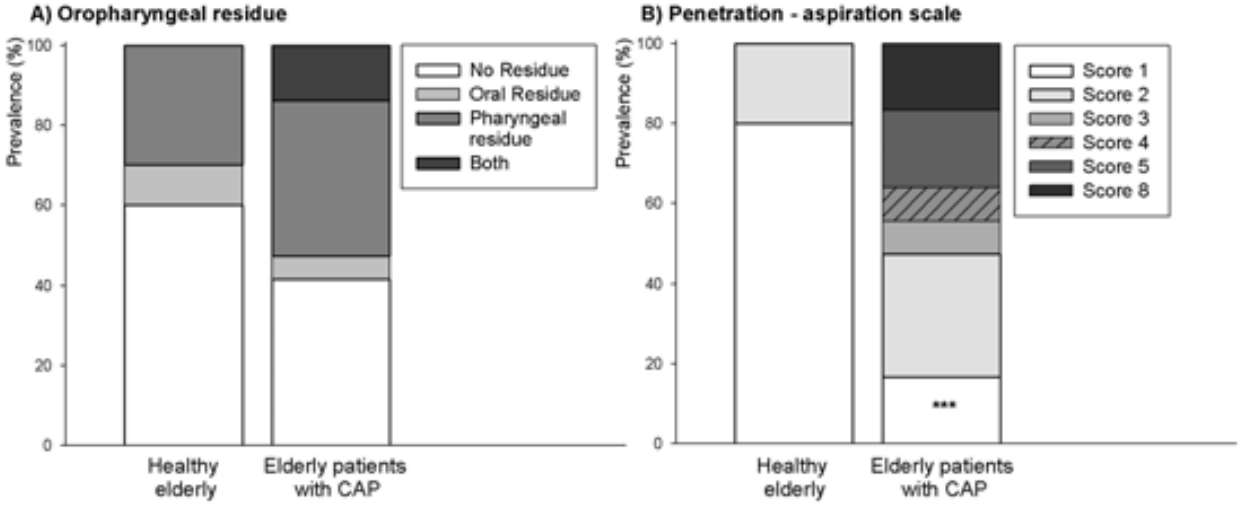


Figure 2. Laryngeal vestibule closure time. Patients with CAP were divided into patients with safe swallow (scores 1-2) and patients with impaired safety of swallow (scores 3-8). Each box plot graphs the median, 10th, 25th, 75th and 90th percentiles. *p<0.05, **p<0.01, ***p<0.001.

Figure 1. Prevalence of main videofluoroscopic signs of efficacy (A) and safety (B) of swallow. Prevalence is expressed as number of subjects with sign presence versus total number of subjects. ***p<0.001.



Discussion

The most remarkable finding of our study was that oropharyngeal dysphagia is strongly associated with CAP and should be considered as an independent risk factor for CAP in the elderly. The clinical assessment of oropharyngeal dysphagia showed that prevalence of dysphagia and impaired efficacy and safety of swallow among elderly patients with CAP was very high compared to matched controls. These clinical results were confirmed by the gold standard for swallowing evaluation, videofluoroscopy. The videfluoroscopic study showed that 52.8% of elderly patients with CAP presented severe penetrations or aspirations during swallow. We also observed a high prevalence of oropharyngeal residue in these patients. Oropharyngeal residue is also an important finding, as it can predispose to oral colonization and post-swallow aspirations[18]. Finally, the oropharyngeal swallow response was severely impaired in our elderly patients with CAP. A severe delay in the oropharyngeal reconfiguration from a respiratory phase to a digestive phase, caused by slow laryngeal vestibule closure and

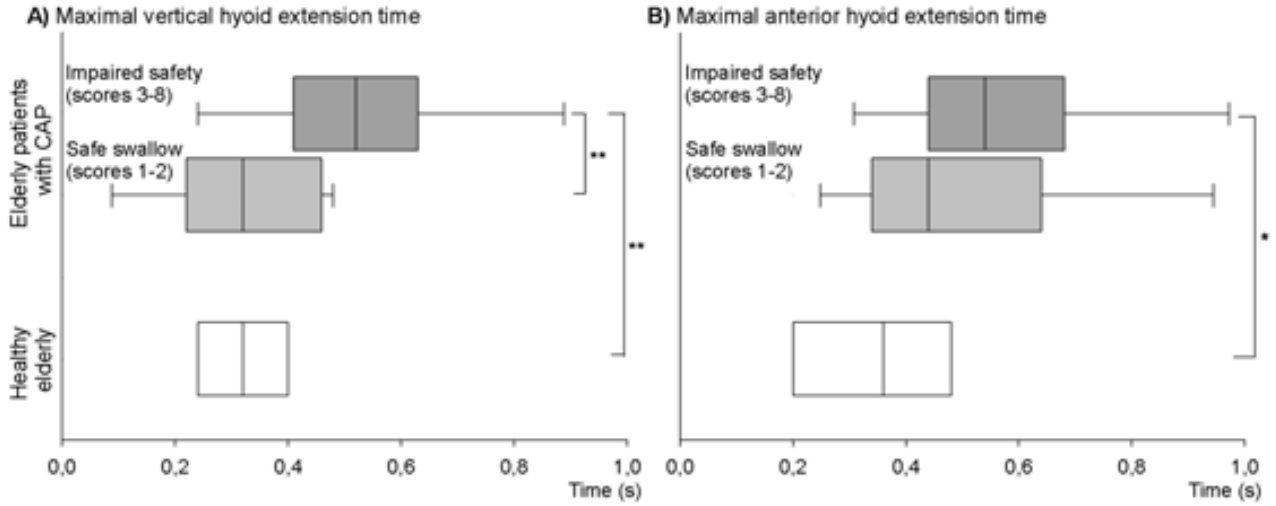


Figure 3. Hyoid movement. Time of maximal hyoid vertical (A) and anterior (B) extension of healthy elderly and patients with CAP divided into patients with safe swallow (scores 1-2) and patients with impaired safety of swallow (scores 3-8). Each box plot graphs the median, 10th, 25th, 75th and 90th percentiles. *p<0.05, **p<0.01.

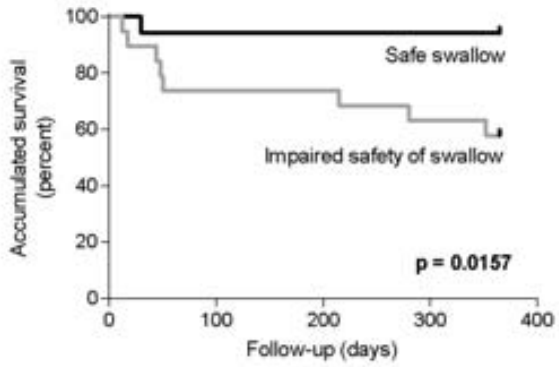


Figure 4. Survival curves. Accumulated survivals of patients with CAP at 1 year according to the impairment of swallow (safe swallow, scores 1-2 and impaired safety of swallow, scores 3-8).

vertical hyoid motion, was the key parameter associated with impaired safety of swallow. Diagnostic etiology of pneumonia was achieved in half the cases. All patients with CAP and safe swallow presented *Streptococcus pneumoniae* as the etiologic agent of pneumonia. Most patients with impaired safety of swallow also presented *Streptococcus pneumoniae* as the etiologic agent, followed by Gram-negative bacilli. Taken together, our data strongly suggests that aspiration among patients with CAP is much more common than was believed and is a relevant pathogenic mechanism for older patients with pneumococcal CAP as well as for those with Gram-negative pneumonia.

Some studies have discussed the importance of aspiration and swallowing impairment in developing CAP[6;12] in elderly patients but, as far as we know, the present study is the first that evaluates the specific role of dysphagia as a predisposing and prognostic factor for CAP in the elderly and that assesses the mechanisms of the impaired swallow response of elderly patients with CAP. Moreover, the assessment of dysphagia was made prospectively, both in cases and controls. The prospective evaluation of dysphagia is a relevant point because dysphagia is often underdiagnosed and several cases may be missed in clinical records. We used an accurate and validated clinical method for the clinical assessment of dysphagia, the volume-viscosity swallow test, and found that not only impaired safety of swallow is associated with CAP, but impaired efficacy of swallow is also a risk factor for CAP in the elderly. In healthy people, the effective clearance of most of pathogens from the oropharynx is due to effective salivary flow and efficient swallowing. Therefore, when the efficacy of swallow is impaired, a reduction in mechanical clearance occurs leading to oropharyngal residue, and potential pulmonary or oropharyngeal pathogens may colonize the oropharynx and be a potential source of pulmonary infections[19]. Teramoto *et al*[20] reported that the prevalence of aspiration pneumonia in patients with CAP aged 70 and older was 60.1% using a wide variety of clinical assessment methods. We found a prevalence of

oropharyngeal dysphagia among patients with CAP of 91.7% by means of the volume-viscosity swallow test and of 75.00% in the videofluoroscopic study, with 52.8% the patients having severe penetrations or aspirations during swallow. This is the first time, to the authors' knowledge, that a gold standard, videofluoroscopy, has been used to assess the prevalence of aspiration during swallow in elderly patients admitted with CAP. Prevalence of silent aspirations in our study was 16.7%. A previous study, using a radioactive tracer, found that the occurrence of silent aspiration during sleep was 71% in CAP patients whereas only 10% of aged matched controls aspirated[21]. The aspiration of small amounts of oropharyngeal secretions during sleep is a common finding in older adults[22;23] and usually happen without consequences due to preserved cough reflex, ciliary transport and immune system and to the low virulence of normal pharyngeal flora. However silent aspiration of large amounts during swallowing is an abnormal and serious finding that, together with several factors common in the elderly such as progressive decrease in pulmonary function, decline in host defenses, impaired cough reflex and increased oropharyngeal colonization with respiratory pathogens[19], can lead to aspiration pneumonia. A key point of our study is that we elucidated the pathogenic mechanism of the aspiration process and impaired airway protection of patients with CAP through videofluoroscopy. Delayed airway protection caused by delayed laryngeal vestibule closure and vertical hyoid movement caused the aspirations and penetrations in elderly CAP patients. This impairment in swallow response is similar to that found in frail elderly patients[14] and patients with neurological diseases[15] and must be treated.

Our results show that impaired safety of swallow is a prognostic factor of mortality in elderly patients with CAP. These results agree with that found by Riquelme *et al*[12] and with one of our previous studies in patients with pneumonia admitted to an acute geriatric unit[24]. Again, use of the videofluoroscopy to determine patients with a predisposition to aspiration improves the diagnosis of aspiration pneumonia and confirms the results found by these previous studies using clinical records or clinical methods of screening.

A limitation of our study is that swallowing ability was not re-evaluated after discharge to assess whether these patients had improved after the acute condition and also those who had deteriorated over time. Therefore our design cannot exclude CAP as the cause of the swallowing problem. Another limitation was the small sample size. It was large enough to determine dysphagia as a risk factor for CAP, to characterize the swallow response of CAP patients and to evaluate the impairment of swallow response as a prognostic factor. However, the small size limits the microbiological and clinical comparisons between CAP patients with and without oropharyngeal dysphagia. Further studies are needed in this area including the assessment of the oral health status and the use of molecular strategies to improve the assessment of the oral microbiota in these patients. On the other hand, although cases and controls were matched by age and sex, they could not be strictly comparable in terms of co-morbidities, functional capacity or frailty. However, the multivariate analysis adjusted for the mentioned factors showed an independent effect of oropharyngeal dysphagia.

In summary, we have confirmed that oropharyngeal dysphagia is a major risk and prognostic factor for CAP in the elderly. We have established its high prevalence by means of a gold standard and determined that the pathogenic mechanism of impairment of swallow response in this cohort of patients with CAP was delayed airway protection. Therefore, we propose universal screening for oropharyngeal dysphagia in elderly patients admitted with CAP and the adoption of strategies to assess and treat oropharyngeal dysphagia when aspiration is suspected.

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CAPÍTULO 4

Capítulo 4

THE EFFECTS OF A XANTHAN GUM-BASED THICKENER ON THE SWALLOWING FUNCTION OF PATIENTS WITH DYSPHAGIA

Laia Rofes, Viridiana Arreola, Rajat Mukherjee, Julie Swanson, Pere Clavé. *The effects of a xanthan gum-based thickener on the swallowing function of patients with dysphagia*. Aliment Pharmacol Ther 2014; In press. doi: 10.1111/apt.12696

Abstract

Background: Increasing bolus viscosity of thin liquids is a basic therapeutic strategy to protect patients with oropharyngeal dysphagia (OD) from aspiration. However, conventional starch thickeners increase post-deglutitive residue. The aim of the study was to assess the therapeutic effect of a new xanthan gum-based thickener, Resource ThickenUp Clear (RTUC) (Nestlé Health Science, Vevey, Switzerland) on patients with OD.

Methods: We studied the effect of RTUC using a clinical method and videofluoroscopy (VFS) on 120 patients with OD (66 with stroke, 41 older and 13 with neurodegenerative diseases) and 14 healthy volunteers while swallowing thin liquid, nectar-like, and spoon-thick boluses. We assessed the prevalence of signs of impaired safety and efficacy of swallow and the physiology of the swallow response.

Results: Increasing bolus viscosity with RTUC: a) improved safety of swallow demonstrated by a reduction in the prevalence of cough and voice changes in the clinical study and penetrations and aspirations during VFS. Prevalence of aspirations was 12.7% with thin liquid, 7.7% with nectar-like ($P<0.01$) and 3.4% with spoon-thick ($P<0.01$) viscosities. Penetration-Aspiration Scale was reduced from 3.24±0.18 at thin liquid to 2.20±0.18 at nectar-like ($P<0.001$) and to 1.53±0.13 at spoon-thick ($P<0.001$) viscosities; b) did not enhance pharyngeal residue; c) nectar-like viscosity did not affect bolus velocity nor timing of swallow response; and d) spoon-thick viscosity reduced bolus velocity.

Conclusions: RTUC improves the safety of swallow without increasing residue providing a viscosity-dependent therapeutic effect for patients with OD. At nectar viscosity, the effect is due to intrinsic texture properties, spoon-thick viscosity adding changes in swallow physiology.

Introduction

Oropharyngeal dysphagia (OD) is a gastrointestinal motility disorder specifically recognized by the World Health Organization in the International Statistical Classification of Diseases and Related Health Problems ICD-9 and ICD-10 [1]. OD is a highly prevalent clinical condition, present in up to 50% of patients with neurological diseases and in the elderly. Approximately 50-75% of these dysphagic patients present impaired safety of swallow, with bolus penetrations into the laryngeal vestibule and 20-25% tracheobronchial aspirations during swallow response [2]. Delayed laryngeal vestibule (LV) closure is the main mechanism impairing airway protection in patients with neurogenic dysphagia and in the elderly and leads to severe respiratory complications [2]. In stroke patients, OD triplicates the relative risk of pneumonia, which increases to 11 times if the patient presents aspirations [3]. Aspiration pneumonia is associated with a 3-fold increased risk of death compared with stroke patients without pneumonia [4]. In the elderly, OD is also an independent risk factor for the development of lower respiratory tract infections and pneumonia [5-7]. The development of evidence-based treatments that increase safety of swallow and protect patients from aspirations is necessary to avoid respiratory complications and improve morbidity and mortality rates of the dysphagic population [8].

One of the basic compensatory interventions in hospitals and long-term care facilities to increase the safety of swallow and avoid aspirations is to thicken liquids. Viscosity is a rheological property that measures the fluid's internal resistance to flow and the rate of flow per unit of force applied. We have previously described how thickening liquids with starch-based thickeners reduced LV penetrations and tracheobronchial aspirations [9,10] with the consequent reduction in the incidence of aspiration pneumonia rates [11]. It has been proposed that slowing down bolus velocity through the pharynx is the main action mechanism of thickeners to protect against aspirations [12]. However, parallel to its therapeutic effect, enhancing bolus viscosity with starch thickeners increases post-deglutitive oropharyngeal residue, especially in patients with deficient bolus propulsion such as elderly patients and patients with neurodegenerative diseases [2,9,10]. This might increase the risk of post-swallow aspirations [13]. Another disadvantage of starch-based thickened liquids is that they are, in general, not well accepted by patients [14].

A new generation of thickeners based on xanthan gum has recently been developed to improve on the therapeutic performance and sensory attributes of the starched–based thickeners. The xanthan gum-based thickeners retain the clarity of clear liquids, possess amylase resistance to keep bolus viscosity stable during saliva contact, are able to thicken a wide range of liquids at different temperatures and maintain stable viscosity over time [15]. However, their clinical therapeutic effect and their mechanisms of action on patients with OD has not been evaluated yet.

The aim of this study was to assess the therapeutic effect of a xanthan gum-based thickener (Resource ThickenUp Clear, RTUC) on the clinical and videofluoroscopic signs of OD and the swallow function of dysphagic patients to provide research-based clinical practice [16].

Materials and Methods

Study population

120 patients consecutively referred to the Gastrointestinal Physiology Laboratory of the Hospital de Mataró (Spain) for swallowing evaluation, were prospectively included in the study. Inclusion criteria were: age more than 18 years, history of swallowing difficulties associated with aging and/or neurological diseases. Exclusion criteria were: allergy to any medication, major respiratory diseases, surgery in the three months prior to the study, background of alcohol or drug dependence or participation in another clinical trial 4 weeks prior. Healthy volunteers (HV) (N=14) were recruited to explore the effect of the xanthan thickener on normal swallow physiology. All participants were informed about the study and gave written consent. The study protocol was approved by the Institutional Review Board of the Hospital de Mataró and was conducted according to the principles and rules laid down in the Declaration of Helsinki and its subsequent amendments. Trial registration: NCT01158313. Demographic, clinical and nutritional characteristics of the study population, as well as severity of dysphagia symptoms, were also collected in all participants.

Experimental Design

The effect of different levels of viscosity on the clinical signs and symptoms of OD was assessed by a clinical test with high diagnostic accuracy, the Volume-Viscosity Swallow Test (V-VST). The effect on videofluoroscopic signs and the swallow response was assessed by videofluoroscopy (VFS).

Clinical Test

The V-VST was performed as described elsewhere [17]. Briefly, the patients' ability to swallow boluses of different volumes (5, 10 and 20 mL) and viscosities (thin liquid, nectar-like, spoon-thick) was evaluated in all patients. In addition, in order to evaluate the minimum amount of thickener needed for each patient, the subgroup of patients that presented impaired safety of swallow at nectar viscosity but safe swallow and residue at spoon-thick viscosity was evaluated with two additional intermediate viscosities: conservative spoon-thick and honey, using the algorithm described elsewhere [17].

Clinical signs of OD. Signs of impaired efficacy of swallow, such as impaired labial seal, oral residue and piecemeal deglutition (multiple swallows per bolus), symptoms of pharyngeal residue, and signs of impaired safety of swallow, such as changes in voice quality (including wet voice), cough and decrease in oxygen saturation ≥3% (measured with a finger pulse-oximeter, Nellcor OxiMax, Philips Medical Systems, Eindhoven, Netherlands) were evaluated for each swallow [18].

Videofluoroscopy

All patients were imaged for the videofluoroscopic study while seated, in a lateral projection which included the oral cavity, pharynx, larynx, and cervical oesophagus. Videofluoroscopic recordings were obtained by using a Super XT-20 Toshiba Intensifier (Toshiba Medical Systems Europe, Zoetermeer, The Netherlands) and recorded at 25 frames/s using a Panasonic AG DVX-100B video camera (Matsushita Electric Industrial Co, Osaka, Japan). Digitization, analysis and measurements of videofluoroscopic images were made using the software Swallowing Observer (Image and Physiology SL, Barcelona, Spain) by an expert clinician not blinded to the viscosity of the bolus. For the videofluoroscopic study, we used the same exploration algorithm as for the V-VST [17].

VFS signs. Impairment in the efficacy of swallow was considered when at least one of the following signs was identified during the VFS study: impaired labial seal, the presence/ absence of oral residue, pharyngeal residue or piecemeal deglutition; and impairment in the safety of swallow was considered when a penetration or an aspiration was detected. The penetrations and aspirations were classified according to the Penetration-Aspiration Scale (PAS) [19].

Timing of swallow response. Quantitative measurements of the effect of the thickener (Resource® ThickenUp Clear, Nestlé Health Science, Vevey, Switzerland) on oropharyngeal swallow response were obtained during 5 mL swallows at each viscosity during VFS studies. Timing of opening and closing of glossopalatal junction (GPJ), velopharyngeal junction (VPJ), laryngeal vestibule (LV), and UES were measured, GPJ opening being given the time value 0.

Bolus kinematics. Mean bolus velocity (m s^{-1}) acquired by the bolus during the transit between the GPJ and the UES was also calculated.

Bolus Rheology

The viscosities used during V-VST and VFS were prepared according to the descriptors of the National Dysphagia Diet Task Force, 1-50 mPa s for thin liquid, 51-350 mPa s for nectar-like, 351-1750 mPa s for honey and conservative spoon-thick and >1750 mPa s for spoon-thick viscosity[20]. For V-VST studies, thin viscosity was obtained by using mineral water at room temperature, nectar-like viscosity by adding 1.2 g of thickener (Resource ThickenUp Clear, Nestlé Health Science, Vevey, Switzerland) to 100 mL mineral water, and spoon-thick viscosity by adding 6 g of thickener to 100 mL mineral water. Honey viscosity was obtained by adding 2.4 g of thickener, and conservative spoon thick by adding 3.6 g, to 100 mL mineral water. Solutions were prepared 5 min before the test. According to the study protocol, the specific levels of viscosity obtained were 21 mPa s for thin liquids, 238 mPa s for nectar, and 1840 mPa s for EST [17]. For VFS studies, thin viscosity was obtained by mixing 1:1 mineral water and the X-ray contrast Gastrografin (Bayer Hispania SL, Sant Joan Despí, Spain) both at room temperature, nectar viscosity by adding 2.4 g of the thickener to the liquid solution containing the X-Ray contrast and the spoon-thick viscosity by adding 5.4 g of the thickener. Honey viscosity was obtained by adding 3.7 g of thickener to 100 mL of the X-Ray contrast solution and conservative spoon thick by adding 4.4 g. The solutions for VFS studies were prepared 3 hours prior the videofluoroscopic examination to obtain equivalent viscosities to those used during the V-VST [15]. Boluses of 5 mL, 10 mL, and 20 mL of each viscosity were carefully given to patients with a syringe during both V-VST and VFS studies to ensure accurate measurement of bolus volume.

Product safety

Any adverse events (AEs) occurring during the study and until one week after the completion of the study procedures (checked by a telephone call) were documented, assessed for severity and relationship to the study product and classified according to the WHO System Organ Class.

Data analysis and statistical methods

Qualitative parameters were described by relative and absolute frequencies and were compared by the Fisher's exact test for independent variables or McNemar's test for paired variables. Quantitative parameters were described by mean±SEM and compared by the nonparametric Mann Whitney U test or Kruskal-Wallis test for paired variables. Differences between viscosities at each volume was tested using the Cochran's-Q test. If the *P* value was less than 5% then each viscosity level was tested against the thin liquid viscosity using McNemar's test corrected for multiplicity (Bonferroni adjusted). Statistical significance was accepted if *P* values were <0.05. Statistical analysis was performed using the stats package in R version 2.15 (www.r-project.org).

Results

Study population

The recruitment of participants was carried out between June 2010 and June 2011. Demographic, clinical data and nutritional risk of the study population are described in **Table 1**. Up to 55% (66) of patients presented OD associated to a previous stroke, 34.2% (41) to aging, and 10.8% (13) to neurodegenerative diseases (mainly Parkinson's disease (3) and multiple sclerosis (3)). Sixty percent (72) of patients were taking one or more drugs with potential effects on swallow function: 39 were taking antidepressants; 29, anxiolytics; 17, antiepileptics; 10, sedatives and 5, antipsychotics.

Table 1. Demographic, clinical and nutritional characteristics of the study population. Healthy volunteers (HV); neurodegenerative diseases (NDD); Mini Nutritional Assessment short form (MNA-SF); Sydney Swallow Questionnaire (SSQ).

	HV	Patients	Patients		
			NDD	*Stroke*	*Elderly*
Subjects	14	120	13	66	41
Sex (men)	57.1% (8)	54.2% (65)	46.2% (6)	56.1% (37)	53.7% (22)
Age (years)	30.5±6.1	74.4±12.4	64.0±19.6	73.5±11.4	79.6±8.2
Drugs/ day	0.0±0.0	7.77±3.7	8.31±0.89	7.46±0.42	8.17±0.69
Dysphagia severity (SSQ)	12.1±4.6	460.5±35.5	546.1±69.3	495.2±55.1	375.5±47.5
Charlson Index	0	3.04±1.92	1.54±1.66	3.82±1.66	2.25±1.82
0	100% (14)	10.1% (12)	17.5% (7)	0.0% (0)	38.5% (5)
1-2	0% (0)	31.1% (37)	40.0% (16)	25.8% (17)	30.8% (4)
3-4	0% (0)	37.0% (44)	35.0% (14)	39.4% (26)	30.8% (4)
≥5	0% (0)	21.8% (26)	7.5% (3)	34.8% (23)	0.0% (0)
Nutritional status (MNA-SF)		9.72±2.76	10.31±3.04	9.29±2.72	10.25±2.69
Malnourished (0-7)		22.9%(27)	23.1% (3)	25.8% (17)	17.9% (7)
At risk (8-11)	---	48.3% (57)	38.5% (5)	53.0% (35)	43.6% (17)
Well nourished (12-14)		28.8% (34)	38.5% (5)	21.2% (14)	38.5% (15)

Effect of RTUC on clinical signs and symptoms of OD

Healthy volunteers. *Safety of swallow.* Only one healthy volunteer presented a voice change after the deglutition of 20 mL of thin liquid and 20 mL of nectar but not at spoon-thick viscosity. None of the HV presented cough or decreased oxygen saturation at any of the studied viscosities. *Efficacy of swallow*. All the HV presented adequate labial seal and were able to swallow all the boluses offered in a single swallow. One healthy volunteer presented oral and pharyngeal residue at spoon-thick viscosity.

Patients. Prevalence of clinical signs of impaired efficacy and safety of swallow in patients with OD at each viscosity series was very high and is depicted in **Figure 1**. *Safety of swallow*. Only 20.8% of patients were able to complete the thin liquid series safely. Up to 60.8% of patients completed the nectar series without presenting any sign of impaired safety of swallow (P<0.001 vs thin liquid) and up to 95.8% safely completed the spoon thick series (P<0.001 vs nectar-like). *Efficacy of swallow.* Increasing thin liquid viscosity to spoon-thick improved the labial seal efficacy of dysphagic patients (P<0.05), did not change the prevalence of oral residue or piecemeal deglutition and increased the prevalence of pharyngeal residue symptoms by 18.9% (P<0.05) (**Figure 1**). *Intermediate viscosities.* Conservative spoon-thick viscosity was administered to 31 patients with impaired safety at nectar and safe swallow but residue at spoon-thick viscosity. Of those, 6 presented signs of impaired safety and 22 symptoms of pharyngeal residue. Honey viscosity was evaluated in 27 patients; 5 of them presented signs of impaired safety and 14 reported pharyngeal residue.

