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ORIGINAL ARTICLE

A Comparative Study Between Modified Starch and Xanthan Gum Thickeners in Post-Stroke Oropharyngeal Dysphagia

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Abstract Thickeners are used in post-stroke oropharyngeal dysphagia (OD) as a compensatory therapeutic strategy against aspirations. To compare the therapeutic effects of modified starch (MS) and xanthan gum (XG) thickeners on swallow safety and efficacy in chronic post-stroke OD patients using clinical and videofluoroscopic (VFS) assessment. Patients were studied by clinical assessment (volume-viscosity swallow test, V-VST) and VFS using 3 volumes (5, 10, 20 mL) and 3 viscosities (liquid, nectar and spoon thick), comparing MS and XG. We studied 122 patients (46MS, 76XG). (A) V-VST showed that both thickeners similarly improved safety of swallow. Prevalence of safe swallowing significantly increased with enhanced viscosity ($P < 0.001$ vs liquid), MS: 47.83 % at liquid, 84.93 % at nectar and 92.96 % at spoon thick; XG: 55.31 % at liquid, 77.78 % at nectar and 97.84 % at spoon thick. Patients on MS reported higher prevalence of pharyngeal residue at spoon-thick viscosities. (B) VFS: increasing bolus viscosity with either thickener increased prevalence of safe swallows ($P < 0.001$ vs liquid), MS: 30.25 % liquid, 61.07 % nectar and 92.64 % spoon thick; XG: 29.12 % liquid, 71.30 % nectar and 89.91 % spoon thick. Penetration–aspiration scale score was significantly reduced with increased viscosity with both thickeners. MS increased oral and pharyngeal residues at nectar and spoon-thick viscosities but XG did not. Timing of airway protection mechanisms and bolus velocity were not affected by either thickener. Increasing bolus viscosity with MS and XG thickeners strongly and similarly improved safety of swallow in chronic post-stroke OD by a compensatory mechanism; in contrast only MS thickeners increased oropharyngeal residue.

Keywords Deglutition · Deglutition disorders · Therapy · Viscosity · Rheology

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Introduction

Oropharyngeal dysphagia (OD) is a major complaint following stroke. A systematic review found that bedside screening techniques identified the lowest prevalence of OD following acute stroke (37–45 %), clinical tests identified more (51–55 %), and instrumental testing identified the highest prevalence (64–78 %) [1]. Stroke patients may recover from OD during the first weeks but it persists in as many as 50 % of patients and complications frequently arise [2]. Stroke patients can present impairments in swallowing efficacy causing malnutrition or dehydration in up to 25 % patients [3], impaired safety of swallow with penetration in up to 40 %, and aspiration in up to 21 % [4]. Aspirations may lead to pneumonia (aspiration pneumonia, AP) associated with high mortality rates [1, 5–7].

Diet modification such as increase in bolus viscosity using thickeners is a common strategy for post-stroke OD.

The level of evidence of this therapeutic strategy has been criticized as the number of papers is small and methodologies diverse [8]. Increased bolus viscosity is associated with increased safety of swallow in patients with OD associated with neurological diseases or ageing [4, 9–11] and reduced mid-term pneumonia episodes [12]. On the other hand, increasing viscosity may impair efficacy of swallow by increasing prevalence of oropharyngeal residue [4] and the effect of thickeners on the physiology of swallow response is not fully understood [4, 13]. A recent review also identified these two key effects with respect to thickened liquids and swallowing [14].

Thickeners are agents with the capacity to bind water. Modified starch (MS) granules are carbohydrate polymers composed of amylose and amylopectin which can absorb water and swell, resulting in an increase of fluid viscosity. MS thickeners present some limitations in taste, viscosity stability and solubility. The resulting solutions are described as having a starchy taste and grainy texture and increase viscosity over time due to continuous water absorption and hydrolysis caused by contact with amylase in the saliva [15, 16]. A new generation of gum-based thickeners has recently been developed. Xanthan gum (XG) molecules become entangled, creating new networks through a quick and stable process. In contrast with MS, XG has a better taste and a stable viscosity over time and is not affected by amylase [16–18]. Two recently published studies suggest that XG-thickened liquids could present therapeutic advantages over MS-thickened liquids [10, 19]. However, data comparing the effects of both groups of thickeners on swallowing function and their therapeutic outcomes are limited.

The aim of this study was to compare the therapeutic effects of two types of thickeners, MS and XG, in patients with chronic post-stroke OD. This was done by evaluating both clinical and videofluoroscopic signs and exploring the specific mechanisms of action of each thickener on swallow physiology.

Materials and Methods

Study Design and Population

We performed a retrospective study on patients with chronic OD as a consequence of a previous stroke episode (>3 months) who were referred for swallowing evaluation to the Gastrointestinal Physiology Laboratory of the Hospital de Mataró (Spain). The study population was divided in two groups. The first group included patients studied between January 2012 and April 2013 who received MS thickener during the clinical and VFS assessment. The second group included patients who were screened during the period from June 2010 to October 2011 with XG as a thickener during assessment. Both groups were treated the same way except for the type of thickener.