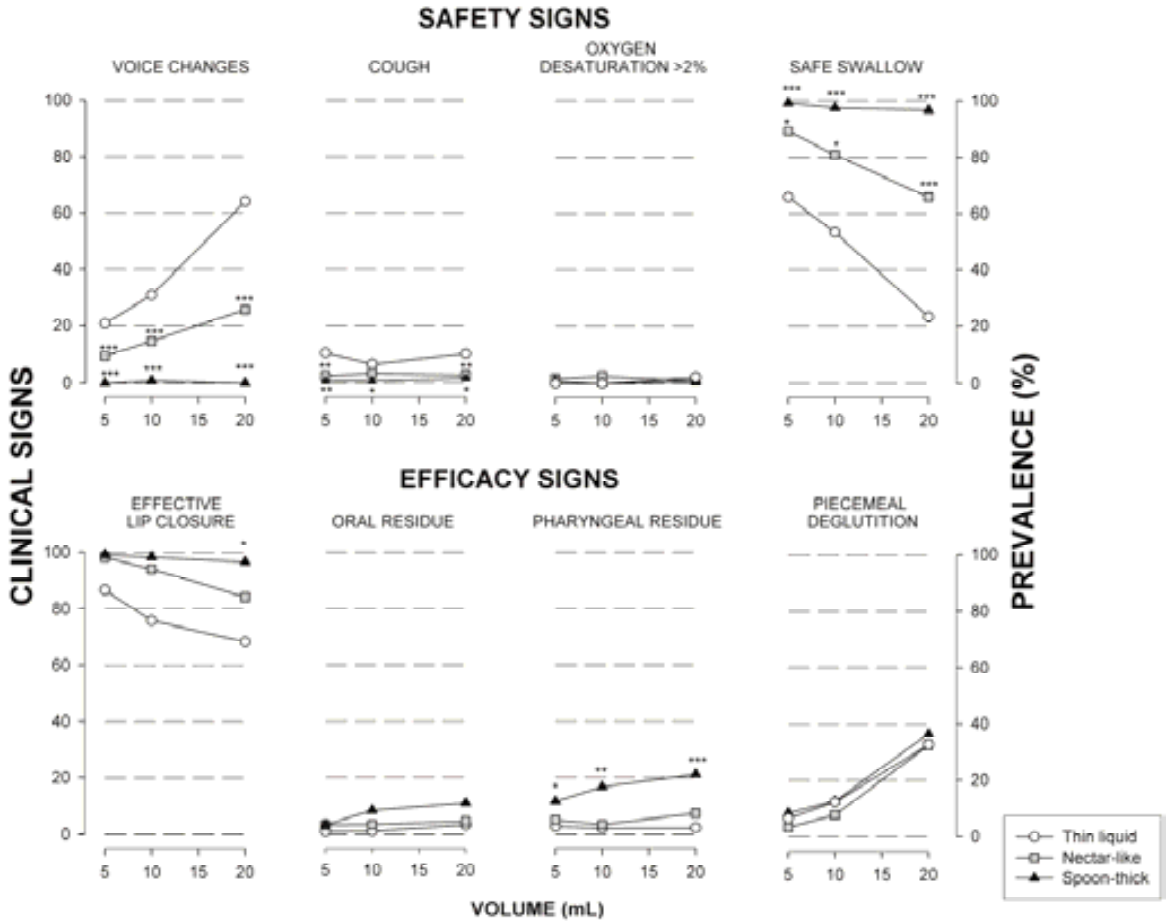

Figure 1. Prevalence of clinical signs of safety and efficacy of swallow for each bolus volume and viscosity in patients with oropharyngeal dysphagia. Safety of swallow was expressed as the percentage of patients that could swallow without voice changes, cough or oxygen desaturation for each bolus volume and viscosity. *P<0.05, **P<0.01, ***P<0.001 vs thin liquid viscosity.

Effect of RTUC on videofluoroscopic signs of OD

Healthy volunteers. *Safety of swallow.* Two HV presented non-pathological penetrations into the LV during the deglutition of thin liquid swallows (score 2 in the PAS) while none of them presented penetrations nor aspirations during the deglutition of nectar and spoon-thick viscosities. *Efficacy of swallow.* Two of the HV presented mild oral residue at liquid and spoon-thick viscosities and three at nectar-like viscosity. None of them presented pharyngeal residue at any of the viscosities tested.

Patients. Prevalence of videofluoroscopic signs of impaired efficacy and safety of swallow is shown in **Figure 2**. *Safety of swallow.* Increasing bolus viscosity with the xanthan gum thickener significantly increased the prevalence of patients able to swallow safely from 23.72% at thin liquid viscosity series, to 55.08% at nectar viscosity (P<0.001) and to 84.74% at spoon-thick viscosity series (P<0.001). **Figure 3** showed distribution of patients according to the maximum score presented in the PAS at each viscosity. It should be noted that prevalence of patients with clinically significant penetrations (scores 3-5) was reduced from 35.3% during thin liquid series to 13.7% at nectar-like viscosity (P<0.01) and to 9.3% at spoon-thick (P<0.01). Prevalence of patients with aspirations (scores 6-8) was reduced from 12.7% during thin liquid series to 7.7% at nectar (P<0.01) and to 3.4% at spoon-thick (P<0.01). The mean score of the PAS was reduced from 3.24±0.18 at thin liquid to 2.20±0.18 at nectar (P<0.001) and to 1.53±0.13 at spoon-thick (P<0.001). *Efficacy of swallow.* At thin liquid viscosity, 12.6% of patients presented significant oral residue and 14.6% presented pharyngeal residue. Increasing bolus viscosity with the xanthan gum thickener did not significantly modify the prevalence of oral, vallecular nor pyriform sinus residue (P>0.05) (**Figure 2**). *Intermediate viscosities.* Conservative spoon-thick viscosity was tested in 21 patients with impaired safety at nectar and safe swallow with residue at spoon-thick viscosity. Of those, 5 still presented penetrations; 10, oral residue and 17, pharyngeal residue. Honey viscosity was also evaluated in 21 patients; 3 of them presented penetrations at the laryngeal vestibule, 1 presented an aspiration. Oral residue was present in 10 patients and pharyngeal residue in 17.

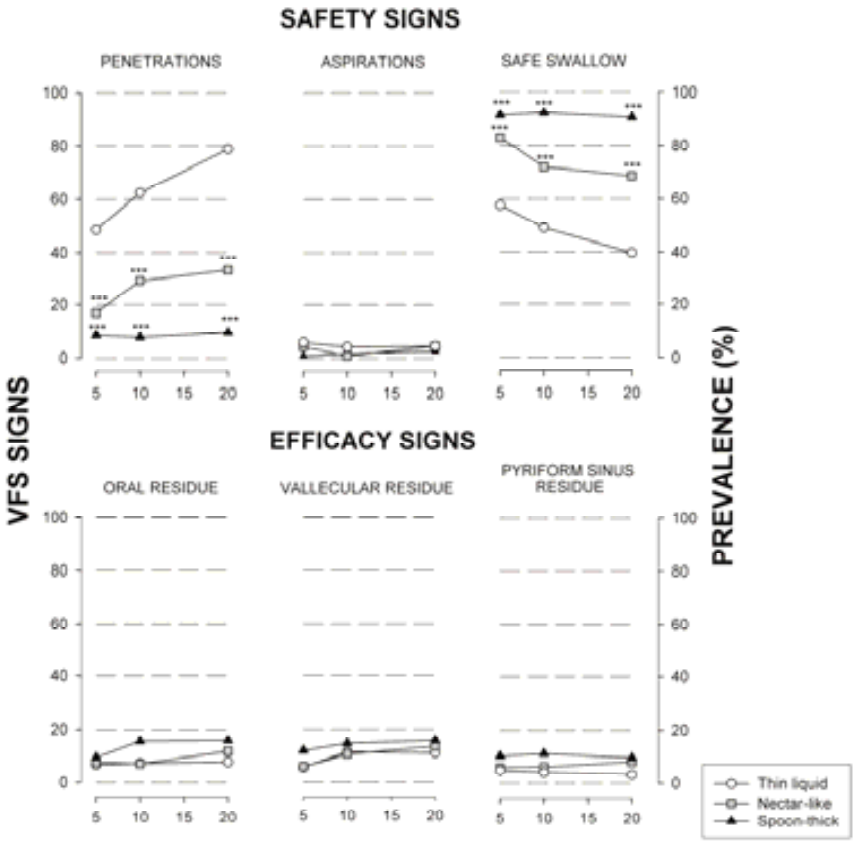

Figure 2. Prevalence of videofluoroscopic signs of safety and efficacy of swallow for each bolus volume and viscosity in patients with oropharyngeal dysphagia. Safety of swallow was expressed as the percentage of patients that could swallow without signs of contrast entering the laryngeal vestibule or traversing the vocal folds for each bolus volume and viscosity. *P<0.05, **P<0.01, ***P<0.001 vs thin liquid viscosity.

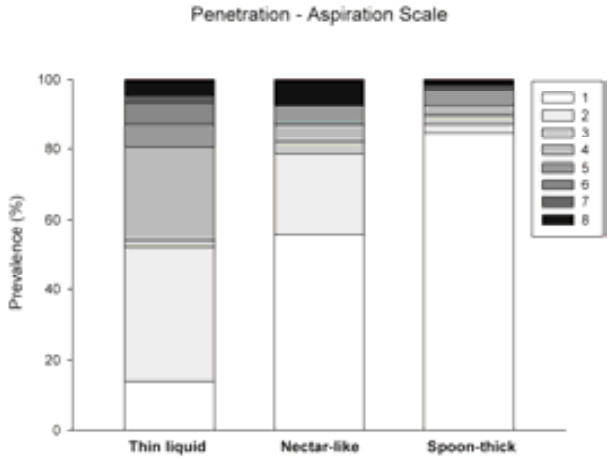

Figure 3. Relative frequencies of patients according to the maximum score presented in the Penetration-Aspiration Scale in each viscosity series.

Effect of RTUC on oropharyngeal physiology

Healthy volunteers

Timing of swallow response. Total duration of swallow (time from GPJ opening to LV opening) of HV during 5 mL thin liquid swallow was 742.9±29.9 ms. The airway closed at 171.4±12.2 ms and the UES opened at 220.0±16.6 ms. Increasing bolus viscosity to nectar did not significantly affect time to LV closure (174.3±11.6 ms, P>0.05) and opening (722.9±22.4 ms, P>0.05) nor UES opening (234.3±8.2 ms, P>0.05). However, increasing bolus viscosity to spoon-thick delayed time to LV closure and UES opening to 230.8±11.2 ms (P=0.003 vs thin liquid) and 283.1±11.5 ms (P=0.003 vs thin liquid) respectively, but not time to LV opening (P =0.261 vs thin liquid).

Patients

Timing of swallow response. Overall, patients included in the study presented prolonged swallow response (988.5±21.2 ms, P<0.001 vs HV) and delayed airway closure (399.6±19.3 ms, P<0.001 vs HV) and UES opening (328.7±14.3 ms, P<0.001) during 5 mL liquid swallow. Considering all patients with OD, increasing bolus viscosity to nectar and spoon-thick viscosities did not significantly affect LV closure time (363.1±11.2 ms at nectar viscosity and 434.8±22.9 ms at spoon-thick, P>0.05 vs thin liquid) or total duration of swallow response (959.3±17.2 ms at nectar viscosity and 1027.1±26.03 ms at spoon-thick, P>0.05 vs thin liquid). However, time to UES opening was increased at spoon-thick viscosity to 427.5±24.3 ms (P=0.009 vs thin liquid). **Figure 4** shows time to LV closure of patients stratified according to the safety of their swallow at each viscosity (presence of penetrations or aspirations). Patients with impaired safety presented a delayed LV closure compared to patients with safe swallow in all three viscosities (P<0.05). Patients with safe swallow at thin liquid and nectar-like viscosities had similar timing to airway closure (386.4±26.8 ms at thin liquid and 350.8±11.8 ms at nectar viscosity, P>0.05), but at spoon-thick viscosity, presented a later time to LV closure (427.8±24.5 ms, P<0.01) and UES opening.

Bolus Kinematics. The mean velocity of a 5 mL thin liquid bolus (0.248±0.010 m/s) was not changed by increasing bolus viscosity to nectar (0.238±0.010 m/s, P=0.438), but was significantly slowed at spoon-thick viscosity (0.214±0.010 m/s, P=0.019 vs thin liquid).

Product safety

A total of 37 minor AEs occurred in 34 (25.4%) persons during the study and the follow-up period, 30 (25.0%) in patients and 4 (28.6%) in HV. Of these, 36 AEs were gastrointestinal system disorders, specifically, 33 episodes of loose stools, 1 of nausea, 1 of vomiting and 1 of bloating were registered. The majority of them were mild and not considered treatment related. There was one serious adverse event (bronchoaspiration) that was considered unlikely to be related to the study product but related to the study procedure.

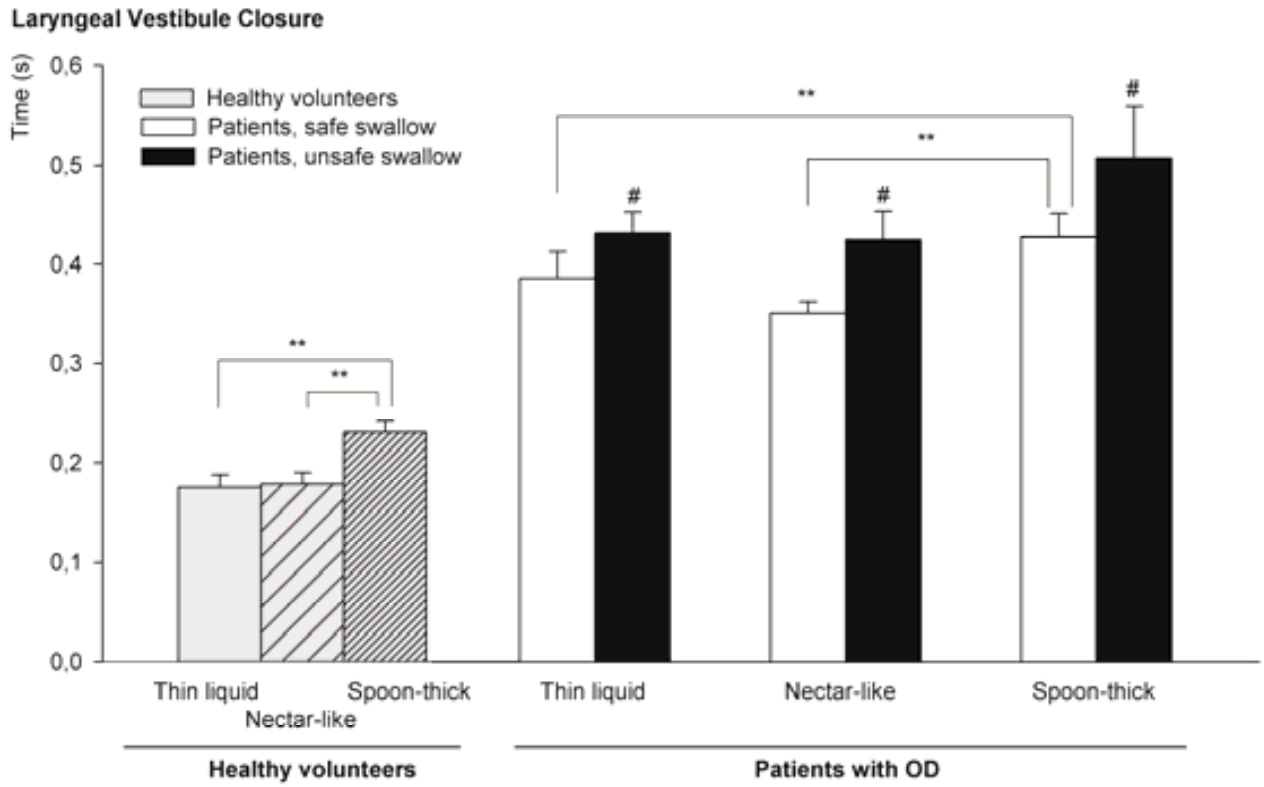

Figure 4. Laryngeal vestibule closure time of healthy volunteers and patients included in the study during 5 mL swallows, stratified according to the safety of swallow. #P<0.05 vs patients with safe swallow; **P<0.01.

Discussion

The main conclusion of this study is that the new xanthan gum-based thickener, RTUC, presents a strong viscosity-dependent therapeutic effect in patients with OD by improving the safety of swallow without increasing oropharyngeal residue. We found that it is possible to provide safe swallow to more than 84% of patients with OD by using RTUC at spoon-thick viscosity irrespective of the bolus volume offered to the patient. Moreover, prevalence of oropharyngeal residue after deglutition of thickened boluses is significantly lower than those reported in previous studies using starched-based thickeners [2,9,18] an advantage of xanthan gum thickeners versus conventional agents.

Thickening of fluids is a basic strategy in OD management, prescribed to the majority of dysphagic patients [14]. Even though a lack of consensus exists in terms of rheological properties, terminology, descriptors and definitions of modified fluids, thickening liquids is perceived as an effective strategy by health professionals providing care for dysphagic patients [14]. Despite widespread use and good acceptance, there are few studies objectively assessing the therapeutic effect of thickeners and the level of evidence is low [21]. In addition, there are many thickeners and gelling agents commercially available, all presenting different components and rheological properties with potentially different therapeutic effects. Thus, the objective assessment of the real effectiveness of these agents in specific clinical trials is crucial for adequate management of dysphagic patients and to ensure airway protection to avoid respiratory complications. This study shows, for the first time, the strong viscosity-dependent therapeutic effect of a new xanthan gum-based thickener providing research-based evidence of its clinical usefulness in OD management.

In this study we included patients representing the most prevalent populations and phenotypes of patients at risk for OD that can be found in primary care, general hospitals and nursing homes such as the elderly and patients with stroke and neurodegenerative diseases. Prevalence of

malnutrition, co-morbidities and polymedication with potential effects on swallowing function among our population was very high, putting them at high risk for developing life-threatening respiratory complications if not managed properly. We previously found that 80% of hospital readmissions for aspiration pneumonia in elderly patients were attributable to oropharyngeal dysphagia [8]. One-year mortality rates of our elderly patients with OD are above 50% [2]. The RTUC was also evaluated in a group of HV to provide normality values and to obtain data on the effect of the thickener on normal swallow response and its safety profile.

In our study, the therapeutic effect of the thickener RTUC was determined by means of a validated clinical test (V-VST) and a videofluroscopic study. In the clinical study we observed that increasing bolus viscosity reduced prevalence of cough and voice changes associated to swallow, indicating a strong effect on clinical signs of safety of swallow. This effect was confirmed in the videofluoroscopic study, as a viscosity-dependent reduction in the prevalence of penetrations and aspirations was clearly observed. This therapeutic effect on safety of deglutition exerted by RTUC in this study is higher to that we observed using boluses of similar levels of viscosity obtained by starch thickeners in previous studies in patients with neurological diseases (non-progressive and neurodegenerative) [9], a mixed cohort of patients including head and neck diseases [18] and in frail elderly patients [2]. In terms of efficacy of deglutition, we observed in the clinical study that pharyngeal residue increased at spoon-thick viscosity when compared with thin liquids. However, this effect was not confirmed by the videofluoroscopy. This discrepancy could be explained because in the clinical study, the pharyngeal residue is not a sign directly observed by the clinician but is assessed as a symptom reported by the patient (feeling that the bolus sticks in the throat). Pharyngeal and laryngeal sensory abnormalities, often described in dysphagic patients, could contribute to this symptom. Using videofluoroscopy, we did not observe any significant enhancement in vallecular or pyriform sinus residue by increasing bolus viscosity. These results agree with a previous study in HV that did not find any increase of pharyngeal residue by increasing bolus viscosity with different concentrations of xanthan gum [22]. In contrast, previous studies evaluating the effect of starch thickeners [2,9,18], reported an important increase in pharyngeal residue at spoon-thick viscosities. Post-deglutitive residue can be easily aspirated in the inhalation process and put the patient at risk for respiratory complications. Therefore, the highest protection offered by the xanthan gum-based thickeners compared with the starch thickeners, together with the absence of pharyngeal residue increment, confers to this new generation of thickeners a greater therapeutic value.

We observed that thin and nectar-like liquids moved more quickly through the pharynx than boluses at spoon-thick viscosity both in HV and in patients. In HV, the timing of reconfiguration of oropharyngeal structures from a respiratory pathway to a digestive pathway adapted to the bolus transit, and the increased bolus velocity of thin and nectar-like liquids was associated with an earlier LV closure and UES opening times. Dysphagic patients presented delayed airway protection (LV closure time), specifically prolonged in patients with impaired safety, responsible for the observed penetrations and aspirations into the airways. It has been proposed that slowing down bolus flow velocity through the pharynx confers thickeners their main therapeutic effect [12]. However, we have observed that a moderate level of viscosity, such as nectar-like viscosity, strongly improved airway protection without modifying bolus velocity nor timing of the oropharyngeal swallow response compared to thin liquids. Therefore, RTUC is able to improve swallow safety without producing any change in swallow physiology, suggesting that the intrinsic proprieties of the thickened bolus are responsible for the observed therapeutic effect at this level of viscosity. We have also observed that, at spoon-thick viscosity, bolus velocity is reduced, suggesting that at high viscosity levels, the therapeutic effect of RTUC depends not only on its intrinsic texture properties, but also to additional effects produced by changes in swallow physiology. Looking at the other timing related events, we observed that UES opening time was delayed at spoon-thick viscosity. As the UES requires bolus pressure in order to open, the reduced velocity of spoon-thick viscosities that thus

takes more time to reach the sphincter, delay UES opening time. Total duration of swallow response (time from GPJ opening to LV opening) was not affected by any level of bolus viscosity in HV nor in patients.

The therapeutic effect of xanthan gum thickeners versus starch thickeners at similar levels of viscosity should be further explored by comparative clinical studies, and be based not only on rheological characteristics such as bolus viscosity but also on textural properties such as hardness, cohesiveness, adhesiveness or gumminess, especially at mid-levels of viscosity. It has been reported in post-stroke dysphagic patients that semisolids with high cohesiveness were more likely to accumulate in the pharynx while high gumminess could lead to tracheobronchial aspirations [23]. However, data on the effect of these textural properties on the safety and efficacy of swallow is scarce and further studies are necessary to characterize their influence on the effect of thickeners. Finally, results of this study show that RTUC is a safe product with low incidence of AEs. Most of the AEs affected the gastrointestinal tract, were mild and probably related to the X-Ray contrast that causes a well-known osmotic laxative effect on small bowel and enhances colonic motility.

In conclusion, increasing bolus viscosity with the xanthan gum thickener RTUC exerts a strong viscosity-dependent therapeutic effect on patients with OD by improving the safety of swallow without increasing oropharyngeal residue, an advantage of this new generation of xanthan gum thickeners over conventional agents. Our study also suggests that RTUC exerts its therapeutic effect through two sequential mechanisms: at nectar-like viscosity the therapeutic effect relies on the intrinsic rheological or texture properties of the thickener whereas with spoon-thick viscosity, significant changes in swallow physiology also occur.

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CAPÍTULO 5

Capítulo 5

NATURAL CAPSAICINOIDS IMPROVE SWALLOW RESPONSE IN OLDER PATIENTS WITH OROPHARYNGEAL DYSPHAGIA

Laia Rofes, Viridiana Arreola, Alberto Martin, Pere Clavé. *Natural capsaicinoids improve swallow response in older patients with oropharyngeal dysphagia.* Gut 2013; 62(9):1280-7.

Abstract

Background: There is no pharmacological treatment for oropharyngeal dysphagia (OD). The aim of this study was to compare the therapeutic effect of stimulation of oropharyngeal transient receptor potential vanilloid type 1 (TRPV1) with that of thickeners in older patients with OD.

Methods: A clinical videofluoroscopic non-randomised study was performed to assess the signs of safety and efficacy of swallow and the swallow response in: a) 33 patients with OD (75.94±1.88 years) while swallowing 5, 10 and 20 mL of liquid (20.4 mPa.s), nectar (274.4 mPa.s), and pudding (3930 mPa.s) boluses, b) 33 patients with OD (73.94±2.23 years) while swallowing 5, 10 and 20 mL nectar boluses, and two series of nectar boluses with 150 μM capsaicinoids and c) 8 older controls (76.88±1.51 years) while swallowing 5, 10 and 20 mL nectar boluses.

Results: Increasing bolus viscosity reduced the prevalence of laryngeal penetrations by 72.03% ($P<0.05$), increased pharyngeal residue by 41.37% ($P<0.05$), delayed the upper esophageal sphincter opening time and the larynx movement and did not affect the laryngeal vestibule closure time and maximal hyoid displacement. Treatment with capsaicinoids reduced both penetrations by 50.00% ($P<0.05$) and pharyngeal residue by 50.00% ($P<0.05$) and shortened the time of laryngeal vestibule closure ($P<0.001$), upper esophageal sphincter opening ($P<0.05$) and maximal hyoid and laryngeal displacement.

Conclusion: Stimulation of TRPV1 by capsaicinoids strongly improved safety and efficacy of swallow and shortened the swallow response in older patients with OD. Stimulation of TRPV1 might become a pharmacologic strategy to treat OD.

Introduction

Oropharyngeal dysphagia (OD) is a major complaint among the elderly. It affects more than 20% of independently-living older persons[1] and up to 56-78% of elderly institutionalized patients.[2] OD is a severe condition in older persons and may cause two groups of clinically relevant complications: (i) a decrease in the efficacy of deglutition, leading to malnutrition and/or dehydration in up to 33% of patients and (ii) a decrease in the safety of deglutition, resulting in laryngeal vestibule penetrations or in tracheobronchial aspirations, which can lead to aspiration pneumonia with an associated mortality of up to 50%.[3, 4, 5] Currently, the standard of care for the majority of these older patients suffering from OD is very poor as most of them are not even diagnosed and do not receive any treatment for this condition.

An overall decrease in the sensitivity of the pharyngeal and supraglottic areas has been described in elderly persons[6, 7] and also in stroke patients with OD, much more marked in those with aspiration.[8] A lack of afferent myelinated nerve fibers in the superior laryngeal nerve has been described in the elderly, and may be related to age-related sensorial dysfunction of the upper aerodigestive tract.[9, 10] In stroke patients, the deficit could be caused by the disruption of the connection of the sensory afferents with the cortex and the brainstem. These sensory deficits are involved in the pathophysiology of the impaired swallow response of these dysphagic patients[11] and predispose to aspiration and aspiration

pneumonia. We hypothesized that enhanced oropharyngeal stimuli might improve the afferent sensorial input to the central pattern generator in the swallowing centre of the brainstem, achieving earlier the threshold to trigger the swallow response.[12] Moreover, repetitive sensorial stimuli may reorganize the motor cortex, facilitating deglutition.[13,14] The most effective afferent areas to trigger the swallow response are the anterior faucial pillars, the palatopharyngeal arch and the posterior pharyngeal wall (innervated by the pharyngeal branch of the glossopharyngeal nerve, GPN*ph*, IX cranial nerve), and the epiglottis and the aryepiglottic arch (innervated by the superior laryngeal nerve, SLN, branch of the X cranial nerve).[15] These afferents are sensitive to mechanical stimuli, to changes in temperature and to chemical stimuli, and express the polymodal Transient Receptor Potential Vanilloid 1 (TRPV1).[16] Afferents project to the supra-medullar structures and to the nucleus tractus solitarius in the brainstem, allowing the involuntary onset of swallow response and modulating volitional swallowing.[15] Several clinical studies found TRPV1 agonists such as piperine (main component of *Piper nigrum*)[14] and capsaicin (component of several species of *Capsicum sp*)[17-19] reduced the time to swallowing onset in elderly patients with dysphagia. Other TRPV1 agonists such as acid[20] or high temperature[21] also showed positive clinical results in improving swallow in dysphagic patients. In addition, natural capsaicinoids increased the amplitude and velocity of esophageal body peristalsis[22] and we believe they could be a safe and effective alternative to test the effects of TRPV1 agonists on dysphagic patients. However, the specific effects of natural capsaicinoids on the physiology of the swallow response are not known, nor their possible therapeutic potential among patients with OD compared with other established treatments.

The aim of our study was to explore, in a clinical study, the physiological and therapeutic effects of natural capsaicinoids added to the alimentary bolus, in order to assess its potential as a pharmacological tool to treat patients with OD.

Materials and Methods

Patients

We designed a non-randomised videofluoroscopic study to assess and compare the effects of capsaicinoids on the deglutition of older patients with mild OD with the effects of standard treatment with thickeners[23]. The study was carried out in the Gastrointestinal Physiology Lab and in the Radiology Unit of the Hospital de Mataró (Spain). All participants were recruited from the Acute Geriatric Unit and from the Neurology Unit of the Hospital de Mataró. The volume-viscosity swallow test (VVST) was used for bedside clinical screening of OD[24] and the Sydney Swallowing Questionnaire was used to clinically assess the severity of the symptoms of dysphagia.[25] We studied: a) 8 older controls (76.88±1.51 years, 5 men) without symptoms of OD and with a negative VVST, and b) 66 older patients (74.94±1.45 years, 36 men) with mild OD (clinical complaints and positive VVST) associated to aging (n=20), neurodegenerative diseases (n=16) or chronic OD following stroke (n=30). The sample size was calculated in a bilateral test for a statistical power of 80%, alpha error 0.05, expected reduction of laryngeal vestibule closure time of 100 ms, expected standard deviation of 130 ms and expected loss to follow up of 20%. Patients with severe clinical signs of aspiration including oxygen desaturation ≥3% were not included in this initial study. The study protocol was approved by the Institutional Review Board of the Hospital de Mataró and was conducted according to the principles and rules laid down in the Declaration of Helsinki and its subsequent amendments. Trial registration: ISRCTN31088564.

Videofluoroscopic procedures

All patients were imaged for the videofluoroscopic study while seated, in a lateral projection which included the oral cavity, pharynx, larynx, and cervical esophagus. Videofluoroscopic recordings were obtained by using a Super XT-20 Toshiba Intensifier (Toshiba Medical Systems Europe, Zoetermeer, The Netherlands) and recorded at 25 frames/s using a Panasonic AG DVX-100B video camera (Matsushita Electric Industrial Co, Osaka,

Japan). Older controls were studied during the deglutition of a series of one bolus of 5 mL, one bolus of 10 mL and one bolus of 20 mL at nectar viscosity (274.42±13.14 mPa s). Patients with oropharyngeal dysphagia were divided into 2 treatment groups: a) 33 patients (75.94±1.88 years, 20 men) were studied during the deglutition of a series of one bolus of 5 mL, one bolus of 10 mL and one bolus of 20 mL at nectar viscosity, a series of liquid (20.40±0.23 mPa s) and a series of pudding viscosity (3931.23±166.15 mPa s) with the same bolus volumes; b) 33 patients (73.94±2.23 years, 16 men) were studied during the deglutition of one series of nectar boluses (one bolus of 5 mL, one bolus of 10 mL and one bolus of 20 mL) (pH = 6.35±0.026) and two series of nectar boluses of the same volumes supplemented with a capsaicinoid concentration of 150 μM (pH = 3.36±0.01), each patient acting as his or her own control. The two supplemented bolus series were administered 10 min apart and a sensitization process was conducted on each patient by administering two 5 mL boluses also supplemented with 150 μM capsaicinoids 5 min before the first treatment bolus series. A 9-point visual analogue scale was administered to patients to assess the acceptability of the offered boluses. Punctuations range from 1 (extremely unpleasant) to 9 (extremely pleasant) being the point 5 “neither pleasant nor unpleasant”. Liquid viscosity was obtained by mixing 1:1 mineral water and the X-ray contrast Gastrografin (Berlimed SA, Madrid, Spain), nectar viscosity by adding 3.5 g of the thickener Resource ThickenUp (Nestlé Nutrition, Barcelona, Spain) to 100 mL of liquid solution and pudding viscosity by adding 8 g of the thickener. Bolus density for liquid was 1.19±0.007 g mL^{-1}, nectar 1.23±0.007 g mL^{-1}, and pudding 1.27±0.001 g mL^{-1}. Boluses were carefully offered to patients with a syringe.

Drugs

Capsaicinoid concentration in capsaicinoid sauce (McIlhenny Co, Avery Island, LA, USA) was determined using liquid chromatography (AOAC 995.03 method), and a concentration of 185.5 μg/g was obtained. Final concentrations were obtained by dissolution of the capsaicinoid sauce in the nectar bolus.

Videofluoroscopic signs

Videofluoroscopic signs of safety and efficacy of deglutition were identified accordingly to previously accepted definitions:[3,23] impaired efficacy of a swallow act was identified when one or more of the following signs were detected: decreased lingual control or bolus propulsion, presence of oral, vallecular or sinus pyriform residue or impaired upper esophageal sphincter (UES) opening; similarly, impaired safety of a swallow act was identified when a penetration and/or an aspiration occurred. Penetration was defined as the entrance of swallowed material into the laryngeal vestibule and aspiration as the passage of this material below the vocal folds.

Oropharyngeal swallow response

Digitization, analysis and measurements of videofluoroscopic images were made using the software Swallowing Observer (Image and Physiology SL, Barcelona, Spain).[3,23,24] Quantitative measurements of oropharyngeal swallow response were obtained during 5 mL swallows: a) *Oropharyngeal reconfiguration:* timing of opening and closing of glossopalatal junction (GPJ), velopharyngeal junction (VPJ), laryngeal vestibule (LV), and UES were measured, GPJ opening being given the time value 0.[26] b) *Hyoid motion:* vertical and anterior hyoid position was determined in an *xy* coordinate system in each frame: the anterior-inferior corner of C3 was used as the origin, and the vertical axis was defined by a line connecting the anterior inferior corners of C3 and C5.[26] c) *Laryngeal movement*: maximal vertical and anterior displacement of the larynx was also determined. The position of the anterior superior corner of the supraglottic air column was referenced to the *xy* coordinate system.[27] d) *Bolus kinematics:* maximal velocity (m s^{-1}) acquired by the bolus prior to entering the UES was evaluated.[3]

Statistical methods

Categorical variables were described as percentages (number of deglutitions with specific signs of impaired safety and/or efficacy of swallow versus total number of deglutitions) and compared

by the Fisher's exact test. Quantitative parameters were described by mean ± SEM. Comparisons between groups were assessed by the nonparametric Mann–Whitney U-test and comparisons within each group were assessed by the nonparametric Wilcoxon matched pairs test. Hyoid profiles were compared by two-way ANOVA analysis. A sub-analysis in patients with previous stroke was also performed to evaluate the effect of capsaicinoids on this specific population. Statistical significance was accepted if *P* values were <0.05. Statistical analysis was performed using GraphPad Prism 4.01 (San Diego, CA, USA).

Results

Patient demographics and clinical assessment of OD

Age, sex, and clinical characteristics of patients included in both group of treatments were very similar (**Table 1**). Older controls did not present clinical signs of OD. The prevalence of clinical signs of impaired safety and/or efficacy of swallow and clinical severity scores for OD were very homogeneous between both branches of treatments: up to 65.38% of patients treated with thickeners and 54.84% (P=0.588) of patients treated with capsaicinoids presented signs of both impaired safety and efficacy of swallow, 7.69% of patients treated with thickeners and 16.13% (P=0.436) of patients treated with capsaicinoids showed impairment only in safety and 26.9% of patients treated with thickeners and 29.03% (P=1.00) of patients treated with capsaicinoids showed impairment only in efficacy. The Sydney Swallow Questionnaire score for severity of OD was low for older controls (115.00±80.69) and was significantly higher in older patients with dysphagia (372.2±43.67, P<0.01). Assessing the scores of the two treatment groups, non significant difference were found between dysphagic patients treated with thickeners (432.90±73.60) and capsaicinoids (315.15±47.97, P=0.40).

Acceptability of the boluses

Punctuations of the visual analogue scale were 4.54±0.227 for the nectar control bolus and 4.37±0.245 for the capsaicinoids supplemented bolus (*P*=0.628).

Table 1: Patient demographics and clinical characteristics. Data presented as number of cases (percentage), except *mean±SEM.

	Thickener group (n=33)	**Capsaicinoids group (n=33)**	*P value*
Age (years)	75.94±1.88*	73.94±2.23*	**0.497**
Sex (men)	16 (48.48%)	20 (60.61%)	**0.480**
Dysphagia related pathology:			
Stroke	15 (45.45%)	15 (45.45%)	**1.000**
Aging	6 (18.18%)	4 (12.12%)	**0.733**
Chronic pulmonary diseases	3 (9.09%)	4 (12.12%)	**1.000**
Multiple sclerosis	3 (9.09%)	3 (9.09%)	**1.000**
Alzheimer disease	0 (0.00%)	1 (3.03%)	**1.000**
Parkinson disease	3 (9.09%)	3 (9.09%)	**1.000**
Dementia	2 (6.06 %)	1 (3.03%)	**1.000**
Myasthenia gravis	1 (3.03%)	1 (3.03%)	**1.000**
Inclusion body myositis	0 (0.00%)	1 (3.03%)	**1.000**

Effect of capsaicinioids on videofluoroscopic signs of efficacy and safety of swallow

All older controls presented a safe and efficacious swallow at videofluoroscopy. In contrast, elderly patients with dysphagia included in both groups of treatment presented a high prevalence of videofluoroscopic signs of impaired safety and/or efficacy of swallow that are summarized in **Figure 1**. There were no significant differences in the prevalence of videofluoroscopic signs of impaired safety or efficacy of swallow at nectar viscosity of both groups. a) Increasing bolus viscosity to pudding strongly reduced prevalence of penetrations (-72.03%, $P<0.05$) and significantly increased oral residue (+20.89%, $P<0.05$) as well as pharyngeal residue in vallecula and pyriform sinus (+41.37%, $P<0.05$). Nectar viscosity also reduced the prevalence of penetrations (-80.91% vs liquid viscosity, $P<0.05$). b) Treatment with capsaiciniods strongly reduced the prevalence of penetrations (-50.00%, $P<0.05$) and also pharyngeal residue (-50.00%, $P<0.05$), without significant changes in oral residue (**Figure 1**). Moreover, prevalence of impaired tongue propulsion, impaired glossopalatal seal closure and impaired UES opening were not changed by either treatment (data not shown).

Effect of capsaicinoids on oropharyngeal swallow response

a) Oropharyngeal reconfiguration: Total duration of swallow response in older controls (GPJ opening-LV opening) for 5 mL nectar boluses was 0.895±0.038 s and the interval for oropharyngeal reconfiguration from a respiratory to a digestive pathway was very short: it takes 0.230±0.040 s for LV closure. Patients with OD in both treatment groups presented a significant delay in the reconfiguration phase, LV closure time was >0.390 s ($P<0.05$ vs older controls) and there were no significant differences in the oropharyngeal swallow response times at nectar viscosity of both groups. Changes in bolus viscosity did not affect total duration of swallow response nor delayed timing of LV closure, but increasing bolus viscosity to pudding delayed UES opening in patients with OD.

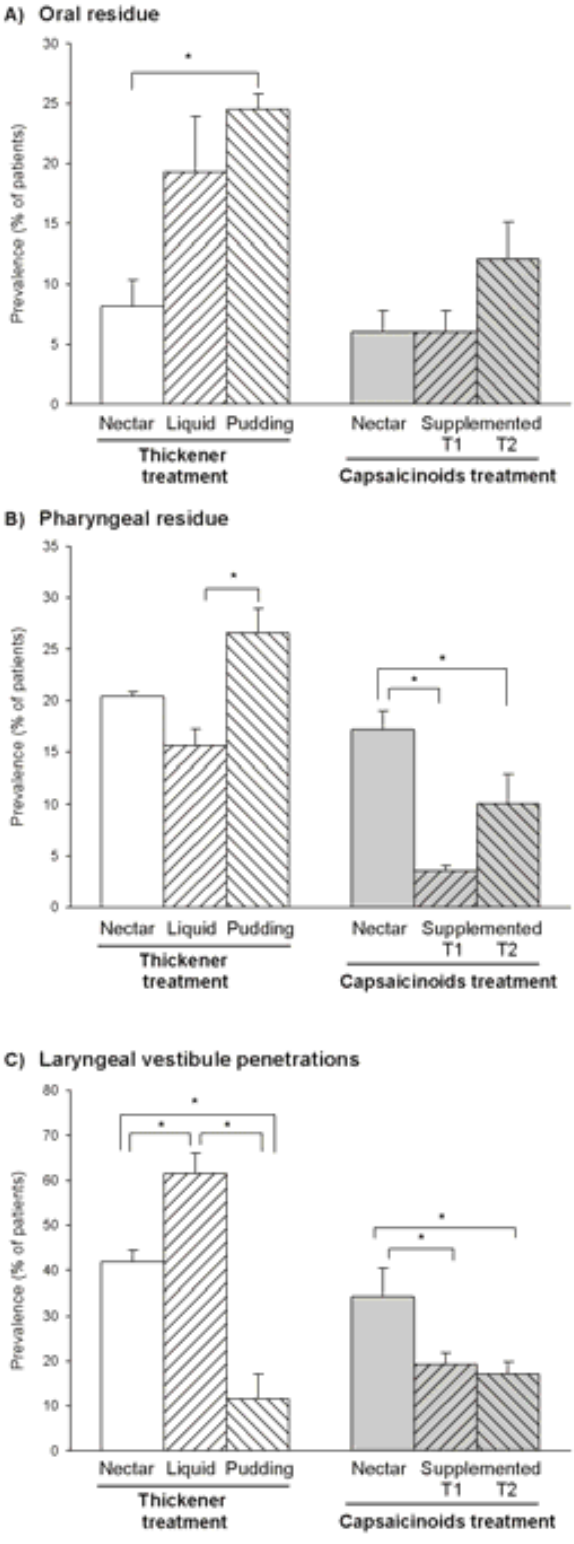

Figure 1: Videofluoroscopic signs. Effect of thickeners (white bars) and capsaicinoids 150 µM (grey bars) on the prevalence of main signs of efficacy (**A**, oral residue and **B**, pharyngeal residue) and safety (**C**, laryngeal vestibule penetrations) of swallow. Prevalence is expressed as the mean of subjects who presented the sign at each viscosity versus total number of subjects ± SEM.*$P<0.05$.

In contrast, bolus supplementation with capsaicinoids greatly shortened time to LV closure (from 0.410±0.024 s to 0.296±0.026 s, P<0.001) and time to UES opening (from 0.372±0.024 s to 0.299±0.020 s, P<0.05) without affecting total duration of swallow response (1.00±0.036 s at nectar bolus vs 0.901±0.026 s with capsaicinoids, P=0.095) (**Figure 2**).

b) Hyoid motion: Hyoid movement was affected by both thickeners and capsaicinoids. Increasing bolus viscosity to pudding reduced the hyoid movement profile but did not significantly change the timing of maximal and vertical hyoid excursion. In contrast, capsaicinoids caused an overall improvement in the hyoid movement profile and patients with this treatment reached the maximum vertical extension earlier (0.493±0.040 s at nectar bolus vs 0.354±0.034 s at bolus with capsaicinoids, P<0.05) (**Figures 3 and 4**).

c) Laryngeal movement: Neither bolus viscosity nor capsaicinoids affected the maximal vertical and anterior extension achieved by the larynx (data not shown). Thickeners (pudding viscosity) delayed the maximal vertical and anterior laryngeal displacement, whereas capsaicinoids shortened this time (**Figure 4**).

d) Bolus kinematics: Bolus velocity was reduced by pudding viscosity (0.342±0.037 m s^{-1} vs 0.445±0.040 m s^{-1} in nectar bolus P<0.05) and enhanced by capsaicinoids (0.424±0.030 m s^{-1} vs 0.340±0.025 m s^{-1} in nectar control bolus, P<0.01).

Stroke patients

The supplementation of the alimentary bolus with capsaicinoids also improved the efficacy and the safety of swallow of the subgroup of elderly patients with previous stroke (n=15): pharyngeal residue was reduced by -93.81% (P<0.01), prevalence of penetrations by -47.39% (P=0.09), time of LV closure by -19.5% (P=0.09) and time of maximal vertical extension of the hyoid bone by -40.4% (P<0.05).

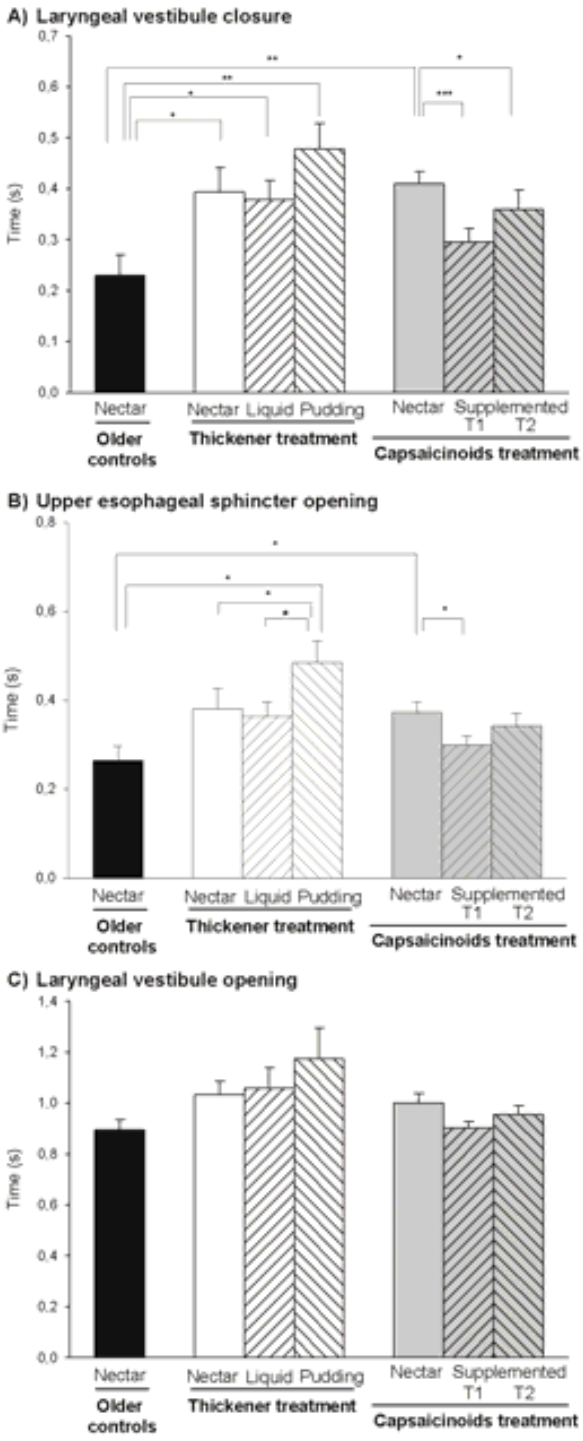

Figure 2: Oropharyngeal reconfiguration. Timing of main events of the oropharyngeal swallow response during 5 mL swallows in healthy elderly (black) and elderly patients with dysphagia. Effect of thickeners (white) and capsaicinoids (grey) on the laryngeal vestibule closure time (**A**), upper esophageal sphincter opening time (**B**) and laryngeal vestibule opening time (**C**), was determined. *P<0.05, **P<0.01, ***P< 0.001.

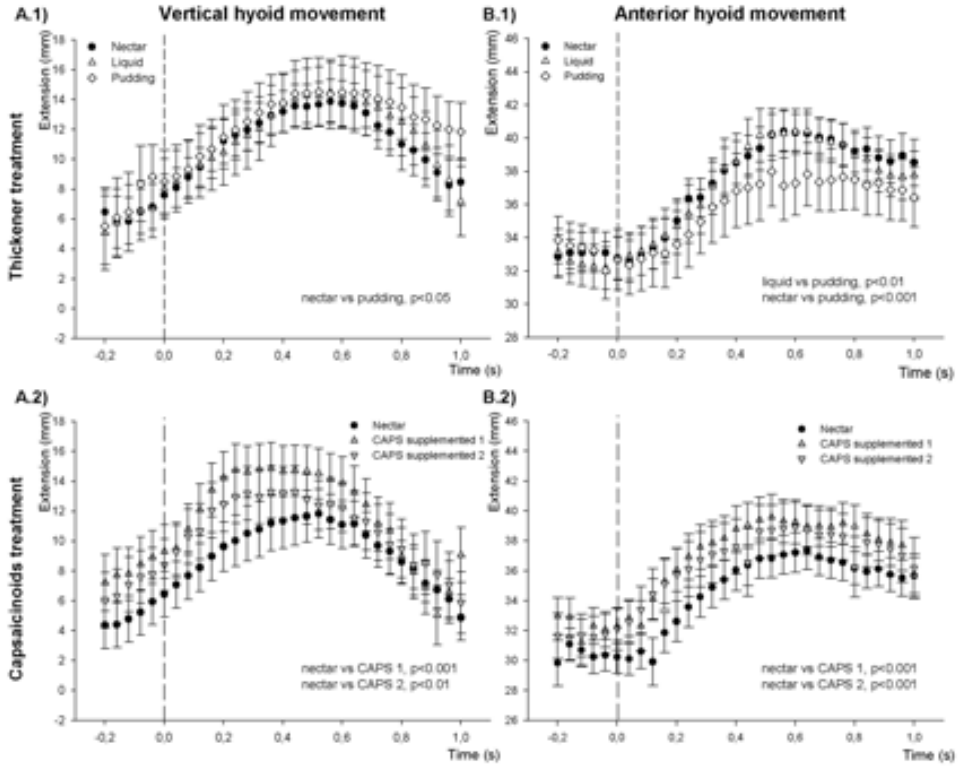

Figure 3: Hyoid motion. Vertical (**A**) and anterior (**B**) hyoid movement during 5 mL swallows in older patients with dysphagia: Effect of thickener (**A.1** and **B.1**) and capsaicinoids (**A.2** and **B.2**) treatment on the hyoid motion profiles compared using two-way ANOVA analysis.

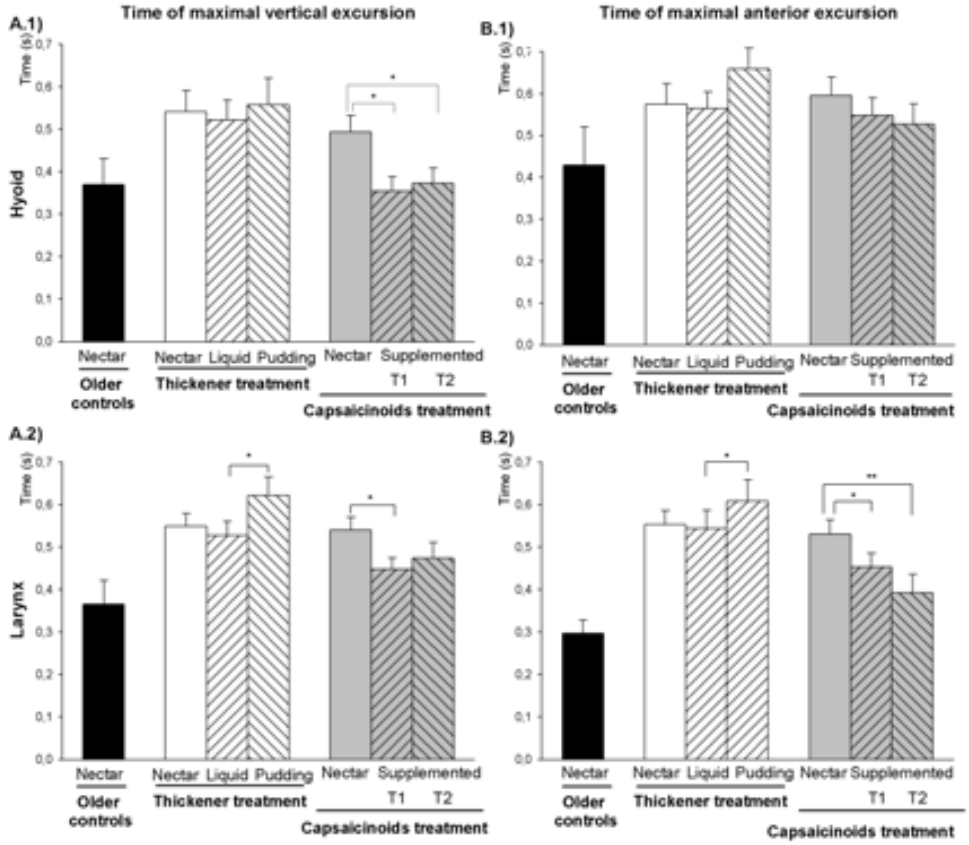

Figure 4: Maximal hyoid and larynx displacement times. Time of maximal vertical (**A**) and anterior (**B**) displacement of the hyoid bone (**A.1** and **B.1**) and the larynx (**A.2** and **B.2**) of older controls (black) and patients with dysphagia treated with thickener (white) and capsaicinoids (grey). *P< 0.05, **P< 0.01.

Discussion

The main results of this study are that stimulation of oropharyngeal TRPV1 by natural capsaicinoids improved safety and efficacy of swallow and the physiology of swallow response in older patients with OD. We also found that the standard treatment for dysphagic patients, starch based thickener, improved safety of swallow without affecting the physiology of swallow response. Following our results, we believe stimulation of TRPV1 might become a new pharmacological strategy in patients with OD.