Data Collected

Clinical records of all post-stroke patients were reviewed and demographic and clinical data were retrospectively summarized and collected by the same investigator. These included days from stroke to the date of the assessment, type (ischemic or hemorrhagic) and localization (right or left hemisphere) of the stroke, functional capacity (Barthel Index) and comorbidities (Charlson Index). Swallowing symptoms measured with the Eating Assessment Test-10 (EAT-10) and nutritional status according to the body mass index (BMI) (kg/m^2) and the Mini Nutritional Assessment short form (MNA-sf) were collected by the same clinicians during the swallowing assessment visit. Both clinical test (V-VST) and VFS studies were performed by the same dysphagia team, using the same clinical and instrumental protocols and equipment. All the swallowing assessment tests were analysed by the same dysphagia team.

Experimental Design

To assess the effect of two types of thickeners on efficacy and safety of swallowing, the results of the clinical volume-viscosity swallow test (V-VST), and the videofluoroscopic (VFS) exploration were taken into account. In addition, the effect of both thickeners on the physiology of swallow response was assessed using VFS.

Clinical Assessment

The V-VST is a clinical assessment method that uses swallow boluses of different volumes (5, 10 and 20 mL) and viscosities (thin liquid, nectar-like and spoon thick). The test allows safety and efficacy to be measured with the minimum risk for the patient, following the methodology previously described. Clinical signs of OD—*Signs and symptoms of impaired efficacy of swallow*—Signs of impaired efficacy of swallow: the presence of oral residue (part of the bolus remaining in the oral cavity after swallow), efficiency of labial seal (ability to maintain the whole bolus in the oral cavity during the preparatory phase of swallow) and fractional swallow (multiple swallows per bolus), were evaluated for each swallow. The symptom of impaired efficacy of swallow, pharyngeal residue, was detected by asking patients if something felt stuck or remained in the throat after each swallow. *Signs of impaired safety of swallow* changes in voice quality (including wet voice), cough and decrease in oxygen saturation $\geq$3 % from the basal level (measured with a finger pulse-oximeter, Nellcor OxiMax, Philips Medical

Systems, Eindhoven, Netherlands) were also evaluated for each bolus [20].

Videofluoroscopy Study

For the VFS study, all patients were imaged seated, in a lateral projection which included the oral cavity, pharynx, larynx and cervical oesophagus. The same bolus volumes and viscosities were used as for the clinical test, following the algorithm also described in previous studies [20]. VFS signs of impairments in the efficacy of swallow were the presence of oral and/or pharyngeal residue, the latter in the vallecular and/or the pyriform sinus. VFS Signs of impaired safety of swallow were ones in which a penetration or an aspiration was detected [20] and the safety of each swallow was rated according to the penetration–aspiration scale (PAS) [21]. Penetration was defined as material passing into the laryngeal vestibule but not below the vocal folds (PAS score 2–5) and aspiration was defined as material passing below the level of the vocal folds (PAS score 6–8) [21].

Oropharyngeal Swallow Response

Quantitative measurements of the effect of each bolus on oropharyngeal swallow response were obtained during 5 mL boluses at each viscosity during the VFS study. Glossopalatal junction (GPJ) opening was given the time value 0 and the time interval in ms from GPJ opening to laryngeal vestibule (LV) closure was the main physiological parameter used to measure impaired airway protection [7]. Bolus propulsion was assessed by measuring the final velocity ($m\ s^{-1}$) acquired by the bolus in the segment between the GPJ and the upper esophageal sphincter (UES). Final bolus velocity was calculated for each 5 mL bolus as: bolus acceleration (m/s^2) by UES opening time (ms), where acceleration is calculated as twice the distance from GPJ to UES (mm) divided by UES opening time squared, as described in our previous studies [3, 4].

Bolus Preparation

For each thickener, three different viscosities (thin liquid, nectar, and spoon thick) were used during V-VST and VFS, according to the viscosity ranges of the National Dysphagia Diet Task Force which are 1–50 mPa s for thin liquids, 51–350 mPa s for nectar, and >1750 mPa s for spoon thick, measured at 25 °C and at a shear rate of 50 s^{-1} as previously described [23].

(a) MS (Resource ThickenUp®, Nestlé Health Science, Vevey, Switzerland). For V-VST boluses with MS, thin liquid viscosity was obtained by using mineral water at room temperature, nectar viscosity by adding 4.5 g/100 mL MS and spoon-thick viscosity by adding 9 g/100 mL [22]. The VFS solutions for MS were obtained by mixing 1:1 mineral water and the X-ray contrast Gastrografin® (Bayer Hispania SL, Sant Joan Despí, Spain) at room temperature. Thin liquid was obtained by mixing 1:1 mineral water and the X-ray contrast, nectar viscosity by adding 3.5 g/100 mL MS and spoon-thick viscosity by adding 8 g/100 mL [4]. Solutions were prepared 5 min before starting the V-VST and 10 min before the VFS. All were carefully administered with a syringe.