The two main strategies used in the treatment of OD in the elderly are modification of food textures for solids and liquids and behavioural treatments with swallow postures, manoeuvres and exercises.[28,29] In previous studies, we found that enhancing bolus viscosity greatly increased safety of swallowing with a maximal therapeutic effect at pudding viscosity (3931.2 mPa s) in patients with neurogenic dysphagia and frail older patients.[3,23] The present study also confirms the strong therapeutic effect of thickeners on safety of swallow in older persons with OD. However, increasing bolus viscosity using starch thickeners increased oropharyngeal residue.[3,23,24] Otherwise, the level of evidence of the effect on the elderly of the classical rehabilitation and behavioural treatments with postures, manoeuvres and exercises is very weak and the variability in its application very high.[29] In addition, modified food textures or behavioural treatments are widely recognized to be compensatory strategies that do not change the impaired swallow physiology in patients with OD.[29]

Our present study evaluates the possibility of treating swallowing disorders of patients with OD through a pharmacological approach involving the stimulation of oropharyngeal TRPV1.[30] To do this, we used a strategy of supplementation of the alimentary bolus with natural agonists of TRPV1. A capsaicinoid sauce was used as a source of natural TRPV1 agonist, because of its high content of capsaicinoids (185 µg/g), because it is a safe alimentary product, and because it has already been used in previous studies on humans showing its effectiveness in enhancing motility of the esophageal body in patients with esophageal disorders.[22] We found that the swallow response was severely impaired in our elderly patients with OD with a serious delay in the early phase of oropharyngeal reconfiguration from a respiratory to a digestive pathway (time to LV closure and UES opening). These results, agree with an earlier study by Kahrilas[26] that found prolonged intervals to LV closure and UES opening are the key abnormalities of swallow response leading to unsafe deglutition (penetrations into laryngeal vestibule or aspiration into the airway) in neurological patients and also agree with our previous studies on frail elderly patients and neurological patients.[3,23] Time to LV closure is the time interval during which the potential penetration or aspiration occurs, and a delay in UES opening increases the risk for bolus overflow into the LV. Central or peripheral denervation[10] or direct brain stem damage might reduce the excitability of the central pattern generator and explain this serious delay in the initial reconfiguration phase of swallow response.[32] We found capsaicinoids had a strong therapeutic effect by enhancing the afferent sensorial input through stimulation of oropharyngeal TRPV1 channels, shortening LV closure and UES opening time and also, the time to maximal vertical extension of hyoid and larynx. Activation of suprahyoid muscles (geniohyoid, mylohyoid and anterior belly of the digastric), responsible for hyoid movement, is an early event in the swallow response following activation of the central pattern generator.[33] Hyoid motion drives laryngeal movement, LV closure and UES opening,[26,34] therefore the early occurrence of these events caused by capsaicinoids is in close association with the reduction of LV penetrations observed during capsaicinoid treatment. It is worth noting that capsaicinoids did not modify total duration of swallow response, their effects were concentrated in the first phase of swallow, that is the reconfiguration from a digestive pathway to a respiratory pathway. Animal studies showed that acetic and citric acids, which provide a sour taste, applied to the mucosa of the pharyngolaryngeal region had a similar strong facilitatory effect on swallow initiation caused by an increase in sensory inputs via the SLN and GPN*ph*.[35] In addition, trigeminal nerve fibers also express several receptors that respond to chemicals including TRPV1 and acid sensing ion channels (ASIC).[36] These experimental findings are consistent with the

classical clinical observation that sour taste facilitates the onset of swallowing.[20,37] This effect of acid, exerted at least in part, through the TRPV1,[30,38] could contribute to the observed response, as pH of the supplemented bolus was more acidic than pH of the nectar control bolus. Other studies using TRPV1 agonists also show positive clinical results on the deglutition of patients with dysphagia.[14,17-19,21] For the first time, our study shows that this pharmacological strategy strongly and specifically improves the initial phase of the swallow response by speeding the interval to LV closure, to UES opening and to maximal vertical hyoid extention as well as stronger lingual propulsion. Our results agree with those of Pelleiter[39] who observed that high citric acid stimuli (0.128 M) led to higher peak lingual swallowing pressures than water. Desensitization was not observed in response to capsaicinoids in our clinical study. A study using 30-day treatment with capsaicin (10^{-6}M/ three times at day) also found improvement in patients with OD.[18] The modification of the state of phosphorylation of TRPV1 by substance P and other neurotransmitters released by nerve afferents, might prevent their desensitization.[40] A possible limitation of the study is that, in order to minimize the exposition to the radiation of the patients, only one swallow per volume was tested in each patient, regardless of the possible within-subject variability. Further studies are needed to define the long-term effect of capsaicinoids on the impaired swallow response of chronic dysphagic patients and also to assess their effects in specific phenotypes of dysphagic patients.

In summary, our study found that the swallow response could be improved by stimulation of oropharyngeal TRPV1 by natural capsaiciniods in older patients with OD, opening the door for pharmacological modulation and treatment of impaired swallow response and oropharyngeal dysphagia in older patients.

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CAPÍTULO 6

Capítulo 6

EFFECT OF ORAL PIPERINE ON THE SWALLOW RESPONSE OF PATIENTS WITH OROPHARYNGEAL DYSPHAGIA

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Abstract

Background: Oropharyngeal dysphagia (OD) is a major gastrointestinal motility disorder that causes severe nutritional and respiratory complications in elderly and neurological patients. In an earlier study, we found that stimulation of pharyngeal sensory neurons by capsaicinoids acting on transient receptor potential vanilloid 1 (TRPV1) improved the swallow response of dysphagic patients. The aim of this study was to explore the effect of piperine, a dual TRPV1/TRPA1 agonist, on the swallow response of dysphagic patients.

Methods: A videofluoroscopic study was performed to assess the signs of impaired safety and efficacy of swallow and the swallow response of 40 dysphagic patients while swallowing one series of nectar control boluses and two series of nectar boluses supplemented with piperine. Patients were randomized into two groups: one group received 150 μM piperine and the other one 1 mM.

Results: Piperine improved the safety of swallow by: a) reducing the prevalence of unsafe swallows by -34.48% (P=0.004) at 150 μM and -57.19% (P<0.001) at 1 mM, and the severity score of the penetration-aspiration scale from 3.25±0.51 to 1.85±0.27 (P=0.003, 1mM), and b) shortening the time to laryngeal vestibule closure from 0.366±0.024s to 0.270±0.022s with 150 μM piperine (P<0.001) and from 0.380±0.032s to 0.306±0.028s with 1 mM (P<0.05).

Conclusion: Supplementing the alimentary bolus with piperine speeds swallow response and strongly improves safety of swallow in patients with OD, with a maximal therapeutic effect at 1mM. Our results suggest that activation of TRPV1/A1 in oropharyngeal sensory neurons is a very promising neurostimulation strategy for dysphagic patients.

Introduction

Oropharyngeal dysphagia (OD) is a severe and prevalent gastrointestinal motility disorder specifically classified by the World Health Organization in the International Classification of Diseases, ICD-9 and ICD-10 [1]. It mostly affects older people (from 23% of independently-living elderly [2] to up to 51% of institutionalized elderly [3]), patients with a previous stroke (from 37% in the chronic phase to 78% in the acute phase) [4] and patients with neurodegenerative diseases (such as 82% of symptomatic patients with Parkinson's disease [5] and more than 30% with multiple sclerosis [6]). OD in these patients is characterized by reduced safety of swallow with aspiration of food into the airways due to delayed laryngeal vestibule closure time and slow hyoid motion, and also by high prevalence of oropharyngeal residue, due to weak bolus propulsion forces and impaired pharyngeal clearance [7,8]. Severe pharyngeal and laryngeal sensory deficits have also been described in post-stroke patients and elderly dysphagic patients [9,10].

OD causes clinically relevant complications such as malnutrition, dehydration and aspiration pneumonia, leading to prolonged institutionalization, decreased quality of life and high mortality rates [11]. However, therapeutic strategies for dysphagic patients are scarce, have a low level of evidence and tend to focus on compensating for the motor impairments instead of aiming to improve the swallow response [12].

We have recently found that the swallow physiology of patients with OD could be improved by administering natural capsaicinoids, which act at transient receptor potential cation channel, subfamily V, member 1 (TRPV1) [13]. Prevalence of pharyngeal residue and penetrations into the laryngeal vestibule were reduced with this treatment. These results gave rise to the pharmacological neuromodulatory treatment of impaired swallow response and OD through activation of TRP channels. Other clinical studies have shown that agonists of other TRP channels (such as piperine [14], acid [15,16], menthol [17] and temperature changes [18]) also modify swallow physiology. Piperine, the main component of *Piper nigrum*, activates both TRPV1 and the transient receptor potential channel, subfamily A, member 1 (TRPA1) [19]. Nasal inhalation of black pepper oil shortens the latency of swallow reflex, in both acute and chronic settings, and increases the regional cerebral blood flow in the right medial orbitofrontal cortex and the left insular cortex [14]. These promising preliminary results need further confirmation, as the specific effects of oral piperine on the physiology of swallow response and the appropriate dose to use remain unknown.

The aim of our study was to examine the effect of oral piperine on the prevalence of videofluoroscopic signs of dysphagia and on the physiology of the swallow response of dysphagic patients in order to explore its potential value as a pharmacological therapeutic tool.

Material and Methods

Study population

A clinical study was carried out in the Gastrointestinal Physiology Laboratory and in the Radiology Unit of the Hospital de Mataró (Spain) between June 2011 and February 2012. We studied 40 patients (75.8±2.0 years, 17 men) with clinical signs of OD according to the Volume-Viscosity Swallow Test [20] associated with aging (>70 years) (n=23), neurodegenerative diseases (n=4) or stroke (n=13). Study protocol was approved by the Institutional Review Board of the Hospital de Mataró and was conducted according to the principles and rules laid down in the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from each of the included patients.

Study design

This was a double-blind, interventional, controlled study, with a pre- post-treatment design, each patient acting as his/her own control. Patients were randomly assigned into two groups and received 1 mM or 150 μM piperine (Sigma-Aldrich, St Louis, MO, USA) corresponding to maximal and EC_{50} concentrations obtained in calcium imaging studies. Baseline characteristics were collected before the intervention: sociodemographic data, functional capacity according to the Barthel Index, co-morbidities according to the Charlson Comorbidity Index and nutritional status according to the Mini Nutritional Assessment short form [21]. Clinical dysphagia symptoms were also obtained by means of the Eating Assessment Tool (EAT-10) [22] and the Sydney Swallow Questionnaire (SSQ) [23]. All participants were then imaged for the videofluoroscopic study, seated, in a lateral projection which included the oral cavity, pharynx, larynx, and cervical esophagus. Videofluoroscopic recordings were obtained with a Super XT-20 Toshiba Intensifier (Toshiba Medical Systems Europe, Zoetermeer, The Netherlands) and recorded at 25 frames/s using a Panasonic AG DVX-100B video camera (Matsushita Electric Industrial Co, Osaka, Japan). Patients were studied during the deglutition of one series of 5, 10 and 20 mL nectar control boluses (pH=6.35±0.03) and two series of 5, 10 and 20 mL nectar boluses supplemented with the corresponding concentration of piperine: 150 μM, pH=6.49±0.08 and 1 mM, pH=6.57±0.03. Following the nectar control series, a sensitization process was conducted on each patient by administering two 5-mL boluses, also supplemented with the corresponding concentration of piperine (1mM or 150 μM depending on the group), 5 min before the first treatment bolus series, and then the two piperine-supplemented bolus series were administered 10 min apart. Nectar viscosity (274.42±13.14 mPa s) was obtained by adding 3.5 g of thickener Resource ThickenUp (Nestlé Nutrition, Barcelona, Spain) to 100 mL of liquid made 1:1 with mineral water and the X-ray contrast Gastrografin (Bayer Hispania SL, Sant Joan Despí, Spain). Boluses were carefully offered to patients with a syringe.

Data analysis

Videofluoroscopic signs. Videofluoroscopic signs of safety and efficacy of deglutition were identified accordingly to previously accepted definitions: impaired tongue propulsion, oral residue and inefficient glossopalatal seal were assessed in the oral phase; vallecular, pyriform sinus residue, laryngeal vestibule penetrations and aspirations (classified according to the Penetration-Aspiration Scale [24]), and upper esophageal sphincter opening were assessed in the pharyngeal phase [7,8].

Oropharyngeal swallow response. Digitization, analysis and measurements of videofluoroscopic images were made using the software Swallowing Observer (Image and Physiology SL, Barcelona, Spain). The following quantitative measurements of oropharyngeal swallow response were obtained during 5 mL swallows: a) *Oropharyngeal reconfiguration* - timing of the opening and closing of the glossopalatal junction (GPJ), velopharyngeal junction (VPJ), laryngeal vestibule (LV), and upper esophageal sphincter (UES), GPJ opening being given the time value 0; b) *Hyoid motion* - vertical and anterior hyoid position was determined in an *xy* coordinate system in each frame. The anterior-inferior corner of C3 was used as the origin and the vertical axis was defined by a line connecting the anterior inferior corners of C3 and C5, and c) *Bolus kinematics* – mean bolus velocity (m s^{-1}) from the GPJ to the UES was also calculated.

Adverse events

Adverse events occurring during the study were documented and possible relationship to the study procedures assessed according to the Karch and Lasagna algorithm.

Statistical methods

Categorical variables were described as relative and absolute frequencies and compared by the Fisher's exact test (comparisons between groups) or the McNemar's test (comparisons within each group). Quantitative parameters were described by mean±SEM. Comparisons between groups were assessed by the non-parametric Mann–Whitney U-Test and comparisons within each group were assessed by the non-parametric Wilcoxon matched pairs test. Statistical significance was accepted if *P* values were less than 0.05. Statistical analysis was performed using GraphPad Prism 5.01 (San Diego, CA, USA).

Results

Baseline characteristics

Demographic and clinical characteristics of the study population are summarized in **Table 1**. Patients included in the study presented advanced age (75.8±2.0 years), multimorbidity (Charlson Comorbidity Index 2.7±0.3), impaired functional capacity (Barthel Index 76.1±5.2), high risk of malnutrition (Mini Nutritional Assessment short form, MNA-SF 10.5±0.5), and clinical complaints of OD (EAT-10 and SSQ questionnaires). According to the V-VST, 62.5% of patients presented signs of both impaired safety and efficacy of swallow, 7.5% only in safety and 30.0% only in efficacy.

Effect of piperine on videofluoroscopic signs of impaired safety and efficacy of swallow

All patients included in the study presented severe impairment in swallow physiology characterized by high prevalence of videofluoroscopic signs of impaired safety (70%) and/or efficacy (45%) of swallow, summarized in **Figure 1**. There were no significant differences between groups in the prevalence of videofluoroscopic signs of impaired safety or efficacy of swallow at nectar control viscosity. Treatment with piperine reduced the prevalence of penetrations by -34.48% (*P*=0.004) at 150 μM and -57.19% (*P*<0.001) at 1 mM (**Figure 1**). Maximum score on the Penetration-Aspiration Scale was not significantly affected by the treatment with 150 μM of piperine (2.10±0.25 control bolus and 1.95±0.36 150 μM piperine supplemented bolus, *P*=0.521) but was significantly reduced in the group of patients treated with 1 mM piperine (3.25±0.51 nectar control bolus to 1.85±0.27 1 mM piperine supplemented bolus, *P*=0.003). Prevalence of oral and pharyngeal residues were not significantly affected by piperine (**Figure 1**).

Table1. Demographic, clinical and nutritional characteristics of the study population. MNA-SF, Mini Nutritional Assessment short form; EAT-10, eating assessment tool -10; SSQ, Sydney Swallow Questionnaire.

	All (N=40)	150 µM group (n=20)	1 mM group (n= 20)	P value
Age (years)	75.8±2.0	76.6±2.4	75.05±3.3	0.797
Sex (men)	17 (42.5%)	9 (45%)	8 (40%)	1.00
Associated pathologies:				
Aging (>70 years)	23 (60.5%)	11 (55.0%)	12 (60.0%)	
Non-progressive neurological disease	13 (32.5%)	5 (25%)	8 (40%)	0.094
Neurodegenerative disease	4 (10.0%)	4 (20.0%)	0 (0.0 %)	
Barthel Index	76.1±5.2	78.0±6.9	74.2±7.9	0.668
Charlson Index	2.7±0.3	2.6±0.3	2.9±0.5	0.701
MNA-SF:				
Normal nutritional status (12-14)	17 (47.2%)	10 (52.6%)	7 (41.2%)	0.638
At risk of malnutrition (8-11)	12 (33.3%)	5 (26.3%)	7 (41.2%)	
Malnourished (0-7)	7 (20.6%)	4 (21.0%)	3 (17.7%)	
EAT-10	11.8±1.3	11.5±1.8	12.1±1.9	0.957
SSQ	529.6±44.9	541.0±69.2	518.1±59.1	0.787

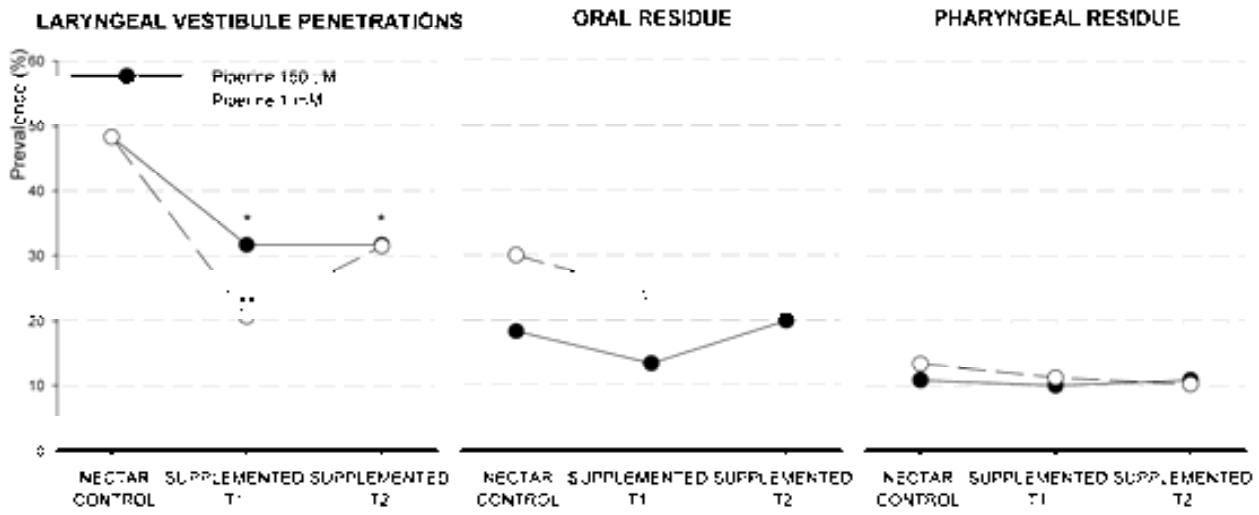

Figure 1. Effect of piperine on videofluoroscopic signs of impaired safety and efficacy of swallow Effect of piperine 150 µM (black circles) and 1 mM (white circles) on the prevalence of laryngeal vestibule penetrations (left), oral residue (middle) and pharyngeal residue (right). *p<0.05, **p<0.01

Effect of piperine on the physiology of impaired swallow response

a) Oropharyngeal reconfiguration. Bolus supplementation with piperine greatly shortened time to LV closure: 150 µM piperine reduced closure time from 0.366±0.024 s to 0.270±0.022 s (-26.2%, *P*<0.001) and 1 mM piperine from 0.380±0.032 s to 0.306±0.028 s (-19.5%, *P*<0.05). In contrast, UES opening time was not affected by piperine at either concentration. Total duration of swallow response (GPJ opening-to LV opening time) was shortened in the first series of boluses

supplemented with 150 µM piperine (1.00±0.045 s at control bolus vs 0.896±0.039 s at 150 µM piperine supplemented boluses, -10.4%, *P*<0.01) but not during the administration of 1 mM piperine concentration (1.03±0.051 s at control bolus vs 0.972±0.071 s at 1 mM piperine supplemented boluses, *P*>0.05) (**Figure 2**). When the population was divided according to patient phenotype we found that, in older patients, bolus supplementation with piperine shortened the LV closure time from 0.363±0.023 s to 0.294±0.027 s (-19.0%, *P*<0.01) and, in patients with stroke, from 0.372±0.043 s to 0.255±0.019 s (-31.5%, *P*<0.01)

b) Hyoid motion. Maximal vertical (20.11±1.56 mm) and anterior (41.68±1.34 mm) extensions were not affected by piperine at either of the concentrations tested; nor was the maximal vertical extension time (0.484±0.031 s). In contrast, the time needed to reach the maximum anterior extension of the hyoid was shortened by both concentrations of piperine, 150 µM piperine (0.668±0.058 s at nectar control bolus vs 0.514±0.038 s at bolus with 150 µM piperine, *P*<0.05), and 1 mM piperine (0.728±0.064 s at nectar control bolus vs 0.571±0.047 s at bolus with 1 mM piperine, *P*<0.05).

c) Bolus kinematics. Mean bolus velocity was not affected significantly by the supplementation of the alimentary bolus with piperine at either of the two tested concentrations (from 0.209±0.018 m/s to 0.238±0.018 m/s, *P*=0.066, at 150 µM and from 0.196±0.019 m/s to 0.217±0.018 m/s, *P*=0.320, at 1 mM).

Adverse events

One adverse event (abdominal pain) was registered in the 1 mM piperine group, but it was not considered serious nor related to the study product.

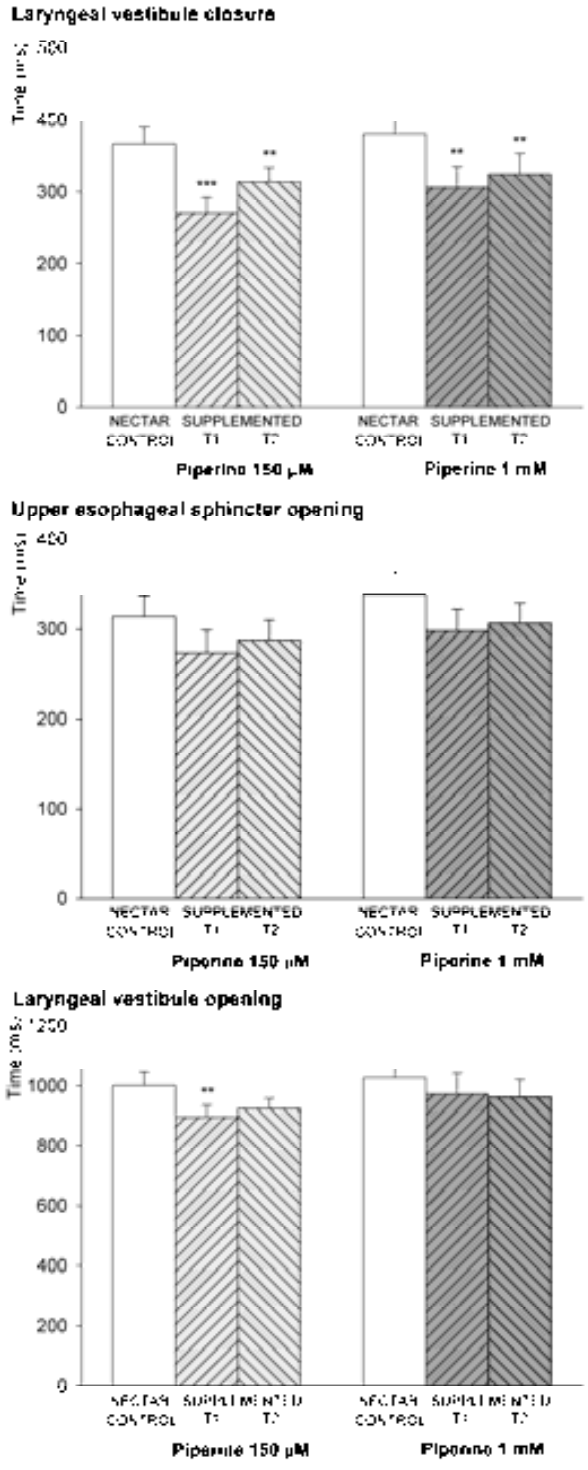

Figure 2. Effect of piperine on the timing of oropharyngeal reconfiguration Timing of main events of the oropharyngeal swallow response during 5 mL swallows. Effect of piperine 150 µM (light grey bars) and 1 mM (dark grey bars) on the laryngeal vestibule closure time (top), upper esophageal sphincter opening time (middle) and laryngeal vestibule opening time (bottom), was determined. **p<0.01, ***p<0.001.

Discussion

This study shows that the dual TRPV1/TRPA1 agonist piperine specifically and significantly improved safety of swallow of patients with dysphagia by speeding the time to airway closure, leading to a reduction in the prevalence and the severity of penetrations and aspirations. Our results suggest that impaired swallow response can be treated pharmacologically.

Standard treatment of OD consists of compensatory therapies, such as increasing liquid viscosity with thickeners, modifying texture of solids and adopting postural strategies, and rehabilitation therapies that aim to improve the swallow function through maneuvers and motor exercises. Compensatory strategies improve the safety of swallow but do not modify swallow biomechanics and do not promote swallow recovery and current rehabilitation strategies require a better cognitive level than many dysphagic patients present. Moreover, despite their widespread use, the level of evidence of these behavioral therapies is low [12].

In recent years, a new set of therapies based on neurostimulation have emerged. They aim to restore impaired swallow physiology by stimulating neural plasticity [25]. They can be classified into those that directly stimulate the pharyngeal motor cortex and corticobulbar pathways, the non-invasive brain stimulation techniques, and those that enhance the oropharyngeal afferent input by means of physical [26], electrical [27,28] or chemical [13] stimuli. The non-invasive brain stimulation techniques include repetitive transcranial magnetic stimulation (rTMS) [29] and transcranial direct current stimulation (tDCS) [30], both of which showed promising results in the first studies performed, but are limited by needing specific (and expensive in the case of rTMS) equipment and well-trained professionals to manage them. In addition, application seems limited to specific etiologies of dysphagia such as post-stroke patients. On the other hand, the neurostimulation techniques applied to the somatosensory system aim to induce reorganization of neural connections by applying peripheral stimulus in the oropharynx. Piperine is a sensory chemical stimulant that activates the TRPV1 and TRPA1 channels expressed in the sensory neurons of the oropharynx, such as the maxillary branch of trigeminal nerve (V cranial nerve), the pharyngeal branch of the glossopharyngeal nerve (GPN*ph*, IX cranial nerve) and two branches of the vagus nerve (X cranial nerve), the pharyngeal branch (X*ph*) and the superior laryngeal nerve (SLN) [31] and increases the sensory input to the brainstem and to the cortex, facilitating the triggering of the swallow response and potentially promoting neuronal reorganization. In addition, piperine could also act retronasally, activating the TRP channels expressed in olfactory sensory neurons [32] and enhancing the activation of the cortex [14]. Supplementing the alimentary bolus with piperine or other TRP agonists is an easy and cheap strategy that does not require patient collaboration, specific equipment or trained staff.

Patients included in the present study presented oropharyngeal dysphagia associated to aging, neurodegenerative diseases or stroke. This is an important point as most of the new neuromodulation techniques focus on post-stroke dysphagic patients and their effect on other dysphagia etiologies has not been investigated. The vulnerability of our population is apparent in their advanced age, multimorbidity, and poor functional and nutritional status and solutions that minimize the risk of further complications are necessary, the treatment of dysphagia being a priority. In our study, piperine reduced the prevalence of penetrations into the laryngeal vestibule at both concentrations and the severity of the penetrations at the highest concentration. Protecting patients from penetrations and aspirations is the main aim of dysphagia therapy as it has been extensively reported that impaired safety of swallow is a poor prognostic factor related with aspiration pneumonia and high mortality rates in frail elderly people [8], in elderly patients with pneumonia [33,34], in post-stroke [4,35,36] and in elderly hospitalized patients [37]. Hitherto, modification of bolus properties (viscosity and density) has been used to improve swallow safety by adapting boluses to impaired swallow physiology. This study shows that piperine protected the airways without any modification in the rheological properties of the bolus but by changing the swallow physiology, specifically by accelerating the laryngeal vestibule closure time. This effect was reported in a previous study using natural capsaicinoids at acidic pH [13]. However,

questions were raised over whether the acidic pH used in that study was partly responsible for the TRP stimulation and the observed therapeutic effect. In this study, the pH of the supplemented bolus and the control bolus was similar, so the observed effect can only be attributable to piperine. Piperine is a dual TRPV1/A1 agonist, although it activates TRPV1 more strongly than TRPA1 [19]. This could mean that the contribution of TRPV1 in the observed effects is higher than TRPA1. In order to determine the specific contribution of TRPA1, a further study using a selective TRPA1 agonist, such as cinnamaldehyde, should be performed. Likewise, unspecific TRP-independent effects cannot be completely ruled out in our study as we did not use TRP antagonists. In contrast to the study with capsaicinoids, when we supplemented the bolus with piperine no effects were observed in terms of oropharyngeal residue or bolus kinematics, indicating that we obtained a pure neurological effect without changing muscle performance. Unfortunately, no neuroimages or neurophysiologic studies could be performed to confirm the effects of oral piperine at the neurological level but a previous study evaluating the effect of nasal inhalation of piperine reported greater activation of the anterior cingulate cortex and the left insular cortex after treatment with this stimulant [14]. Further studies should be performed to measure the long-term effects of the therapy, as well as the effects on specific phenotypes of dysphagic patients.

In summary, supplementing the alimentary bolus with piperine improves swallow response in dysphagic patients. The study confirms that the activation of the TRPV1/A1 of sensory neurons is a valid strategy that could be used to develop a pharmacological treatment for these patients.

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CAPÍTULO 7

Capítulo 7

EFFECT OF SURFACE SENSORY AND MOTOR ELECTRICAL STIMULATION ON CHRONIC POST -STROKE OROPHARYNGEAL DYSFUNCTION

Rofes L, Arreola V, López I, Martin A, Sebastián M, Ciurana A, Clavé P. *Effect of surface sensory and motor electrical stimulation on chronic poststroke oropharyngeal dysfunction.* Neurogastroenterol Motil 2013; 25(11):888-e701

Abstract

Background: Chronic post-stroke oropharyngeal dysfunction (OD) is a common condition, leading to severe complications, including death. Treatments for chronic post-stroke OD are scarce. The aim of our study was to assess and compare the efficacy and safety of treatment with surface electrical stimulation at sensory and motor intensities in patients with chronic post-stroke OD.

Methods: Twenty chronic post-stroke patients with OD were randomly assigned to: a) sensory electrical stimulation (treatment intensity: 75% of motor threshold) or b) motor electrical stimulation (treatment intensity: motor threshold). Patients were treated during 10 days, 1 hour per day. Videofluoroscopy was performed at the beginning and end of the study to assess signs of impaired efficacy and safety of swallow and timing of swallow response.

Results: Patients presented advanced age (74.95±2.18), 75% were men. The mean days post-stroke was 336.26±89.6. After sensory stimulation, the number of unsafe swallows was reduced by 66.7% (P<0.001), the laryngeal vestibule closure time by 22.94% (P=0.027) and maximal vertical hyoid extension time by 18.6% (P=0.036). After motor stimulation, the number of unsafe swallows was reduced by 62.5% (P=0.002), the laryngeal vestibule closure time by 38.26% (P=0.009) and maximal vertical hyoid extension time by 24.8% (P=0.008). Moreover, the motor stimulus reduced the pharyngeal residue by 66.7%, (P=0.002), the upper esophageal sphincter opening time by 39.39% (P=0.009) and increased bolus propulsion force by 211.1% (P=0.008). No serious adverse events were detected during the treatment.

Conclusion: Surface electrical stimulation is a safe and effective treatment for chronic post-stroke dysphagic patients.

Introduction

Oropharyngeal dysfunction (OD) is a common condition after stroke, present in up to 78% of acute stroke patients [1]. The swallowing function recovers spontaneously in about 50% of patients the first weeks after stroke, but chronically persist in the other half of patients and severe complications frequently arise [2]. OD can produce two types of complications in stroke patients [3]: malnutrition and/or dehydration caused by alterations in the efficacy of deglutition, and aspiration pneumonia (AP) caused by impairment in the safety of swallow. AP is one of the major causes of mortality in stroke patients the first year after discharge [4].

The standard of care for the majority of patients with stroke suffering from OD is very poor as 80% of them are not even diagnosed and do not receive any treatment for this condition [5]. For many years, dysphagia therapy for stroke patients has been focused on behavioral compensatory strategies including changes in viscosity of fluids with thickeners, modifying texture of solid food as well as postures and maneuvers [6]. These behavioral strategies have been proved to improve safety of swallow but not the impaired swallow biomechanics [3] and do not lead to recovery of damaged neural swallow networks.

The surface electrical stimulation (e-stim) with the application of external electrical stimulation to the

muscles necessary for pharyngeal contraction was approved by the FDA in 2002 for dysphagia treatment. The first study to examine its effects on post-stroke dysphagic patients reported a significant improvement which lasted two years after treatment [7]. Since then, however, several studies have explored the safety and efficacy of e-stim, most of them reporting positive results, but many have been criticized for poor methodological quality [8;9].

Additionally, in recent years, two groups of treatments focusing on cortical neuroplasticity to recover swallowing function have been developed: those applied to the central nervous system (such as repetitive transcranial magnetic stimulation (rTMS) [10;11] or transcranial direct current stimulation (tDCS) [12] and those applied to the periphery (such as intra-pharyngeal electrical stimulation [13], tactile-thermal stimulation [14] and chemical stimulation [15]). Even though these new strategies (like rTMS and tDCS) have demonstrated their positive effects on swallow function recovery, they are still under investigation and most are not available for clinical practice. Recent studies suggest that the integration of the surface electrical stimulus by the oropharyngeal sensory neurons might also induce neuroplastic changes that could be, in part, responsible for swallowing recovery, and propose the application of surface e-stim at the sensory threshold [16]. As the number of well designed studies are limited, the optimal stimulation parameters have not been established, nor the effects of the therapy on the swallow physiology nor the mechanisms of action of the therapy. Much more research has been recommended to determine whether surface electrical stimulation has a role to play in the management of post-stroke oropharyngeal swallowing disorders [17;18].

The aim of this study was to assess and compare the efficacy and safety of 10 days of treatment with surface electrical stimulation at sensory and motor intensities, on chronic post-stroke patients with OD.

Material and Methods

Patients

Patients over the age of 18, with a previous stroke (over 3 months prior), clinical complaints of OD on discharge and who signed the informed consent, were screened for eligibility in the study, from January 2012 to October 2012, in the Gastrointestinal Physiology Laboratory of the Hospital de Mataró (Spain). Study protocol was approved by the Institutional Review Board of the Hospital de Mataró and was conducted according to the principles and rules laid down in the Declaration of Helsinki and its subsequent amendments. Trial registration: NCT01363973.

Study design

This was a proof of concept study to evaluate and compare the safety and efficacy of surface e-stim applied at sensory and motor intensities on patients with chronic post-stroke OD. A randomized, double-blind, parallel group study was designed where each patient acted as his or her own control. A initial visit was performed before the intervention and sociodemographic data, functional capacity according to the Barthel Index, co-morbidities according to the Charlson Comorbidity Index and nutritional status according to the Mini Nutritional Assessment short form [19] were collected. Clinical dysphagia symptoms were obtained by means of the Eating Assessment Tool (EAT-10) [20] and the Sydney Swallow Questionnaire (SSQ) [21]. A videofluoroscopic study was performed on all participants. Patients who presented a score of 3 or higher on the Penetration–Aspiration scale (PAS) [22] were randomized to receive 10 days of surface e-stim treatment in one of two procedures: sensory electrical stimulation (treatment intensity, 75% of motor threshold; electrode placement, thyro-hyoid) or motor electrical stimulation (treatment intensity, motor threshold; electrode placement, supra-hyoid). Both the sensory and the motor threshold were determined three times before each session. Treatment consisted of the application, at rest, of 80 Hz of transcutaneous electrical stimulus (biphasic, 700 μs) using the Intelect VitalStim device (Chattanooga Group, Hixson, TN, USA), 1 hour per day. The VitalStim device is the only e-stim device approved by the FDA for dysphagia treatment. Sessions were applied from Monday to Friday for two weeks. Five days after the last treatment session, patients were re-evaluated by videofluoroscopy and swallowing questionnaires.

Videofluoroscopic procedures

Patients were imaged while seated, in a lateral projection which included the oral cavity, pharynx, larynx, and cervical esophagus. Videofluoroscopic recordings were obtained by a Super XT-20 Toshiba Intensifier (Toshiba Medical Systems Europe, Zoetermeer, The Netherlands) and recorded at 25 frames/s using a Panasonic AG DVX-100B video camera (Matsushita Electric Industrial Co, Osaka, Japan). Patients were studied during the deglutition of one series of nectar boluses (274.42±13.14 mPa s), one series of liquid boluses (20.40±0.23 mPa s) and one series of pudding boluses (3931.23±166.15 mPa s). Nectar viscosity was obtained by adding 3.5 g and pudding by adding 8 g of thickener Resource ThickenUp (Nestlé Nutrition, Barcelona, Spain) to 100 mL of liquid made with 1:1 mineral water and the X-ray contrast Gastrografin (Bayer Hispania SL, Sant Joan Despí, Spain). Boluses were carefully offered to patients with a syringe.

Efficacy measurements

Swallowing questionnaires. The Eating Assessment Tool (EAT-10) and the Sydney Swallow Questionnaire (SSQ) were administered to all patients before and after the treatment [23]. The EAT-10 is a 10-item screening questionnaire consisting of 10 questions with answers graded 0-4 (0=no problem, 4=severe problem) on the symptoms, and clinical and social impact of oropharyngeal dysphagia. The SSQ is a 17-item clinical inventory designed to evaluate physiological aspects of oral and pharyngeal swallowing functions and establish the severity of oropharyngeal dysphagia. Each question is answered on a 100 mm visual analogue scale.

Videofluoroscopic findings. Signs of safety and efficacy of deglutition were identified accordingly to previously accepted definitions [3;24]. Efficacy signs: presence of oral, vallecular and pyriform sinus residue was assessed in each deglutition. Safety signs: laryngeal vestibule penetrations and tracheobronquial aspirations, classified according to the PAS, were assessed in each deglutition. A score of 3 or higher in the PAS was considered an unsafe swallow.

Oropharyngeal swallow response. To assess the rearrangement of the oropharyngeal structures from a respiratory pathway to a digestive pathway and the return to the respiratory pathway when the deglutition is finished, the videofluoroscopic images were digitized and analyzed using the software Swallowing Observer (Image and Physiology SL, Barcelona, Spain). Quantitative measurements of oropharyngeal swallow response were obtained during 5 mL swallows. a) Temporal analysis of swallow: timing of the opening and closing of the glossopalatal junction (GPJ), velopharyngeal junction (VPJ), laryngeal vestibule (LV), and upper esophageal sphincter (UES) were measured, GPJ opening was given the time value 0, being considered the beginning of the pharyngeal phase of swallow; b) Hyoid motion: vertical and anterior hyoid position was determined in an xy coordinate system in each frame, the anterior-inferior corner of C3 was used as the origin and the vertical axis was defined by a line connecting the anterior-inferior corners of C3 and C5; c) Bolus kinematics: mean bolus velocity (m/s) was calculated measuring the distance between the GPJ and the UES and calculating the time that the bolus spent from the GPJ to the UES, and bolus propulsion force (mN) was measured by means of Newton's second law of motion [24].

Adverse events

Any adverse events occurring during the study were documented and assessed for relationship to the study procedures.

Statistical analysis

Qualitative data are described as absolute and relative frequencies and compared by the Fischer's exact test (for comparison between groups) and McNemar's test (for evaluation before-after treatment). Quantitative data are described by the mean±SEM and compared by the U Mann-Whitney test (for comparisons between groups) or the Wilcoxon signed rank test (for comparisons before-after treatment). Statistical significance was accepted if P values were less than 0.05. Statistical analysis was performed using GraphPad Prism 5.01 (San Diego, CA, USA).

Results

Patient characteristics

A total of 42 patients were screened for eligibility in the study. Of these, 22 patients dropped out of the study before the treatment because they presented safe swallow in the VFS (PAS<3), were not able to follow the protocol or wished to withdraw. The remaining 20 were randomized, 10 to the sensory group and 10 to the motor group. All the randomized patients completed the treatment (**Figure 1**). Patients included in the study presented advanced age (74.95±2.18) and 75% (15] were men. The mean days post-stroke was 336.26±89.6, the etiology of the stroke was mainly ischemic (84.2%) and 63.2% were left-sided. Both treatment groups had comparable data at baseline (**Table 1**).

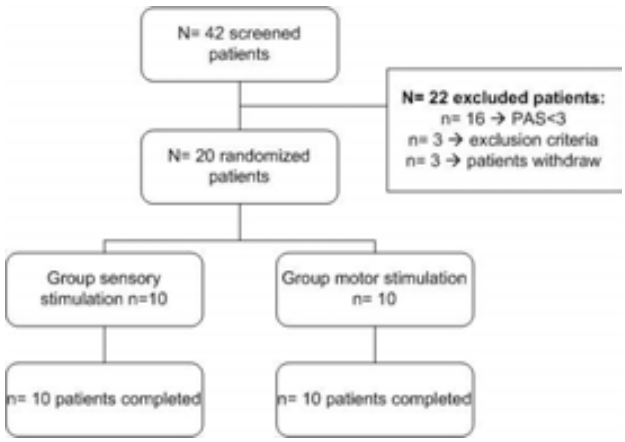

Figure 1. Trial flow chart.

Table 1. Demographic, clinical and nutritional characteristics of the study population. MNA-SF, Mini Nutritional Assessment short form; EAT-10, eating assessment tool -10; SSQ, Sydeny Swallow Questionnaire.

	Sensory group 1 (n=10)	**Motor group 2 (n=10)**	**P value**
Age (years)	72.2 ±3.6	77.7 ±2.3	0.363
Sex (men)	7 (70.0%)	8 (80.0%)	1.00
Stroke characteristics:			
Days from episode	228.3±48.3	433.4±162.6	0.438
Etiology			
Ischemic	9 (90%)	8 (80.0%)	1.00
Hemorrhagic	1 (10 %)	2 (20.0%)	
Laterality			
Left	8 (80 %)	6 (60.0%)	
Right	1 (10%)	2 (20.0%)	0.707
Brainstem	1 (10%)	2 (20.0%)	
Charslon co-morbidity index	4.1±0.48	2.8±0.36	0.078
Barthel functionality index	81.5±7.8	82.5±7.5	0.725
Nutritional status (MNA-SF)			
Well nourished	1 (10%)	1 (10%)	1.00
At risk of malnutrition	4 (40%)	4 (40%)	
Malnourished	5 (50%)	5 (50%)	
Swallowing questionnaires			
EAT-10	8.3±2.8	4.9±0.6	0.349
EAT-10 <3	3 (30%)	2 (20%)	1.00
SSQ	312.1±81.1	317.4±21.2	0.660

Effect of treatments

Swallowing questionnaires. The basal scores of the symptom questionnaires EAT-10 and SSQ are included in **Table 1** and are similar between both groups. After the treatment, patients in both groups reported improved oropharyngeal dysphagia symptoms. Patients allocated to the motor group presented significant improvement in the SSQ (-31.4%, P=0.028) but not in the EAT-10 (-26.5%, P>0.05). However, the decrease in the questionnaire score was not statistically significant in the group that received the sensory stimulus (-26.5% in the EAT-10 and -20.1% in the SSQ, P>0.05).

Videofluoroscopic signs. Before the treatment, prevalence of unsafe swallows and oropharyngeal residue were 29.8% and 43.3% respectively. Maximum PAS score in the VFS screening was 3 in 35% of patients, 4 in 35%, 5 in 15%, 7 in 5% and 8 in 10%. Safety of swallow was significantly improved by both treatment intensities. The sensory stimulus reduced the number of unsafe swallows by 66.7% (P<0.001) and the motor stimulus had a similar effect, reducing unsafe swallows by 62.5% (P=0.002) (**Figure 2A**). However, the mean PAS score was only reduced in the group of patients that were treated with the sensory stimulus (from 5.0 to 2.7, P=0.009), not the motor group (from 3.6 to 3.3, P=0.521). Regarding efficacy of swallow, oral residue was significantly reduced by both treatment intensities: the sensory stimulus reduced the prevalence of oral residue by 66.2% (P=0.011) and the motor stimulus by 70.7% (P=0.002). Pharyngeal residue was only significantly reduced by the motor treatment (66.7%, P=0.002), not in patients treated with sensory intensities (20.7%, P=0.211) (**Figure 2B**).

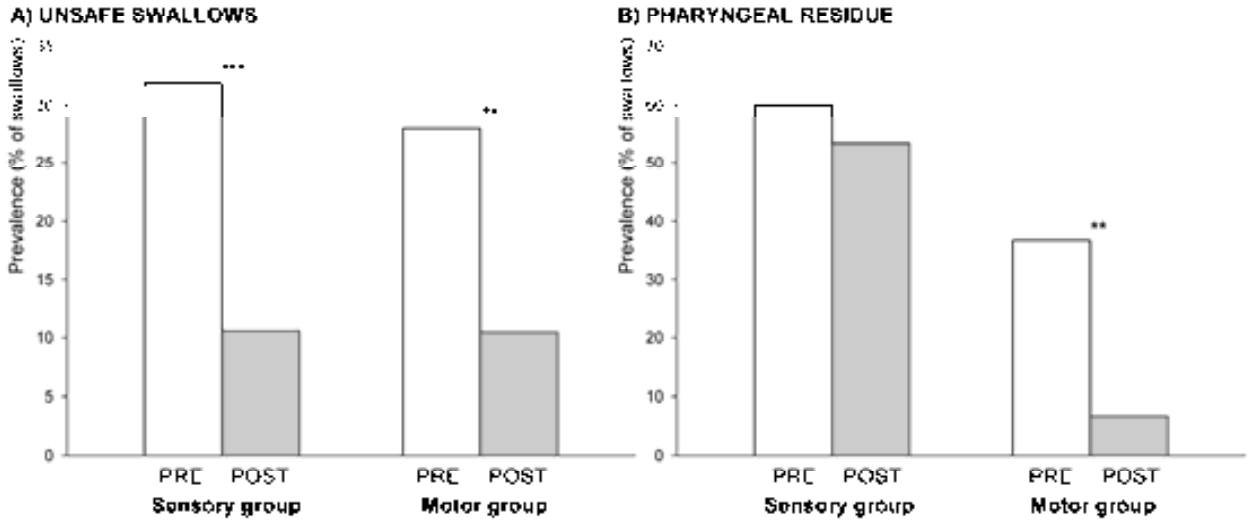

Figure 2. Videofluoroscopic signs. A) Prevalence of unsafe swallows before (white bars) and after (grey bars) the treatment with surface electrical stimulation at sensory (left) and motor (right) intensities. **B)** Prevalence of pharyngeal residue before (white bars) and after (grey bars) the treatment with surface electrical stimulation at sensory (left) and motor (right) intensities. Prevalence is expressed as the number of swallows that presented the sign during the videofluoroscopic study versus total number of swallows performed. ***P*<0.01; ****P*<0.001.

Oropharyngeal swallow response. Temporal analysis of swallow: Patients included in the study presented a prolonged and delayed swallow response. The LV closed at 448±31 ms, opened at 1080±45 ms and the UES opened at 396±34 ms. The LV closure and opening times were significantly reduced by both treatment intensities. The sensory stimulus reduced the LV closure time by 22.94% (P=0.027) and the LV opening time by 14.89% (P=0.009). Similarly, the motor treatment reduced the LV closure time by 38.26% (P=0.009) and the LV opening time by 10.85% (P=0.029). On the other hand, the UES opening time was not significantly reduced by the sensory stimulus (26.26%, P=0.108) but was reduced after the motor treatment (39.39%, P=0.009) (**Figure 3**). Hyoid motion: the maximum vertical and anterior extension was not changed by the surface electrical stimulation treatment at any of the intensities tested (**Figure 4**). In contrast, the time when the hyoid reached the maximal vertical extension was reduced significantly in both treatment groups (18.6% in the sensory group, P=0.036 and 24.8% in the motor group, P=0.008) and the time when the hyoid reached the maximal anterior extension was reduced after the motor treatment (33.8%, P=0.041) (**Figure 4**). Bolus kinematics: The sensory treatment did not significantly affect bolus velocity (from 0.241±0.035 m/s to 0.299±0.023 m/s, P=0.109) and bolus propulsion force (from 0.010 N before the treatment to 0.014 N after the treatment, P=0.148). In contrast, these parameters were significantly increased after the treatment at motor intensities: bolus velocity increased from 0.216±0.026 to 0.329±0.034 m/s (P=0.008) and bolus propulsion force from 0.009±0.002 N before the treatment to 0.019±0.003 N after the treatment (P=0.008).

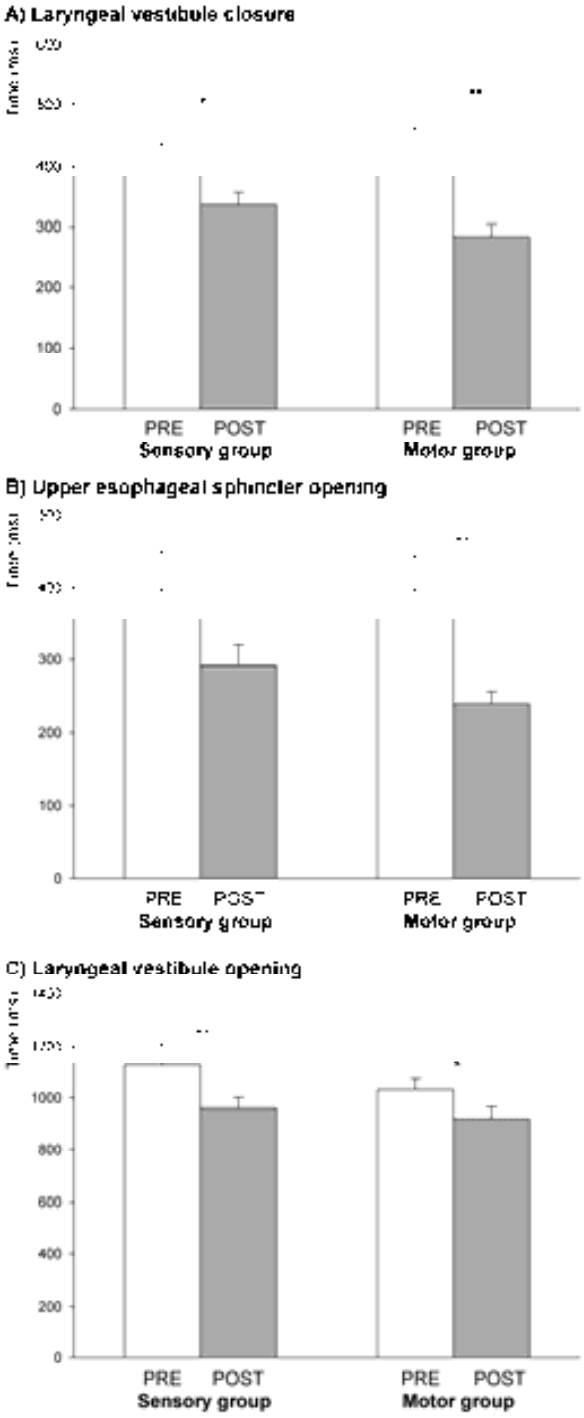

Figure 3. **Temporal analysis of swallow.** Timing of main events of the oropharyngeal swallow response during 5 mL swallows before (white bars) and after (grey bars) the treatment with surface electrical stimulation at sensory (left) and motor (right) intensities. **A)** Laryngeal vestibule closure time; **B)** Upper esophageal sphincter opening time; and **C)** Laryngeal vestibule opening time were determined. **P*<0.05, ***P*<0.01.

Adverse Events

Two adverse events were registered during the study (blood glucose increase and dental pain), both in the group of sensory stimulation, but none of them were considered serious nor related to the study intervention.

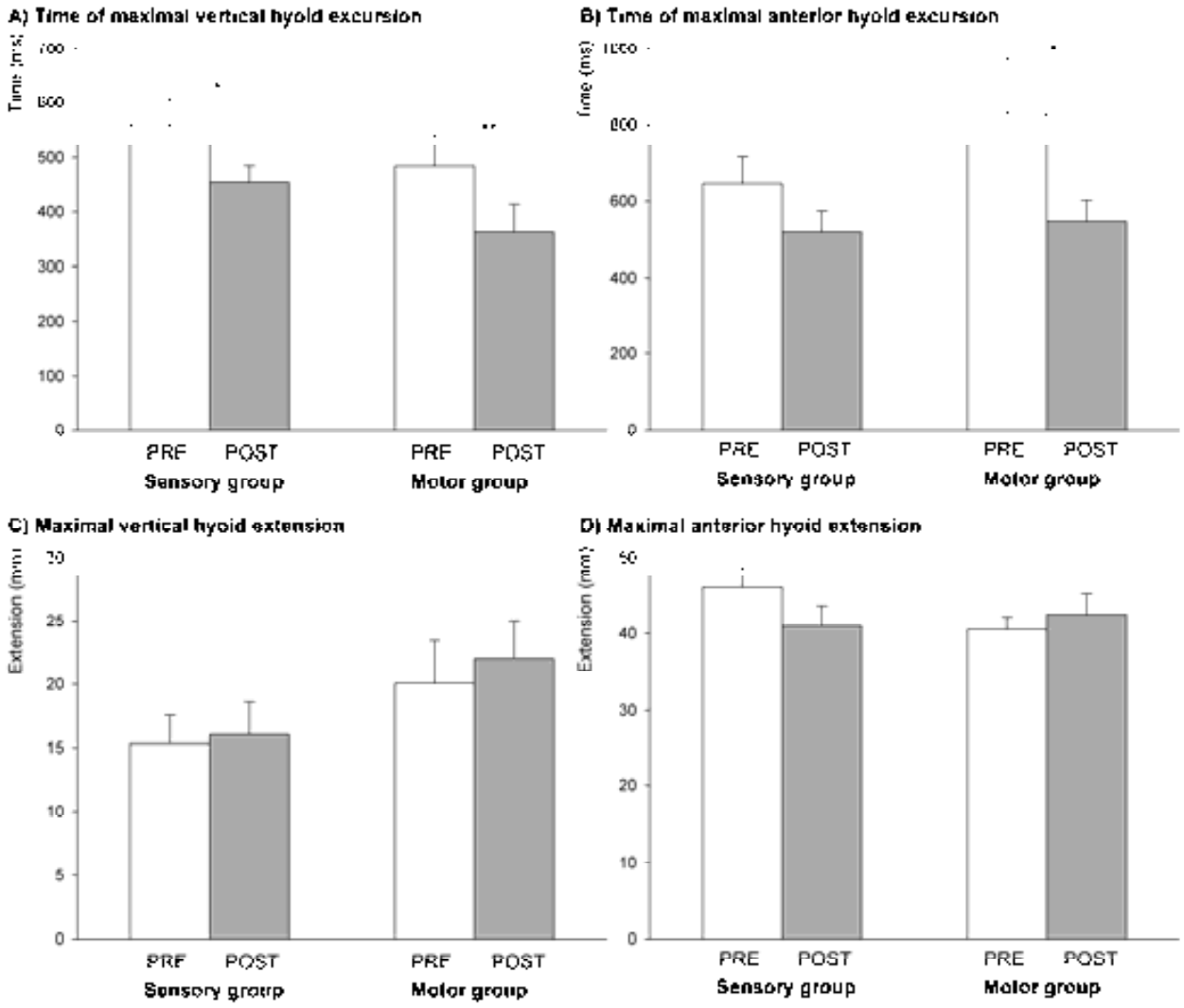

Figure 4. Maximal hyoid displacement times. Time of maximal vertical (**A**) and anterior (**B**) displacement of the hyoid bone during 5 mL swallows before (white bars) and after (grey bars) the treatment with surface electrical stimulation at sensory (left) and motor (right) intensities. * *P* <0.05, ** *P* <0.01.

Discussion

The main conclusion of this study is that surface electrical stimulation is a safe and effective therapy for chronic OD associated to stroke. Surface electrical stimulation improved the swallow response and safety of swallow both at sensory and motor intensities, and the efficacy of swallow after the motor treatment. In addition, the therapy demonstrated an excellent safety profile as any serious adverse events related to the study product were detected.

Since its approval in 2002, the e-stim therapy has been widely used, mainly in the USA. However, despite being well accepted by clinicians [25], the therapy has also been widely criticized for not meeting evidence-based medicine criteria [26].

In the present study, we used two different therapeutic approaches of surface e-stim: on the one hand, we used a sensory intensity to stimulate the peripheral sensory system through thyro-hyoid electrodes to increase afferent drive and promote cortical plasticity and, on the other hand, the electrical stimulus was applied at the motor threshold with the electrodes placed in a sub-mental position to induce muscular contraction and improve hyoid motion and laryngeal protection. We selected the sub-mental position, as previous studies showed that electrodes at motor intensity placed in a thyro-hyoid position depress the hyolaryngeal complex, a movement in the opposite direction from

that required for swallowing [27;28]. The electrodes placed in the sub-mental region target the anterior belly of the digastric, the mylohyoid and the geniohyoid muscles, pulling the hyoid bone upward and toward the mandible [29], an action that facilitates airway protection and UES opening [24]. For the sensory therapy, the thyro-hyoid position was selected, as we aimed to target the laryngo-pharyngeal sensory afferents (the glossopharyngeal nerve and the superior laryngeal nerve) that carry the sensory input to the swallowing centre of the brainstem and to the cortical and sub-cortical structures.

Patients included in the study presented chronic OD associated to stroke, advanced age, polymorbidity, and poor functional and nutritional status. Taken together, these conditions make patients vulnerable and at high risk of further complications, specifically for developing aspiration pneumonia, the major cause of mortality of stroke patients during the first year after discharge [4]. As spontaneous swallowing recovery is highly improbable at this stage of the disease, the treatment of dysphagia becomes a priority to improve the outcome of these stroke patients.

The therapeutic effect of the treatment was clinically evaluated by means of two swallowing questionnaires and a videfluoroscopic study, the gold-standard method to assess swallowing function. Patients treated with the sensory stimulus presented an important improvement in the EAT-10 and the SSQ scores, even though they did not reach statistically significance, probably because of a low statistical power due to the small study sample. On the other hand, patients treated with the motor stimulus presented significant improvement in the SSQ but not in the EAT-10. The higher complexity of the SSQ versus the EAT-10 questionnaire can explain the better sensitivity to change of the questionnaire.

One of the main results of the study is that 10 days of treatment at motor intensities reduced the prevalence of unsafe swallows of post-stroke dysphagic patients by accelerating the laryngeal vestibule closure time and the vertical hyoid movement. In addition, the treatment accelerated the anterior hyoid movement leading to the earlier opening of the UES which decreased the probability of bolus overflow into the pharynx, and increased bolus propulsion forces, reducing the prevalence of oral and pharyngeal residues. These results show that swallow physiology can be improved by this treatment even in the chronic phase of stroke. Previous controlled studies evaluating the effect of surface e-stim at motor intensities in post-stroke patients found contradictory results [7;30-32]. While Freed and Lin reported greater swallowing function after the treatment with electrical stimulation when compared with thermal-tactile stimulation, Permsirivanich and Bulow reported no significant improvement of patients treated with e-stim when compared with traditional therapy (therapeutic maneuvers and techniques). These studies differed in the stimulation parameters used, such as number of sessions performed and electrode configuration, and only reported functional swallowing changes after treatment. Our study included physiological measures and reported how chronic e-stim changes the physiology of swallow leading to an improvement in the safety of swallow. In addition, the previous studies used concurrent stimulation of infra- and supra-hyoid muscles while we used only supra-hyoid stimulation, which, as discussed above, could be more suitable to treat these patients.

The treatment with sensory stimulus also led to a strong improvement of the safety of swallow, similar to that presented by patients treated with motor stimulus, but did not significantly affect the efficacy of swallow. In a previous non-controlled study, Gallas *et al* [14] also reported that swallowing dysfunction could be improved using sensitive surface electrical stimulation. In that study, however, the sensory electrical stimulation was combined with swallowing exercises that could have been partly responsible for the observed effects. Even though the study of Gallas *et al* failed to demonstrate any effect of the therapy at cortical levels, previous studies using similar paradigms of peripheral sensory stimulation had. The application of an intrapharyngeal electrical stimulus increased the cortical excitability of dysphagic post-stroke patients that was strongly associated to an improvement of the swallowing behavior [13]. Our results suggest that impaired airway protection can be treated at sensory level. In contrast, the impairment in bolus transfer should be treated at motor intensities.

The mechanisms underlying the efficacy of surface electrical stimulation in the treatment of post-stroke OD are not well known. It has been proposed that both peripheral and central modifications can be responsible for the effect of the therapy. At the peripheral site, modifications in muscle activation by the nervous system and/or alterations in muscle structure can occur and improve force production, coordination and precision of the contraction. Moreover, peripheral sensory nerves, that have a lower threshold of excitability compared with the sarcolemma surrounding muscle fibers, can also be activated and lead to cortical activation promoting both short-term and long-term neuroplasticity, facilitating deglutition and airway protection. We hypothesize that the improvement in safety of swallow achieved by the sensory stimulation is due to the stimulation of these peripheral pharyngeal and laryngeal sensory nerves. The greater effect observed when the stimulus was applied at motor intensities may be due to two reasons: on the one hand, the muscle contraction produced by the motor stimulus might lead to modifications in the supra-hyoid muscles or their innervation that sensory stimulus could not achieve and, on the other hand, the higher intensity of the stimulus used in the motor group could lead to higher activation of the central nervous system structures. A dose-response relationship has been reported between the intensity of the peripheral nerve electrical stimulation and the intensity of activation of the primary sensory and motor cortex, cingulate gyrus and cerebellum, for the lower extremities of healthy subjects [33]. Although it remains unknown whether a similar dose-response relationship exists regarding pharyngeal stimulation in individuals with stroke, the greater activation of the cortical and subcortical areas together with muscle rehabilitation could explain the effects of the motor e-stim. Sensory e-stim, however, seems limited to neural controlled events and not to affect muscle strength.

The absence of serious adverse events was also an important finding of the study, demonstrating that it is a safe and well tolerated therapy for dysphagia treatment.

A limitation of the study was that it was designed as a quasi-experimental study (pre- post- treatment study) with a small sample size and without a control group. Even though spontaneous recovery of the swallowing function can be practically dismissed as patients were studied in the chronic phase of stroke, we did not compare our intervention with standard swallowing treatment, and therefore we cannot discount that similar results could not have been reached by the current therapeutic alternatives nor completely rule out the possibility of a “placebo effect”. Further large randomized controlled trials will be necessary to assess and evaluate the effect of the therapy on clinical outcome of patients for factors such as incidence of aspiration pneumonia, nutritional status and mortality rates. Moreover, neurophysiologic studies including the measurement of cortical excitability will be necessary to confirm the action mechanism of the therapy.

In conclusion, our study shows that surface e-stim is a safe and effective therapy for chronic post-stroke dysphagic patients, with specific effects on the safety and efficacy of swallowing. However, further investigation involving a control group, greater number of patients, prolonged follow-up and effect on clinical outcomes are needed to confirm the clinical utility of this therapy.

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DISCUSIÓN GENERAL

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La presente Tesis Doctoral consta de un conjunto de estudios clínicos, todos ellos publicados en revistas internacionales indexadas y con factor de impacto, que han pretendido abordar de forma integrada diferentes aspectos de la disfagia orofaríngea en el paciente adulto, que van desde el estudio diagnóstico al fisiopatológico, y con especial énfasis, se centra en el desarrollo de nuevas estrategias terapéuticas para los pacientes con disfagia neurógena y asociada al envejecimiento. Cabe destacar que todos los estudios de los que consta esta Tesis Doctoral se han realizado utilizando la técnica patrón de oro para el estudio de la deglución, la videofluoroscopia (VFS), permitiendo así una evaluación exhaustiva de los mecanismos deglutorios y sus alteraciones en los diferentes grupos de pacientes estudiados y un análisis objetivo del efecto de los tratamientos. En los diferentes capítulos que forman esta Tesis Doctoral se han tratado los siguientes puntos:

En el **Capítulo 1**, se presenta:

- La precisión diagnóstica de un cuestionario de cribado (EAT-10) y un método de evaluación clínica para la disfagia orofaríngea (MECV-V). Hemos determinado la sensibilidad, especificidad y valores predictivos positivos y negativos de ambos métodos frente al test de referencia, la VFS. Para el cuestionario de cribado EAT-10 hemos establecido el punto de corte de la puntuación del cuestionario para identificar a los pacientes con DO.

En los **Capítulos 2** y **3**, se aborda el:

- Estudio de la fisiopatología deglutoria de dos fenotipos de pacientes en riesgo de disfagia orofaríngea: el anciano frágil y el anciano con CAP. Se caracteriza el proceso deglutorio de estos pacientes con el objetivo de identificar las alteraciones biomecánicas críticas que conducen a las alteraciones de seguridad y eficacia de la deglución que presentan.

- Estudio de la disfagia orofaríngea como factor de riesgo para el desarrollo de CAP en el anciano y como factor de mal pronóstico clínico en el anciano frágil y en el anciano con CAP.

En los **Capítulos 4**, **5**, **6** y **7** se evalúan nuevas alternativas terapéuticas para el tratamiento de los pacientes con disfagia orofaríngea. Específicamente se evalúa:

- Un tratamiento compensador: efecto de los espesantes de goma xantana.

- Un tratamiento de neuro-estimulación: efecto del aumento del *input* sensorial a través de la adición al bolo alimentario de agonistas naturales de la familia de receptores TRP, y

- Un tratamiento neuro-rehabilitador: efecto de dos protocolos de estimulación eléctrica transcutánea (nivel de estimulación sensorial y motora) en pacientes con disfagia que han sufrido un ictus.

Precisión diagnóstica de un cuestionario de cribado y un método de evaluación clínica para la DO

La disfagia es un trastorno del sistema digestivo específicamente clasificado por la WHO en la *International Statistical Classification of Diseases and Related Health Problems* (ICD-10), recibiendo el código R13 para identificar su diagnóstico [1]. Sin embargo, a pesar de la alta prevalencia y las graves consecuencias de la DO en el paciente anciano y en el paciente neurológico, la DO continúa siendo un trastorno infra-diagnosticado, y en consecuencia, infra-tratado [2,3]. Sin embargo, los métodos instrumentales de referencia para el estudio y el diagnóstico del trastorno deglutorio no

están disponibles en todos los centros sanitarios. Además, el conocimiento del trastorno deglutorio por parte del profesional sanitario es bajo, lo que contribuye a una situación de desatención y falta de equidad al trato del paciente con DO. A pesar de que las guías de práctica clínica, por ejemplo de manejo del paciente con ictus, recomiendan la evaluación de la función deglutoria lo más pronto posible [4], la realidad es que las auditorías realizadas en nuestro país demuestran que sólo se realizan un 45.8% (IC 95% 42.7-48.8) de tests de disfagia válidos para evaluar la función deglutoria antes del inicio de la dieta o medicación oral en la fase aguda del ictus [5]. En contraposición a este hecho, se ha descrito que cuando se implementan programas estructurados que evalúan la presencia y tratan la DO en los hospitales y otros centros sanitarios, se reduce la incidencia de neumonía, los costos en antibióticos y las tasas de mortalidad de forma sistemática [6;7]. Por este motivo, es de especial interés el desarrollo de métodos de cribado y de evaluación clínica que puedan ser aplicados de forma amplia y nos permitan seleccionar aquellos pacientes que deben ser derivados a realizarse la prueba instrumental o que nos permitan abordar su tratamiento en el caso que la prueba instrumental no esté disponible. Los métodos de cribado y evaluación clínica del paciente con DO deberían ser sensibles, específicos, de fácil y rápida administración, así como coste-efectivos [8]. En la literatura, hay disponibles una gran variedad de métodos de cribado y de evaluación clínica para la DO. La decisión de cuál de ellos debemos implementar y usar en la práctica clínica debería basarse en su fiabilidad, validez, capacidad discriminatoria y propósito evaluativo [9]. En el **Capítulo 1** de esta Tesis Doctoral hemos evaluado un cuestionario de cribado, el EAT-10, y un método de evaluación clínica, el MECV-V, que consideramos cumplen los requisitos necesarios para ser implementados en la práctica clínica habitual del algoritmo diagnóstico del paciente en riesgo de DO.

El proceso de cribado de la DO debería detectar aquel paciente en riesgo de padecer alteraciones deglutorias. Para el profesional sanitario familiarizado con la disfagia este proceso puede llevarse a cabo mediante la anamnesis y la exploración física del paciente. Sin embargo, tal y como se ha mencionado anteriormente, la dificultad de perfilar el conocimiento de la disfagia orofaringea dificulta la identificación de los pacientes en riesgo. Es aquí donde los cuestionarios de síntomas deglutorios podrían tener su mayor aplicación, ya que de una manera rápida y sencilla podrían facilitar esta identificación al profesional sanitario que no está específicamente entrenado en el diagnóstico de la disfagia, especialmente aquellos que se enfrentan a poblaciones en las que la prevalencia de disfagia no es muy elevada como puede ser el ámbito de atención primaria. Cuando buscamos una herramienta de cribado de primera línea en un proceso diagnóstico, la sensibilidad debe primar sobre la especificidad, ya que el interés principal es no dejar de diagnosticar ningún posible paciente afectado (no tener falsos negativos) a pesar de que aumentemos el ratio de falsos positivos, ya que el coste de no identificar un paciente con disfagia (factor de mal pronóstico tal y como se ha mostrado en los **Capítulos 2** y **3** y se discutirá posteriormente) es mucho mayor al de incluir un paciente sano en el proceso diagnóstico el cual podrá ser descartado con exploraciones posteriores más específicas y que comportan un mínimo riesgo. Este hecho es especialmente importante en una enfermedad con complicaciones potencialmente muy severas como es el caso de la DO. El cuestionario EAT-10 (ver **Anexo 1**) puede ser una buena alternativa en este proceso de

cribado gracias a la alta sensibilidad y PPV que presenta. Nuestros resultados permiten recomendar utilizar un punto de corte de 2 para determinar aquellos pacientes en riesgo de disfagia que deberían remitirse a un examen deglutorio más exhaustivo, a pesar de que en un estudio previo [10] se recomendó utilizar un punto de corte de 3. Esta recomendación se fundamenta en dos grupos de datos: primero, porque de acuerdo con los resultados de la curva ROC (*Receiver Operating Characteristic*) disminuir el punto de corte de 3 a 2 implica un aumento de sensibilidad de un 5% sin que disminuya la especificidad del test; y segundo, porque el punto de corte de 3 se estableció tomando el límite superior del intervalo de referencia de una población sana (media + 2 desviaciones estándar), el cual se puede superponer con el límite inferior del intervalo en la población enferma, lo cual puede llevar a la clasificación errónea de pacientes con disfagia, con el riesgo que esto conlleva.

El MECV-V es uno de los dos métodos de exploración clínica, junto con el *Toronto Bedside Swallowing Screening Test* (TOR-BSST) [11], recomendados para la exploración de pacientes neurológicos según una reciente revisión sistemática [12]. La calidad metodológica de los estudios en los que se validaron estos dos métodos, junto con sus características psicométricas, así como su aplicabilidad los hacen superiores a tests ampliamente usados como el test del agua [13;14]. El estudio de validación del MECV-V frente a VFS en la que se basa esta revisión fue publicado en 1998 por Clavé *et al* [15]. En este nuevo estudio hemos re-validado el test utilizando un nuevo espesante (Resource ThickenUp Clear, Nestlé Health Science, Lausanne, Switzerland) y ampliado la población de estudio no limitándonos sólo a los pacientes neurológicos si no incluyendo también pacientes ancianos, ya que será la población final en la que será utilizado el test. Estos resultados confirman que el test posee las características psicométricas adecuadas para ser implementado en la práctica clínica. Además, se ha podido determinar la correlación entre evaluadores, parámetro que no se evaluó en el estudio inicial [15], y que ha sido considerada buena. Nuestra principal conclusión es que el MECV-V es un método que, si es aplicado por personal entrenado, ofrece unas características óptimas para la detección y manejo del paciente con DO.

Fisiopatología de la DO en ancianos: el fenotipo frágil y los ancianos con neumonía adquirida en la comunidad

La prevalencia de disfagia orofaríngea en la población anciana es elevada. Se han reportado prevalencias que van desde el 11.4%- 33.7% en ancianos de la comunidad [16-18], de entre el 40-51% en ancianos hospitalizados [19;20], y hasta el 55% de los ancianos hospitalizados con neumonía [21]. El proceso natural de envejecimiento conduce a una pérdida progresiva de masa muscular y fuerza, conocida como sarcopenia [22]. Además, el envejecimiento también se asocia a un proceso progresivo de neurodegeneración, tanto a nivel de sistema nervioso central como periférico. Esta pérdida de funcionalidad tanto de los elementos neuronales como musculares, acaba conduciendo, entre otros, a cambios no patológicos en el proceso deglutorio conocidos como *presbifagia*. Estos cambios incluyen una disminución de la presión lingual isométrica y un enlentecimiento en el movimiento de las principales estructuras orofaríngeas durante la deglución [23]. Sin embargo, cuando esta pérdida de reserva funcional se combina con otros factores como pueden ser diferentes co-morbididades y/ o sus tratamientos,

pueden conducir a un deterioro patológico del proceso deglutorio y a la presencia de disfagia orofaríngea. El segundo objetivo de esta tesis ha sido la caracterización de las alteraciones de la deglución en el anciano frágil [24] y en el anciano con neumonía adquirida en la comunidad (CAP), dos fenotipos de ancianos en especial riesgo de sufrir disfagia orofaríngea. Nuestro objetivo ha sido identificar aquellos factores fisiopatológicos críticos que conducen a las alteraciones de la seguridad y de la eficacia de la deglución en estos dos fenotipos de pacientes para identificar aquellos puntos clave en los cuales deberíamos focalizar el tratamiento de la disfagia para compensarlos o revertirlos y así evitar las complicaciones que de ellos se derivan.

En el estudio en pacientes ancianos frágiles (**Capítulo 2**) observamos que, en efecto, este grupo poblacional presentaba un patrón motor deglutorio retardado y prolongado, mostrando un retraso en el cierre del vestíbulo laríngeo (LV) y en la apertura del UES, así como una duración total de la respuesta motora orofaringea mayor comparada con los voluntarios jóvenes. Presentaban además alteraciones en el movimiento del hioides y débil fuerza de propulsión del bolo que vimos reflejada en la baja velocidad de tránsito faríngeo. Estos cambios en la fisiología deglutoria, conducen a alteraciones patológicas en nuestro grupo de ancianos frágiles (evidenciadas como signos videofluoroscópicos), grupo con alto número de co-morbididades y síndromes geriátricos: hasta el 57,1% presentaron penetraciones en el LV y un 17,1% aspiraciones durante la deglución de líquidos. Pudimos observar que el factor clave que determinaba la presencia de alteraciones de la seguridad de la deglución era un retraso en el cierre del vestíbulo laríngeo, y en menor medida un movimiento vertical del hioides también retardado. Por otro lado, la eficacia de la deglución también estaba afectada en este grupo de pacientes, reflejada por la alta prevalencia de residuo oral y faríngeo. Se observó que el factor crítico que diferenciaba los pacientes con alteración de la eficacia de la deglución de los que presentaban deglución eficaz, además de un retraso en la respuesta motora orofaríngea, era especialmente una débil fuerza de propulsión del bolo alimentario. La fuerza de propulsión del bolo fue calculada mediante el análisis de las imágenes VFS, tal y como se ha descrito en la Introducción. Actualmente estamos correlacionando en nuestra Unidad este método indirecto de evaluación de la fuerza de propulsión del bolo alimentario frente métodos directos de evaluación de la presión lingual (*Iowa Oral Performance Instrument*, IOPI).

En resumen, hemos identificado los dos grandes factores responsables de la DO en estos dos grupos de pacientes, factores a los que deberían dirigirse los tratamientos para la disfagia: el primero de ellos, primordialmente de origen neurológico, es el **retraso en el cierre de la vía respiratoria**, y el segundo de ellos, primordialmente de origen muscular, la **débil fuerza de propulsión del bolo alimentario**. Resultados similares fueron encontrados en el grupo de pacientes ancianos con CAP (**Capítulo 3**). El 52.8% de estos pacientes presentaron alteraciones de la seguridad, y del mismo modo que en el grupo de ancianos frágiles, se relacionaron con un retraso en el cierre del vestíbulo laríngeo y en el movimiento vertical del hioides. Estudios anteriores realizados por nuestro grupo en pacientes neurológicos [25;26], también encontraron que el tiempo que transcurría entre la apertura del selllo glosopalatino y el cierre del LV era el predictor principal de la presencia de penetraciones y aspiraciones. Ambos estudios identificaban también el retraso en la apertura del UES como un factor clave que condiciona la seguridad de la deglución. Sin embargo, en

nuestros estudios con ancianos el retraso en la apertura del UES no se asoció con alteraciones de la seguridad. Es cierto que un retraso en la apertura del UES puede ocasionar el acumulo del bolo alimentario en la hipofaringe que puede llegar a rebosar a la vía respiratoria, causando aspiraciones durante la deglución y por otro lado, incrementar el residuo faríngeo, lo que contribuye al desarrollo de aspiraciones post-deglutorias. En nuestros estudios actuales, las penetraciones/ aspiraciones que ocurren durante la deglución son las que hemos observado con mayor frecuencia.

La DO como factor de riesgo para el desarrollo de CAP y factor de mal pronóstico en el anciano frágil y en el anciano con CAP

Las alteraciones de la seguridad y de la eficacia de la deglución que hemos descrito en estos dos fenotipos de ancianos pueden conducir a graves complicaciones: la alteración de la eficacia de la deglución se asocia a la presencia de malnutrición y la alteración de la seguridad, al desarrollo de infecciones respiratorias [27].

La disfagia y sus complicaciones son factores íntimamente ligados que se retroalimentan: las alteraciones deglutorias aumentan el riesgo de malnutrición y de aparición de infecciones respiratorias; la malnutrición es un factor que se ha asociado al desarrollo de sarcopenia, fragilidad y alteración del sistema inmunológico en el anciano. Estos factores cierran el círculo empeorando aún más el trastorno deglutorio y el estado nutricional, y aumentando el riesgo de infecciones respiratorias (**Figura 1**). Todos estos factores que se retroalimentan entre ellos forman un círculo vicioso que se asocia a una alta mortalidad.

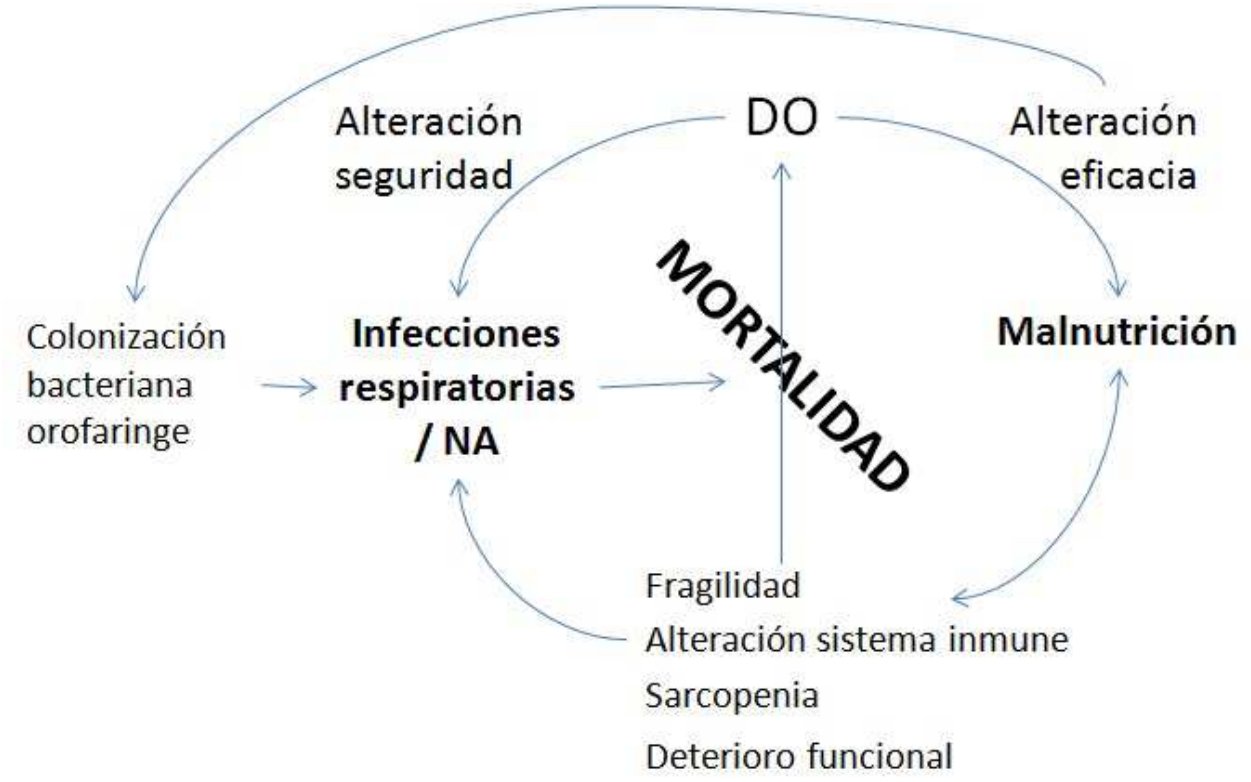

Figura 1: Fisiopatologia de las complicaciones nutricionales y respiratorias asociadas a la disfagia orofaríngea en el anciano. Adaptado de: Rofes *et al* 2011 [27].

La relación entre DO y neumonía aspirativa (AP) está bien establecida en el anciano [28;29], es más, muchos autores consideran el riesgo de aspiración condición *sine qua non* para el diagnóstico de la AP [30;31]. Así pues, la alteración de la seguridad de la deglución, junto con la colonización de la orofaringe por bacterias patógenas (a menudo consecuencia de una mala higiene oral) y la alteración del sistema inmune (frecuentemente asociada a malnutrición), conforman los tres pilares básicos que explican la patogenia de la AP. Sin embargo, la alta incidencia de CAP en el anciano no se asocia en la práctica clínica habitual a la existencia de un trastorno deglutorio, a pesar de que algunos estudios han apuntado su relación [32-34], sino que habitualmente se considera la consecuencia de la alta prevalencia de co-morbididades y/o enfermedades crónicas en esta población de edad avanzada. La alta prevalencia de DO en el anciano, especialmente en los ingresados con neumonía [21], debería llevarnos a pensar que una gran parte de las CAP en esta población podría tener etología aspirativa, pero la literatura existente al respecto presenta importantes discordancias [35;36]. El **Capítulo 3** de esta Tesis Doctoral incluye un estudio de casos-controles realizado para determinar si la disfagia orofaríngea podría ser un factor de riesgo de CAP en ancianos. Para determinar la presencia de DO, tanto los casos como los controles fueron estudiados de forma prospectiva mediante el MECV-V [15]. Éste es un dato importante ya que en los estudios epidemiológicos previos, la relación entre CAP y DO se había realizado utilizando registros clínicos o sistemas de evaluación no validados para determinar la presencia de DO. Al ser la DO un trastorno poco reconocido y considerado, puede llevar al infra-diagnóstico del trastorno deglutorio en pacientes con CAP [32;33]. Y efectivamente, el análisis multivariado mostró que la DO se asociaba de forma independiente con la CAP después de ajustar por los diferentes factores de confusión (capacidad funcional, COPD, insuficiencia cardíaca). Puede ser discutible que la evaluación deglutoria en este estudio se realizase durante el ingreso de los pacientes, momento en el cual podrían presentar un declive funcional transitorio que magnificase la alteración deglutoria, complicando el establecimiento de la relación de causalidad. Sin embargo, en un estudio de cohortes realizado en una población de unas características similares a las estudiadas (ancianos viviendo de forma independiente en la comunidad), después de un año de seguimiento encontraron que las alteraciones de la seguridad de la deglución se relacionaban con una mayor incidencia de infecciones de las vías respiratorias inferiores [37], favoreciendo la hipótesis que la alteración deglutoria sería la causa, y no la consecuencia de la CAP, y de que, tal y como apuntaban Teramoto *et al* [36] en su estudio, una gran parte de las CAP en el anciano podrían ser de etiología aspirativa y la DO podría jugar un papel muy relevante en su patogenia.

Del mismo modo, en el estudio en ancianos frágiles (**Capítulo 2**), también evaluamos si los trastornos deglutorios podrían ser un factor de mal pronóstico clínico. En ancianos frágiles, tanto la alteración de la seguridad como de la eficacia de la deglución se asociaron con unos índices de mortalidad al año significativamente superiores a los de los ancianos que no presentaron estas alteraciones deglutorias. En el caso de los ancianos que fueron ingresados con CAP, la alteración de la seguridad de la deglución también se asoció con una mayor mortalidad al año. El peor estado funcional, la mayor presencia de co-morbididades e índices de fragilidad en aquellos pacientes con disfagia podrían contribuir al peor pronóstico observado; sin embargo, un estudio realizado en nuestro centro en

mayores de 80 años ingresados en la Unidad Geriátrica de Agudos, en que se ajustó la supervivencia por edad, funcionalidad y co-morbididades, determinó que la disfagia orofaríngea era un factor de mal pronóstico independiente [21]. En pacientes que han sufrido un ictus el trastorno deglutorio también se ha asociado a un mayor riesgo de sufrir neumonía por aspiración [38], lo cual también se asocia a un mayor riesgo de mortalidad [39].

Nuevas alternativas terapéuticas para el paciente con disfagia orofaríngea

La necesidad de intervención para romper el círculo descrito en la **Figura 1** se hace evidente. A pesar de la relevancia clínica de la DO, las alternativas terapéuticas de las que disponemos para su tratamiento son escasas. Además, la evidencia científica existente hasta el momento de la eficacia de dichos tratamientos es limitada. Speyer *et al* [40] concluían en su revisión sistemática de los efectos de la terapia administrada por logopedas en la disfagia orofaríngea que, a pesar de que la mayoría de estudios reportaban efectos significativos, las conclusiones no podían generalizarse debido al bajo número de estudios existentes y algunos problemas metodológicos de los mismos. Una reciente revisión Cochrane [41] en la que se evaluó la efectividad de diferentes intervenciones para el tratamiento de la disfagia en pacientes que habían sufrido un ictus concluyó que no existe evidencia suficiente para determinar si las terapias existentes tienen un efecto significativo en la evolución clínica del paciente o sobre la tasa de mortalidad asociada a la DO. Ambas revisiones concluyen que es necesario realizar estudios clínicos adicionales con un buen diseño metodológico para generar un nivel de evidencia mayor que justifique la utilización de los tratamientos actuales así como desarrollar nuevas alternativas terapéuticas más eficaces, diseñadas para combatir específicamente las alteraciones fisiopatológicas del paciente con DO.

Gran parte del trabajo desarrollado durante esta Tesis Doctoral, una vez caracterizado el patrón fisiopatológico del paciente anciano con DO y evaluado dos herramientas diagnósticas que pueden ayudar a su identificación, se ha centrado precisamente en el objetivo de mejorar la terapéutica del trastorno deglutorio, tanto mediante **estrategias compensatorias** (nueva generación de espesantes), como mediante **tratamientos activos** (neuro-estimulación mediante estímulos químicos o eléctricos). En la **Tabla 1** se muestra un resumen del efecto terapéutico de las diferentes estrategias evaluadas en los estudios incluidos en esta Tesis Doctoral en los diferentes fenotipos de pacientes con DO estudiados. La tabla no pretende ser una comparación directa de las diferentes estrategias estudiadas, ya que las poblaciones en las que se han evaluado son distintas, pero sí pretende ser una guía que facilite su discusión.

Tratamiento	Capítulo	Población estudiada (fenotipo)	Condición evaluada	EFECTO TERAPÉUTICO							
				SEGURIDAD				EFICACIA			
				Penetraciones	Aspiraciones	Tiempo cierre LV	Tiempo vertical hioides	Residuo oral	Residuo faríngeo	Velocidad del bolo	Tiempo apertura UES
Espesante almidón	1	Ancianos frágiles	Néctar	-7,5%*	-46,8%*	---	---	NS	+16,8%*	---	---
			Pudín	-64,1%***	-60,2%*			+24,2%*	+47,9%*		
	5	Ancianos	Néctar	-31,7%*	---	NS	NS	NS	NS	NS	NS
			Pudín	-80,9%*		NS	NS	NS	+70,6%*	-23,1%*	+33,3%*
Espesante goma xantana	4	Ancianos + NDG + NNP	Néctar	-61,2%**	-39,4%**	NS	NS	NS	NS	NS	NS
			Pudín	-73,6%**	-73,3%**	NS	NS	NS	NS	-13,7%*	+30,2%*
		Jóvenes sanos	Néctar	NS	NS	NS	---	NS	NS	---	NS
			Pudín	NS	NS	+34,5%**	---	NS	NS	---	+28,6%**
Capsaicina	5	Ancianos	150 µM	-50,0%*	---	-27,8%***	-28,2%*	NS	-50,0%**	+24,7%**	-19,6%*
Piperina	6	Ancianos + NDG + NNP	150 µM	-34,5%**	---	-26,2%***	NS	NS	NS	NS	NS
			1 mM	-57,2%***		-19,5%**	NS	NS	NS	NS	NS
***e-stim* transcutánea**	7	Ictus crónico (PAS>2)	Sensorial	-66,7%***	---	-22,9%*	-18,6%*	-66,2%*	NS	NS	NS
			Motora	-62,5%**		-38,3%**	-24,8%**	-70,7%**	-66,7%**	+52,3%**	-39,4%**

Tabla 1: Resumen del efecto terapéutico de las diferentes estrategias terapéuticas evaluadas en esta Tesis. Los resultados se expresan como el porcentaje (%) de cambio de la condición evaluada respecto a la condición control, que es: líquido, en los estudios con espesantes; néctar sin suplementar en los estudios con capsaicina y piperina; estado antes del tratamiento, en el estudio con *e-stim* trans-cutánea. Se especifica en cada caso el nivel de significación estadística (*P<0,05; **P<0,01; ***P<0,001). Los casos en los que no se detectó cambio significativo de la condición evaluada respecto a la condición control, se han identificado con NS (no significativo). Las variables que no se evaluaron específicamente o no se reportaron en los estudios correspondientes se han marcado con un guión horizontal. NDG, enfermedades neurodegenerativas; NNP, enfermedades neurológicas no progresivas; PAS, escala de penetración-aspiración; LV, vestíbulo laríngeo; UES, esfínter esofágico superior.

Efectos de los tratamientos sobre la seguridad de la deglución

Tradicionalmente, en pacientes que presentan penetraciones en el vestíbulo laríngeo o aspiraciones cuando degluten líquidos, se han utilizado **espesantes** para aumentar su viscosidad y así incrementar la seguridad de la deglución. A pesar de ser una práctica generalizada en el tratamiento de los pacientes con DO, el número de estudios que evalúan específicamente su efecto terapeútico es limitado [25;42;43] por lo que la evidencia científica de la eficacia de los espesantes es escasa [40]. Además, la falta de consenso en cuanto a la nomenclatura, definición y características de los diferentes niveles de modificación de la viscosidad de los líquidos, dificulta aún más la generalización de los resultados obtenidos y la evaluación objetiva del efecto de la terapia. En los últimos tiempos se está trabajando en este sentido y han surgido diferentes iniciativas como la *International Dysphagia Diet Standarisation Innitiative* (http://iddsi.org/) que tiene como objetivo desarrollar definiciones estandarizadas para la modificación de la textura de los alimentos y de los líquidos espesados para personas con disfagia de todas las edades y culturas y en todos los ámbitos de atención [44] o el documento de posición que está elaborando la *European Society for Swallowing Disorders*.

En esta Tesis Doctoral hemos descrito que el aumento de la viscosidad del bolo con un **espesante de almidón**, aumenta significativamente la seguridad de la deglución en pacientes ancianos (**Capítulos 2** y **5**) de una forma concentración-dependiente. Podemos observar como aumentar la viscosidad del bolo hasta néctar, es suficiente para evitar casi la mitad de aspiraciones que se producían con líquido, sin embargo, sólo se reducen ligeramente el número de penetraciones. El máximo efecto terapéutico se consigue con viscosidad pudín, con la cual conseguimos un significativo descenso tanto del número de penetraciones como de aspiraciones. Cuando utilizamos un **espesante de goma xantana** (**Capítulo 4**) también obtuvimos un efecto terapéutico máximo con la viscosidad pudín, sin embargo, el néctar conseguido con este espesante parece tener un efecto terapéutico mucho mayor que el que obtuvimos con el espesante de almidón. Este es un dato relevante ya que, el conseguir proteger a más pacientes con unas viscosidades bajas, podría incrementar la adherencia terapéutica al tratamiento, la cual es baja [45]. No obstante, debemos decir que para sacar conclusiones definitivas, sería necesario un estudio comparativo de los dos espesantes en el mismo grupo de pacientes. Este aumento de la seguridad de la deglución observado con los dos tipos de espesantes a viscosidad néctar, no se relacionó sin embargo con un cambio en aquellos parámetros que detectamos que eran claves para determinar la seguridad de la deglución (tiempo de cierre del vestíbulo laríngeo y tiempo de extensión máxima vertical del hioides), ya que ninguno de ellos se modificaba con el aumento de la viscosidad en los pacientes con DO, lo que nos indica que los espesantes protegen al paciente mediante un mecanismo compensatorio. Se ha propuesto que el principal mecanismo de acción de los espesantes es disminuir la velocidad a la que viaja el bolo por la faringe [46], proporcionando así el tiempo necesario para que se cierre la vía respiratoria en condiciones de seguridad. En efecto, hemos podido observar que esta premisa se cumple en los dos espesantes cuando se utiliza viscosidad pudin. Sin embargo, a viscosidad néctar, no se produce una disminución significativa de la velocidad, lo cual nos estaría indicando que las propiedades intrínsecas del bolo espesado serían responsables del efecto terapéutico observado, evitando las aspiraciones y

penetraciones, sin cambiar la fisiología deglutoria. En este estudio controlamos la viscosidad de los fluidos administrados, sin embargo, existen otras propiedades como la dureza, cohesividad, adhesividad o gomosidad que pueden también influenciar en sus propiedades terapéuticas y que deberán evaluarse en posteriores estudios. Otro dato importante a discutir que se obtuvo del estudio del efecto de los espesantes de goma xantana en la fisiología deglutoria (**Capítulo 4**), es el hecho de que los voluntarios sanos y los pacientes con disfagia pero sin alteración de la seguridad de la deglución, sí son capaces de adaptar la reconfiguración del sistema deglutorio a las características del bolo: de este modo, cuando degluten un líquido o un néctar, que viaja a velocidades altas por la faringe, cierran el vestíbulo laríngeo antes que cuando degluten un pudín, que viaja a velocidades bajas. La inexistencia de este *feedback* sensorial - motor que permite adaptar la respuesta motora orofaríngea a las características del bolo podría ser uno de los responsables de la presencia de alteraciones de la seguridad en pacientes con DO. Una vez más, se pone de manifiesto la importancia del estímulo sensorial en la regulación de la función deglutoria y cómo su alteración se relaciona con alteraciones biomecánicas que conducen a la presencia de degluciones inseguras e ineficaces.

Para favorecer este *feedback*, quisimos comprobar la hipótesis que el incremento del *input* sensorial mediante **agonistas del receptor TRPV1** (**capsaicina** y **piperina**), favorecería la respuesta motora deglutoria en los pacientes con alteraciones de la seguridad de la deglución. Y efectivamente, pudimos observar como mediante ambos agonistas se reducía la prevalencia de penetraciones en el LV al compararlo con un bolo de la misma viscosidad. A diferencia de lo ocurrido cuando se aumentaba la viscosidad del bolo con espesantes, al suplementarlo con los agonistas TRPV1 sí se produjeron cambios en la RMO de los pacientes con DO: el LV se cerró antes, y por lo tanto, se consiguió una protección de la vía respiratoria más temprana evitando las penetraciones observadas en el bolo control. La capsaicina, además, aceleró el movimiento vertical del hioides.

La ***e-stim* trans-cutánea**, por su lado, también aumentó la seguridad de la deglución, en este caso, en un grupo de pacientes con DO crónica asociada a ictus. Anteriormente, Clavé *et al* [25] habían descrito las principales alteraciones fisopatológicas en este grupo poblacional, que, de forma similar a lo que hemos descrito en ancianos frágiles, se caracterizan por alteraciones tanto en la eficacia como en la seguridad de la deglución. Es interesante destacar que, a diferencia de lo que se podría esperar, el tratamiento tuvo efectos similares en cuanto a la mejora de la seguridad de la deglución, tanto a intensidad sensorial como motora. Al igual que con la capsaicina, esta mejora se produjo gracias al significativo acortamiento en el tiempo de cierre del LV y a una aceleración en el movimiento del hioides. El hecho de que estos acontecimientos se modifiquen de forma similar en ambas intensidades, nos podría estar indicando que son fenómenos que están básicamente bajo control neural, son altamente dependientes del *input* sensorial orofaríngeo y poco dependientes de la mejora en el rendimiento muscular. Estudios previos con *e-stim* trans-cutánea e intrafaríngea a intensidades sensoriales mostraron efectos similares en la mejora de la seguridad de la deglución que las observadas en nuestros estudios [47;48], y si bien el estudio de Gallas *et al* [47] falló al relacionar estos cambios con modificaciones en la excitabilidad cortical evaluada mediante TMS, Jayasekeran *et al* [48] sí que observaron que la mejora en los parámetros deglutorios tras estimulación eléctrica intra-faríngea estaban

fuertemente asociados a incrementos en la excitabilidad de la corteza motora faríngea también evaluada mediante TMS.

En resumen, las diferentes estrategias terapéuticas evaluadas mejoran la seguridad de la deglución mediante dos mecanismos principales: los **espesantes** utilizan un **mecanismo compensatorio** con efecto secuencial: a viscosidades bajas no se produce ningún cambio en la fisiología deglutoria y son las propiedades intrínsecas del bolo las que favorecen la protección de la vía respiratoria; a viscosidades altas, además, disminuyen la velocidad del bolo por la orofaringe. De este modo, compensan el retraso en el cierre de la vía respiratoria que presentan los pacientes con DO. Por otro lado, los **agonistas TRPV1** y **la *e-stim* transcutánea** actúan **revirtiendo la disfunción** presente, acelerando el cierre del vestíbulo laríngeo para proteger la vía respiratoria.

Efectos de los tratamientos sobre la eficacia de la deglución

A pesar del elevado efecto terapéutico del aumento de la viscosidad, los **espesantes de almidón** presentan un importante efecto indeseable, y es que aumentan el residuo orofaríngeo, principalmente a viscosidad pudin (viscosidad a la cual presentan el mayor efecto terapéutico). Este residuo que permanece en la faringe después de la deglución pone al paciente en riesgo de presentar aspiraciones post-deglutorias, una vez finaliza la apnea deglutoria. Con el uso de **espesantes de goma xantana** no se observa un incremento significativo de residuo al incrementar la viscosidad, a pesar de que las viscosidades finales utilizadas son comparables a las obtenidas con almidón, lo cual le confiere a este tipo de espesantes una clara ventaja terapéutica frente a los de almidón.

Dentro de las estrategias de neuro-estimulación periférica, la **capsaicina**, además de mejorar la seguridad de la deglución, también mejoró la eficacia, reduciendo el residuo faríngeo. Este fenómeno, sin embargo, no ocurrió cuando utilizamos el otro agonista TRP, la **piperina**. En este caso, el efecto producido por el agonista fue puramente neurológico, sólo se vio afectada la temporalidad de los eventos ocurridos sin que se produjese ninguna alteración en la eficacia de los mismos. Este fenómeno merece ser discutido específicamente puesto que nuestra hipótesis inicial nos hacía esperar un mayor efecto de la piperina, basándonos en dos premisas: en primer lugar, las observaciones realizadas *in vitro* sobre el efecto de ambos agonistas sobre el TRPV1, que han determinado que a pesar de que la piperina es menos potente que la capsaicina en activar el receptor (necesita mayor concentración para alcanzar el mismo efecto), es más eficiente (el efecto máximo alcanzado es mayor) [49;50]; y en segundo lugar, que al ser la piperina un agonista dual TRPV1/ TRPA1, podría esperarse una mayor activación de los terminales nerviosos. Una posible explicación a este fenómeno podría ser que en el estudio de la capsaicina, se utilizó para suplementar el bolo, una mezcla natural de capsaicina y otros capsaicinoides que le confirieron al bolo final un pH ácido, a diferencia del bolo control. Es conocido que los H^+ son también agonistas del TRPV1 y sensibilizan además el receptor a la acción de la capsaicina [51]. Estudios anteriores han determinado que el ácido es también un estimulante de la deglución [52] y que las presiones linguales generadas al deglutir un bolo ácido son mayores en comparación de las presiones generadas con agua [53], lo cual podría ser responsable, al menos en parte, de la mayor eficacia observada al deglutir el bolo acidificado.

En cuanto a la ***e-stim* transcutánea**, sí que observamos diferencias significativas en el efecto de ambas intensidades sobre la eficacia de la deglución. Tal y como se ha discutido en el **Capítulo 7**, nuestra hipótesis es que esta diferencia puede deberse a dos fenómenos principalmente: por un lado, a que la facilitación de la contracción muscular producida durante el tratamiento a intensidades motoras favorezca el rendimiento de la musculatura suprahioidea y por otro lado, que al estar aplicando una intensidad eléctrica mayor, la activación de las estructuras sensoriales corticales sea también mayor y por lo tanto también los efectos consecuencia de esta activación. Es importante destacar también, que el tratamiento de *e-stim* fue administrado con el paciente en situación de reposo. Si bien la *e-stim* transcutánea después de un ictus es un tratamiento rehabilitador habitual que suele administrarse durante los ejercicios de rehabilitación, la *e-stim* para la rehabilitación de la disfagia merece una atención especial. Si bien el fabricante del electroestimulador recomienda la aplicación de la terapia mientras se practican ejercicios deglutorios, nuestra opinión es que el hecho de deglutir de forma continuada durante el tratamiento cuando el paciente tiene alteraciones de la seguridad de la deglución, es decir, presenta aspiraciones, puede conducir a graves complicaciones derivadas del mismo. Es en este sentido que consideramos que es de una gran importancia conseguir mejorar la seguridad de la deglución sin la necesidad de que el paciente degluta de forma continuada y por lo tanto, aumente el riesgo de aspirar y contraer una infección respiratoria.

En resumen, de las diferentes estrategias terapéuticas evaluadas y en referencia al efecto sobre la eficacia de la deglución, sólo la **capsaicina** y la ***e-stim* transcutánea** a intensidad **motora mejoran la eficacia de la deglución**. La **piperina** y la ***e-stim*** a intensidad **sensorial no afectan a la eficacia de la deglución**. Aumentar la viscosidad con **espesantes de goma xantana**, **no aumenta el residuo orofaríngeo**, a diferencia de cuando se utilizan **espesantes de almidón**, que **aumentan** de forma significativa **el residuo**, sobre todo a viscosidad pudin.

Efectos adversos y perfil de seguridad de los tratamientos evaluados

No menos importante que el efecto terapéutico de las diferentes estrategias evaluadas, es la seguridad de las mismas, que debe también ser evaluada rigurosamente para discutir su aplicabilidad.

Los **espesantes de almidón** comercializados en España y financiados por el Sistema Nacional de Salud para la prevención y tratamiento de las aspiraciones en el paciente con DO, gozan de un perfil de seguridad reconocido. Sin embargo, existen algunos aspectos a tener en cuenta en referencia a su uso en pacientes con DO. A pesar de que la biodisponibilidad del agua no se altera con el uso de espesantes [54;55], el consumo diario de agua sí que puede disminuir en pacientes que toman líquidos espesados [56], lo que podría conducir, contrariamente a lo que se pretendía, a un estado de deshidratación. Además, se ha descrito que los líquidos espesados calman menos la sensación de sed que los líquidos sin espesar y que los espesantes pueden alterar la liberación y absorción de determinados fármacos [57] (especialmente los de la Clase III de la *Biopharmaceutics Classification System of medications* (BCS) [58], como por ejemplo Atenolol, Captopril, Cimetidina, Aciclovir, Penicilina, Amoxicilina, Eritromicina) y afectarse, en consecuencia, la acción de los mismos. En una población altamente polimedicada como suelen ser

los pacientes que sufren disfagia, este es un importante punto a tener en cuenta y que requiere ser evaluado rigurosamente.

La **goma xantana** es un aditivo alimentario de uso común que goza también de un perfil de seguridad adecuado para su uso generalizado y sin restricción en humanos [59]. En nuestro estudio con los espesantes de goma xantana no se detectaron efectos adversos graves relacionados con el producto en estudio, ya que las alteraciones gastrointestinales registradas (mayoritariamente deposiciones blandas) es un efecto secundario bien conocido del contraste radiológico utilizado en las exploraciones. Se produjo también un caso de broncoaspiración que fue considerado un efecto adverso grave pero no relacionado con el producto en estudio sino con el procedimiento diagnóstico utilizado en el paciente.

Para realizar el estudio con **capsaicina**, optamos por utilizar los capsaicinoides naturales de un producto alimentario comercializado desde 1868 (Tabasco), que nos aseguraran realizar el ensayo en las mayores condiciones de seguridad posibles. A pesar de ser un estudio agudo y de que las cantidades de capsaicina administrada serían mínimas, se optó por la opción conservadora de utilizar un producto con un perfil de seguridad probado. En nuestro estudio no se detectó ningún efecto adverso grave relacionado con la administración de la salsa de capsaicinoides. Sin embargo, es conveniente tener en cuenta que consumos altos de capsaicina (25-200 mg/día) se han asociado a mayor prevalencia de cáncer del tracto digestivo alto, principalmente cáncer gástrico [60]. Sin embargo, consumos moderados de capsaicina (1.5 mg/día), similares a las dosis de capsaicina que estamos usando actualmente y que podrían usarse en un tratamiento crónico de la disfágia (1.4 mg/día), no han mostrado esta asociación [60]. Tenemos que tener en cuenta también que los canales TRP tienen un amplio patrón de expresión en todo el cuerpo y que están involucrados en una amplia gama de procesos que van desde la osmorregulación a la señalización térmica, química y sensorial, y potencialmente están también asociados a la fisiopatología de varias enfermedades, como el síndrome del intestino irritable, la enfermedad por reflujo gastroesofágico y la tos crónica. Esta situación hace que exista un riesgo potencial de efectos adversos y que sea necesario tener en cuenta estos datos a la hora de diseñar un posible tratamiento crónico de la DO con capsaicina [61].

La **piperina**, por su lado, es considerado un alimento GRAS (*Generally recognized as safe*) por la FDA [62], por lo que la suplementación de la comida con esta sustancia es considerada segura. Sin embargo, se ha descrito que el consumo crónico de cantidades elevadas de piperina (1.5 g/día) podría producir daños en la mucosa gástrica [63]. Debemos también tener en cuenta que la piperina es un inhibidor del citocromo P450 3A4 (CYP3A4), importante enzima involucrada en el metabolismo de xenobióticos y principal responsable de la metabolización de los fármacos [64]. Debido a este efecto inhibitorio del metabolismo de fármacos, la piperina puede incrementar la biodisponibilidad de estos compuestos y por lo tanto, deberían tomarse las precauciones adecuadas a la hora de diseñar un posible tratamiento crónico de la DO con piperina. En nuestro estudio en el que se evaluó el efecto agudo de la piperina, se detectó un efecto adverso leve (dolor abdominal autolimitado) en un paciente del grupo al que se le administró piperina 1 mM, el cual no fue considerado ni grave ni relacionado con la sustancia en estudio.

La ***e-stim*** **transcutánea**, ha sido una terapia controvertida, tanto desde el punto de vista de la eficacia como de la seguridad, desde su aprobación

por la FDA en 2001 [65]. Desde el punto de vista de la seguridad, VitalStim no recomienda su uso sobre procesos infecciosos activos y neoplasias activas, así como recomienda su uso con precaución en pacientes que sufran trastornos convulsivos, con aparatos electrónicos implantados (por ejemplo marcapasos), con demencia avanzada o con reflujo gastroesofágico. Todos estos supuestos fueron considerados, por precaución, criterios de exclusión en nuestro estudio. Además, los electrodos no deben ser colocados sobre el seno carotideo por riesgo de que se desencadene una bradicardia sinusal, y el hecho que se estimulen las aferencias laríngeas conlleva que exista un cierto riesgo de que se desencadene un laringoespasmo. Pocos son los estudios que han evaluado la seguridad de la *e-stim* transcutánea en el tratamiento de la DO, y los efectos adversos más frecuentes reportados son irritación de la piel y sensación de quemazón en la zona de aplicación de los electrodos, dolor de cabeza, mandíbula y cuello, sensación de plenitud gástrica, tos y expectoración [66]. En nuestro estudio, detectamos dos efectos adversos en el grupo de pacientes que recibió *e-stim* a intensidad sensorial (dolor dental y aumento en la concentración sanguínea de glucosa), los cuales no fueron considerados ni graves ni relacionados con la terapia. Debido a la limitada evidencia científica existente de la seguridad y la eficacia de la terapia, organismos como el británico *National Institute for Health and Care Excellence*, en su emisión preliminar de las *NICE guidelines* recomienda la realización de estudios adicionales de calidad que evalúen su seguridad y eficacia [67]. Nuestro estudio apoya el hecho de que la *e-stim* transcutánea es un tratamiento seguro y eficaz para el tratamiento de la DO asociada al ictus, pero cierto es que son necesarios estudios adicionales que confirmen los resultados encontrados y que evalúen específicamente el impacto de la terapia en la evolución clínica del paciente.

En resumen, solo los **espesantes** presentan un perfil de seguridad adecuado para ser aplicados sistemáticamente en la práctica clínica habitual. Nuestra experiencia demuestra que la ***e-stim* transcutánea** es un tratamiento seguro y que a pesar de que son necesarios nuevos estudios que confirmen su eficacia clínica y establezacan el régimen terapeútico más adecuado, su uso en la clínica puede ser considerado en pacientes con DO crónica post-ictus dado que no existen alternativas terapeúticas con un perfil de seguridad significativamente superior. La seguridad de los **agonistas TRPV1** debe ser evaluada exhaustivamente en estudios adicionales que comprendan mayor número de pacientes y evaluaciones a largo plazo, antes de que puedan ser implantadas de forma sistemática en pacientes con DO.

Perspectivas de futuro

Durante décadas los tratamientos para la disfagia orofaríngea se han centrado en compensar la disfunción deglutoria a través de la adopción de diferentes posturas y maniobras durante la deglución. Estos tratamientos son ampliamente aceptados en la práctica clínica, pero la evidencia de su efectividad en la DO asociada al envejecimiento o enfermedades neurológicas es limitada, y los pacientes y cuidadores a menudo tienen dificultades de aprendizaje, enseñanza y/o realización de estas estrategias correctamente [40;68;69]. Las modificaciones de la dieta, tales como el aumento de la viscosidad de los fluidos, han tenido más éxito en la reducción de las aspiraciones y las penetraciones [25] y en la prevención de la neumonía por aspiración [43]. Sin embargo, los **espesantes** pueden modificar el

sabor de algunas bebidas [70], tienen una baja adherencia terapéutica [71] y no mejoran la fisiología de la respuesta deglutoria. A pesar de ser un tratamiento compensador, el uso de espesantes continuaría siendo de elección en aquellos casos en que no existan posibilidades de rehabilitación o cómo tratamiento concomitante durante el proceso rehabilitador. De ahí la importancia de desarrollar productos que mejoren las propiedades de los que tenemos disponibles en la actualidad. La nueva generación de espesantes basados en goma xantana ofrece unas buenas perspectivas terapéuticas tal y como se ha descrito en el **Capítulo 4**. Deberá, no obstante, evaluarse también si mejoran la adherencia al tratamiento, factor clave en el éxito terapéutico de los espesantes [71].

La tendencia actual, sin embargo, en el tratamiento de la disfagia es ir un paso más allá y no quedarnos en la pura compensación del trastorno deglutorio, sino incidir en la recuperación de la función deglutoria. Los estudios realizados en esta Tesis Doctoral han representado el inicio de una nueva línea de investigación en nuestro grupo fundamentada precisamente en este principio, en movernos de los tratamientos compensatorios a los que promueven la recuperación. A pesar de que pueden considerarse exploratorios, los estudios presentados nos han permitido sentar las bases para el diseño de nuevos estudios aleatorizados controlados, que se están realizando actualmente en el grupo, con el objetivo de confirmar si los efectos fisiológicos evidenciados tienen impacto en la evolución clínica de los pacientes y evaluar sus efectos a largo plazo.

Los **agonistas TRP** (**piperina**, **capsaicina**) han mostrado efectos terapéuticos positivos, mejorando diferentes parámetros deglutorios en pacientes con disfagia, aunque los estudios que hemos presentado deben considerarse pruebas de concepto. Se necesitan ensayos controlados aleatorios que exploren poblaciones más grandes y los efectos a largo plazo de estas estrategias. La relación entre los canales TRP y la disfagia abre un nuevo y fascinante camino para desarrollar estrategias farmacológicas para el tratamiento de la disfagia orofaríngea, aunque se necesita mucha más investigación en este campo. Los efectos centrales de los estimulantes farmacológicos no están explorados prácticamente y hay muy pocos datos sobre los efectos de estos productos en términos de la neuroplasticidad cortical, campo que deberemos abordar en el futuro.

Por último, a pesar de su disponibilidad comercial, existe una gran controversia alrededor de la aplicación clínica de la ***e-stim* transcutánea** en la rehabilitación de la deglución. Uno de los principales puntos de discusión se refiere a su aplicación clínica generalizada antes del establecimiento de una investigación exhaustiva que fundamente su aplicación basada en la evidencia. Además, a pesar de ser una técnica que podría tener un potencial de rehabilitación para algunos grupos de pacientes, en determinadas condiciones, no implica que sea sinónimo de que pueda ser un patrón de rehabilitación universalmente eficaz para las alteraciones de la deglución. Se necesitará pues, continuar evaluando exhaustivamente tanto la eficacia como la seguridad de la terapia en cada fenotipo en concreto de pacientes con disfagia, en estudios clínicos futuros. Será también de interés resolver si el efecto observado sobre la biomecánica de la deglución es consecuencia, al menos en parte, de un efecto neuromodulatorio que promocione la reorganización de los circuitos deglutorios corticales.

Para continuar diseñando tratamientos más efectivos para la DO, es esencial la realización de estudios fisiopatológicos y neurofisiológicos

exhaustivos que nos permitan conocer cuáles son los actores implicados en el proceso deglutorio, cómo interactúan, cómo se alteran en la enfermedad y a partir de aquí, cómo podemos intervenir para prevenir o revertir ésta alteración. La combinación de las técnicas actuales de estudio de la función deglutoria como son la VFS y la manometría faringoesofágica, con estudios neurofisiológicos que nos permitan evaluar tanto la vía sensorical aferente, como la función de la corteza cerebral faríngea y la vía eferente, será fundamental para el diseño de futuras intervenciones.

En nuestro grupo estamos empezando a realizar los primeros estudios en este sentido mediante diferentes técnicas como son los potenciales sensoriales evocados faríngeos (evaluados mediante EEG) para el estudio de la vía aferente, y los potenciales motores evocados faríngeos (evaluados mediante TMS) para el estudio de la vía eferente. Resultados provinentes de este tipo de estudios nos premitirán sentar las bases de nuevas estrategias terapéuticas centradas en mecanismos neuromoduladores y en la promoción de la plasticidad cortical.

En resumen, las estrategias de neuro-estimulación, tanto las que hemos evaluado en esta Tesis Doctoral como otras estrategias de estimulación periférica (estimulación eléctrica intrafaríngea), estimulación central (rTMS, tDCS) o estimulación combinada (*Paired associative stimulation*) nos abren una nueva puerta en el tratamiento de la disfagia, que cambia el foco de la rehabilitación o compensación de la alteración biomecánica, para centrarse en los sistemas neuronales subyacentes (Ver **Anexo 2**). Si estas líneas de investigación confirman las buenas perspectivas mostradas en los estudios iniciales y consiguen mejorar el pronóstico clínico de los pacientes, probablemente el tratamiento de la disfagia en unos años tendrá un aspecto totalmente diferente al que tiene actualmente. Sin embargo, aspectos éticos, organizativos y clínicos deberán tenerse en consideración a la hora de realizar la transición de estas nuevas técnicas neuromoduladoras desde el laboratorio de investigación a la rutina de la práctica clínica.

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CONCLUSIONES

CONCLUSIONES

1. El método de cribado EAT-10 y el método MECV-V de evaluación clínica para la DO presentan una alta sensibilidad y especificidad para detectar a los pacientes con disfagia orofaríngea y alteraciones deglutorias y para identificar aquellos pacientes que necesitarán una prueba instrumental o una evaluación clínica más exhaustiva.
2. El anciano frágil y el anciano con neumonía adquirida en la comunidad presentan una elevada prevalencia de signos videofluorscópicos de alteración de la eficacia y de la seguridad de la deglución. El retraso en el tiempo del cierre del vestíbulo laríngeo y en el movimiento vertical del hioides son los factores críticos que determinan la presencia de alteraciones de seguridad (penetraciones y aspiraciones) mientras que la débil fuerza de propulsión del bolo alimentario es el factor crítico que nos determina la presencia de alteraciones de la eficacia (residuo orofaríngeo).
3. La disfagia orofaríngea es un factor de riesgo para la neumonía adquirida en la comunidad en el anciano que no suele ser identificado como tal en la práctica clínica.
4. La disfagia orofaríngea es un factor de mal pronóstico clínico en el anciano frágil y en el anciano con neumonía adquirida en la comunidad, asociándose a unos altos índices de mortalidad.
5. Los espesantes de goma xantana mejoran la seguridad de la deglución de forma concentración-dependiente, sin aumentar el residuo orofaríngeo y sin modificar la respuesta motora orofaríngea. A viscosidad néctar, el efecto terapéutico depende exclusivamente de las características intrínsecas del bolo. A viscosidad pudin, se añade un efecto causado por la disminución de la velocidad del bolo por la faringe.
6. A pesar de que nuestros estudios sugieren una ventaja terapeútica, son necesarios estudios comparativos para confirmar que los espesantes de goma xantana muestran un perfil terapéutico superior a los espesantes de almidón modificado, tanto a nivel videofluoroscópico como a nivel de cumplimiento terapéutico.
7. La suplementación del bolo alimentario con agonistas de los canales TRP (capsaicina y piperina) acorta el tiempo de cierre del vestíbulo laríngeo reduciendo así las penetraciones al vestíbulo laríngeo y aspiracioneos traqueo-bronquiales. La capsaicina, a diferencia de la piperina, también mejora la eficacia de la deglución, reduciendo la prevalencia de residuo orofaríngeo.
8. Nuestros estudios sugieren que los canales TRP son una diana farmacológica interesante para el tratamiento de la DO, pero se deberán explorar los efectos a largo plazo de los agonistas de estos receptores, así como sus efectos a nivel neuro-fisiológico.
9. La estimulación eléctrica transcutánea es un tratamiento seguro y eficaz para la DO crónica después de un ictus. La estimulación eléctrica transcutánea aplicada a intensidad sensorial, acorta el tiempo de cierre del vestíbulo laríngeo, reduciendo las alteraciones de la seguridad de la deglución, mientras que aplicada a intensidad motora sobre la musculatura supra-hioidea también mejora la eficacia de la deglución reduciendo el residuo orofaríngeo.

ANEXO 1

Nestlé Nutrition Institute

EAT-10: Eating Assessment Tool
Despistaje de la Disfagia

FECHA

APELLIDOS | NOMBRE | SEXO | EDAD

OBJETIVO

El EAT-10 le ayuda a conocer su dificultad para tragar.
Puede ser importante que hable con su médico sobre las opciones de tratamiento para sus síntomas.

A. INSTRUCCIONES

Responda cada pregunta escribiendo en el recuadro el número de puntos.
¿Hasta que punto usted percibe los siguientes problemas?

1 Mi problema para tragar me ha llevado a perder peso

0 = ningún problema
1
2
3
4 = es un problema serio ☐

2 Mi problema para tragar interfiere con mi capacidad para comer fuera de casa

0 = ningún problema
1
2
3
4 = es un problema serio ☐

3 Tragar líquidos me supone un esfuerzo extra

0 = ningún problema
1
2
3
4 = es un problema serio ☐

4 Tragar sólidos me supone un esfuerzo extra

0 = ningún problema
1
2
3
4 = es un problema serio ☐

5 Tragar pastillas me supone un esfuerzo extra

0 = ningún problema
1
2
3
4 = es un problema serio ☐

6 Tragar es doloroso

0 = ningún problema
1
2
3
4 = es un problema serio ☐

7 El placer de comer se ve afectado por mi problema para tragar

0 = ningún problema
1
2
3
4 = es un problema serio ☐

8 Cuando trago, la comida se pega en mi garganta

0 = ningún problema
1
2
3
4 = es un problema serio ☐

9 Toso cuando como

0 = ningún problema
1
2
3
4 = es un problema serio ☐

10 Tragar es estresante

0 = ningún problema
1
2
3
4 = es un problema serio ☐

A. PUNTUACIÓN

Sume el número de puntos y escriba la puntuación total en los recuadros.
Puntuación total (máximo 40 puntos) ☐☐

C. QUÉ HACER AHORA

Si la puntuación total que obtuvo es mayor o igual a 3, usted puede presentar problemas para tragar de manera eficaz y segura. Le recomendamos que comparta los resultados del EAT-10 con su médico.

Referencia: Belafsky et al. Validity and Reliability of the Eating Assessment Tool (EAT-10). Annals of Otology Rhinology & Laryngology. 2008; 117 (12):919-24.
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Mini Nutritional Assessment

MNA®

Nestlé Nutrition Institute

Apellidos: Nombre:

Sexo: Edad: Peso, kg: Talla, cm: Fecha:

Responda al cuestionario eligiendo la opción adecuada para cada pregunta. Sume los puntos para el resultado final.

Cribaje

A Ha comido menos por falta de apetito, problemas digestivos, dificultades de masticación o deglución en los últimos 3 meses?
0 = ha comido mucho menos
1 = ha comido menos
2 = ha comido igual ☐

B Pérdida reciente de peso (<3 meses)
0 = pérdida de peso > 3 kg
1 = no lo sabe
2 = pérdida de peso entre 1 y 3 kg
3 = no ha habido pérdida de peso ☐

C Movilidad
0 = de la cama al sillón
1 = autonomía en el interior
2 = sale del domicilio ☐

D Ha tenido una enfermedad aguda o situación de estrés psicológico en los últimos 3 meses?
0 = si 2 = no ☐

E Problemas neuropsicológicos
0 = demencia o depresión grave
1 = demencia moderada
2 = sin problemas psicológicos ☐

F1 Índice de masa corporal (IMC = peso / (talla)² en kg/m²) ☐
0 = IMC <19
1 = 19 ≤ IMC < 21
2 = 21 ≤ IMC < 23
3 = IMC ≥ 23 ☐

SI EL ÍNDICE DE MASA CORPORAL NO ESTÁ DISPONIBLE, POR FAVOR SUSTITUYA LA PREGUNTA F1 CON LA F2.
NO CONTESTE LA PREGUNTA F2 SI HA PODIDO CONTESTAR A LA F1.

F2 Circunferencia de la pantorrilla (CP en cm)
0 = CP<31
3 = CP≥31 ☐

Evaluación del cribaje
(max. 14 puntos) ☐☐

Guardar
Imprimir
Reset

12-14 puntos: ☐ estado nutricional normal
8-11 puntos: ☐ riesgo de malnutrición
0-7 puntos: ☐ malnutrición

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ANEXO 2

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VIEWPOINT

Post-stroke dysphagia: progress at last

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Abstract

Oropharyngeal Dysphagia (OD) is both underestimated and underdiagnosed as a cause of malnutrition and respiratory complications following stroke. OD occurs in more than 50% of stroke patients. Aspiration pneumonia (AP) occurs in up to 20% of acute stroke patients and is a major cause of mortality after discharge. Systematic screening for OD should be performed on every patient with stroke before starting oral feeding, followed, if appropriate by clinical and instrumental (videofluroscopy and/or fiberoptic endoscopy) assessment. Bolus modification with adaptation of texture and viscosity of solids and fluids and postural adjustments should be part of the minimal treatment protocol, but they do not change the impaired swallow physiology nor promote recovery of damaged neural swallow networks in stroke patients. To this purpose, two new neurostimulation approaches are being developed to stimulate cortical neuroplasticity to recover swallowing function: (i) those aimed at stimulating the peripheral oropharyngeal sensory system by chemical, physical or electrical stimulus; and (ii) those aimed at directly stimulating the pharyngeal motor cortex, such as repetitive transcranial magnetic stimulation (rTMS). The study of Park et al. *in this issue of* Neurogastroenterology and Motility *evaluated the effect of rTMS in dysphagic stroke patients and showed a marked improvement in swallow physiology. Other studies also using rTMS showed plastic changes in pharyngeal motor cortical areas relevant to swallowing function. If further randomized controlled trials confirm these initial results, the neurorehabilitation strategies will be introduced to clinical practice sooner rather than later, improving the recovery of dysphagic stroke patients. Progress at last.*

Keywords *aspiration pneumonia, deglutition disorders, neurorehabilitation, oropharyngeal dysphagia, Stroke, swallow response, transcranial magnetic stimulation.*

Oropharyngeal dysphagia (OD) is a serious condition following stroke. A systematic review on the prevalence of OD following acute stroke found that the reported incidence of OD was lowest using bedside screening techniques (37–45%), higher using clinical testing (51–55%), and highest using instrumental testing (64–78%).[1] OD is specifically classified in the latest editions of the International Classification of Diseases (ICD) and Related Health Problems promoted by the World Health Organization ICD-9 (787.2) and ICD-10 (R13).

Despite its enormous impact on functional capacity, quality of life and survival, OD is both underestimated and underdiagnosed as a cause of major nutritional and respiratory complications in stroke patients. The severity of OD following stroke varies from moderate difficulty to complete inability to swallow and may occur with little or no other neurological deficit.[2] From a neuroanatomical perspective, unilateral strokes lead to OD in 40% of cases, bilateral lesions of the cerebral

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hemispheres in 56%, brainstem lesions in 67% and combined lesions in 85%.[3,4] OD can produce two types of severe complications in stroke patients[5]: alterations in the efficacy of deglutition which cause malnutrition and/or dehydration in up to 25% patients, and impaired safety of swallow, which increase the risk for aspiration pneumonia (AP) (RR 3.17 in patients with dysphagia after stroke and RR 11.56 in patients with aspiration).[1] Up to 20% of patients with stroke suffer from early AP and AP is one of the major causes of mortality during the first year after discharge.[6] Malnutrition after stroke is also associated with poor outcome including death, dependency, and institutionalization.[7] Oropharyngeal bacterial colonization and impaired immune system further increase the risk of AP.[8,9] The standard of care for the majority of patients with stroke suffering from OD is very poor as 80% of them are not even diagnosed and do not receive any treatment for this condition.[10] However, the introduction of specific programs for early management of OD in stroke patients reduced the rate of AP and improved survival of patients.[11] A dysphagia stroke program should involve a trained core team composed of physicians, nurses, swallowing and/or speech and language therapists, and experts in nutrition. Ideally, there should be a dysphagia team in each general hospital and long-term care facility. Recently, the European Society for Swallowing Disorders (ESSD) launched its Position Statements on Screening, Diagnosis and Treatment of Oropharyngeal Dysphagia in Stroke Patients to provide a consensus on best practice and the state-of-the-art, unify criteria, and identify best clinical practice among the different healthcare centers and professionals working with stroke patients with OD (www.myessd.org). The ESSD recommend that all acute stroke patients should be kept nil-per-mouth (NPO) until their swallowing ability is screened by trained health care professionals, using a reliable and valid screening tool (such as the EAT-10).[12] The screening should be completed as soon as the patient is awake and alert. If the screening fails, a formalized assessment for dysphagia (such as the V-VST[13] or the TOR-BSST)[14] should be performed before oral intake and, if appropriate, instrumental exploration protocols such as videofluroscopy (VFS) and/or fiberoptic endoscopic evaluation of swallowing (FEES). The diagnosis, once established, should be reported, using validated scoring systems and the ICD and ICF codes, in the medical report of every patient and linked to appropriate compensatory, protective, and rehabilitative procedures. A systematic review, summarizing all randomized controlled trials (RCT) related to therapeutic interventions used in dysphagic adults recovering from a stroke, concluded that the data on the effect of swallowing therapy on functional outcome and death in dysphagic patients with acute or subacute stroke are scarce.[15] The ESSD recommends bolus modification with adaptation of texture of solids and fluids and postural adjustments as part of the minimal treatment protocol, as the evidence for other behavioral treatments and swallowing rehabilitation is currently limited. The ESSD also recommends the establishment of international definitions and terminology and standardization of textures and nutritional adaptations for fluids and solids based on evidence.

However, to treat post-stroke dysphagic patients, it is essential to improve our knowledge of human cortical swallowing processing. The swallow response is generated in the brain stem swallowing center, in the medulla oblongata. This interneuronal network (central pattern generator, CPG) receives both central inputs from the cortex and also peripheral sensory inputs from the pharynx and larynx. The cortical and sub-cortical areas allow volitional swallowing and serve mainly to trigger deglutition and control the swallow motor response. Specifically, the areas implicated in the swallowing process are the caudolateral sensori-motor cortex, the premotor, orbitofrontal and temporopolar cortex, the insula, the cerebellum, and the amygdala.[16] These areas are represented bilaterally, but asymmetrically in the two hemispheres independently of handedness. Dysphagia after stroke is the consequence of damage at the 'dominant' pharyngeal cortex.[17] The periphery sensory inputs allow involuntary onset of the swallow response and modulate volitional swallowing. They are mainly transmitted through the maxillary branch of trigeminal nerve (V cranial nerve), pharyngeal branch of the glossopharyngeal nerve (GPN*ph*, IX cranial nerve), and two branches of the vagus nerve (X cranial nerve), the pharyngeal branch (X*ph*) and the superior laryngeal nerve.[16]

The impairment of swallow safety in stroke patients has been related to a delayed timing of laryngeal vestibule (LV) closure and upper esophageal sphincter (UES) opening time,[5,18] as time to LV closure is the time interval during which the potential aspiration occurs, and a delay in UES opening increases the bolus volume held in the hypopharynx, increasing the potential for bolus overflow into the airway. The pharyngeal delay time has also been described as a strong predictor for aspiration.[19] In addition, pharyngolaryngeal sensory deficits have also been related to the impairment of swallow safety in post-stroke patients.[20] These swallowing impairments recover spontaneously in about 50% of patients during the

first week after stroke, but they persist in the other half of patients and complications frequently arise.[21] Interestingly, after a unilateral hemispheric stoke, the recovery of swallow is related to an increase in the pharyngeal motor representation in the contralesional healthy hemisphere,[22] despite other tasks that are represented unilaterally (such as language) and mainly recover in the ispilateral perilesional regions.

For many years, dysphagia therapy for stroke patients has been focused on compensatory strategies by using changes in liquid viscosity with thickeners, modifying texture and consistency of solid food, and behavioral strategies.[23] These strategies can improve safety of swallow, but do not change the impaired physiology of swallow biomechanics and do not promote recovery of damaged neural swallow networks in stroke patients. However, in the last decade, new neurostimulation techniques focused on promoting cortical neuroplasticity to recover the swallowing function, have been developed. Two sets of strategies have been used to that end: (i) those aimed at stimulating the peripheral sensory system by chemical (capsaicin,[24] acid[25]), physical (tactile-thermal stimulation[26]), or electrical stimulus (by intrapharyngeal electrical stimulation, or by transcutaneous neuromuscular electrical stimulation)[27,28]; and (ii) those aimed at directly stimulating the cortex, such as transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS).

Transcranial direct current stimulation uses low-intensity direct currents applied to broad cortical areas that modify resting membrane potential of cortical neurons. Depending on the electrical stimulus, tDCS can facilitate or reduce cortical excitability: anodal stimulation enhances the excitability of the motor cortex whereas cathodal stimulation reduces it. tDCS has been used with different paradigms to stimulate either the non-affected or the affected hemisphere: anodal tDCS to the non-affected hemisphere[29] induced swallow recovery after treatment and anodal tDCS to the affected hemisphere did not produce significant swallowing improvement after the intervention, but improved swallow 3 months after the intervention. Repetitive transcranial magnetic stimulation (rTMS) uses a more specific approach as the magnetic stimulus is specifically applied to the pharyngeal motor cortex. In this issue of *Neurogastroenterology and Motility*, Park *et al.* examine the effects of high frequency (excitatory) rTMS in the contralesional pharyngeal motor cortex of post-stroke dysphagic patients, in a randomized controlled trial. The authors found that treatment improved the pharyngeal phase of swallow response and reduced the prevalence and severity of penetrations and aspirations immediately and 2 weeks after the treatment, while patients in the sham group did not improve significantly. Interestingly, the approach of Park *et al.*[30] was aimed at increasing the excitability of the contralesional healthy pharyngeal motor cortex, promoting a similar reorganization of neural connections as that observed during the spontaneous recovery of the swallow function after stroke. Again, some authors opted for an opposite strategy using rTMS therapy, and sought to restore the pharyngeal cortex functionality of the affected hemisphere by inhibiting the intact hemisphere to decrease transcallosal inhibition,[31] or by stimulating the affected hemisphere.[32] This strategy is a commonly used paradigm in the rehabilitation of different stroke-related disorders (such as aphasia) with unilateral hemisphere representation. Thus, rTMS therapy is being used to provoke swallowing recovery after unilateral hemispheric stroke by means of two very different strategies: by the disinhibition of neighboring ipsilesional cortical areas or, as has been proposed by Park *et al.*,[30] by increasing the excitability of the contralesional homotopic areas. Of course, further studies will be necessary to compare the effects of these approaches, as the swallow system is bilaterally innervated and has different neuroplastic behavior than unilateral systems so the application of inappropriate therapeutic paradigms could even lead to maladaptive plasticity that may interfere with swallowing recovery. Finally, in addition to the tDCS and the rTMS, new brain stimulation techniques have emerged, such as the paired associative stimulation[33] or intermittent theta burst stimulation.[34] We must look out for subsequent studies that may confirm their potential therapeutic effect in post-stroke dysphagia.

In summary, the article of Park and colleagues is a well-designed study assessing the effect of rTMS therapy in post-stroke dysphagic patients. This study should be used to send two messages to the 'Neurogastroenterology and Motility' community: (i) OD in stroke is a major motility disorder, also for neurogastroenterologists; (ii) a new era of neurostimulation treatments for these patients has started. rTMS and other peripheral and central neuromodulation techniques have the potential to induce plastic changes in pharyngeal motor cortical areas that can be relevant for swallowing function. However, their role in swallowing recovery therapy after stroke is still in the initial stage, as the number of studies is limited and the optimal stimulation parameters in terms of hemisphere targeted, intensity, duration of the treatment,

long-term effects, or the optimal population that could benefit from the therapy are not settled. Large-scale, multicenter, well-blinded RCTs involving all the phenotypes of dysphagic stroke patients and strong clinical endpoints (such as mortality, aspiration pneumonia, and malnutrition rates) are needed. If these studies confirm the initial promising results, dysphagia treatment for stroke will look very different from what it looks today and this will happen sooner than later. This has further implications for dysphagia units, as they need to prepare for the change, with well-trained professionals able to apply these new neurorehabilitation therapies. And it also has further implications for health care professionals involved in the care of these patients, as education in diagnosis and management of dysphagia and its complications is a cornerstone to allow maximal potential recovery of stroke patients. Progress at last.

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COMPETING INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTION

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