(b) XG (Resource ThickenUp Clear®, Nestlé Health Science, Lausanne, Switzerland). For V-VST studies with XG, thin liquid viscosity was obtained by using mineral water at room temperature, nectar viscosity by adding 1.2 g/100 mL XG and spoon-thick viscosity by adding 6 g/100 mL [10, 18, 20]. The VFS solutions were obtained by mixing 1:1 mineral water and the X-ray contrast Gastrografin® at room temperature. Thin liquid was obtained by mixing 1:1 mineral water and the X-ray contrast, nectar viscosity by adding 2.4 g/100 mL XG and spoon-thick viscosity by adding 5.4 g/100 mL [10, 18]. The solutions with XG thickener were prepared 5 min before starting the V-VST and 3 h prior to the VFS in order to obtain an equivalent viscosity to MS boluses as previously described [10, 18]. Boluses were carefully administered with a syringe.

Data Analysis and Statistical Methods

Quantitative parameters were described as mean ± standard deviation (SD) and comparisons were assessed by the non-parametric Kruskal–Wallis and Mann–Whitney tests. Qualitative parameters were described by relative and absolute frequencies. Prevalence of clinical and VFS signs was reported as the ratio between the number of each clinical or VFS sign divided by the total number of swallows at each bolus type (any particular volume/viscosity). Prevalence of safe swallows was described as the number of patients without any sign of impaired safety of swallow divided by the total number of patients who swallowed the bolus. To assess the therapeutic effect of both thickeners, two measurements were made: (a) Prevalence of clinical and VFS signs observed in each bolus volume was compared between viscosities (for example, 5 mL nectar compared with 5 mL thin liquid) and represented in Figs. 1, 2, 4, 5; (b) Prevalence of signs observed in all volumes together (5, 10 and 20 mL) were compared between viscosities (for example, all nectar boluses compared with all liquid boluses) and results from these comparisons were explained in results section. The effect on

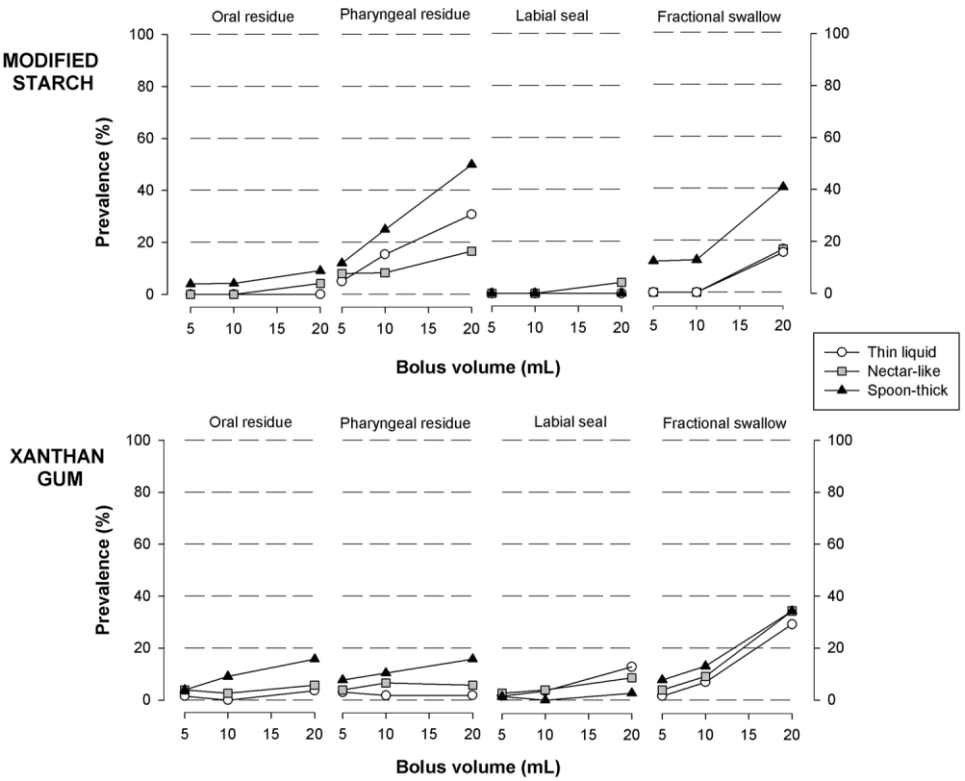

Fig. 1 Prevalence of post-stroke OD patients with clinical signs and symptoms of impaired efficacy (V-VST) of swallow for each volume, viscosity and thickener. No significant differences were found in any of the conditions tested

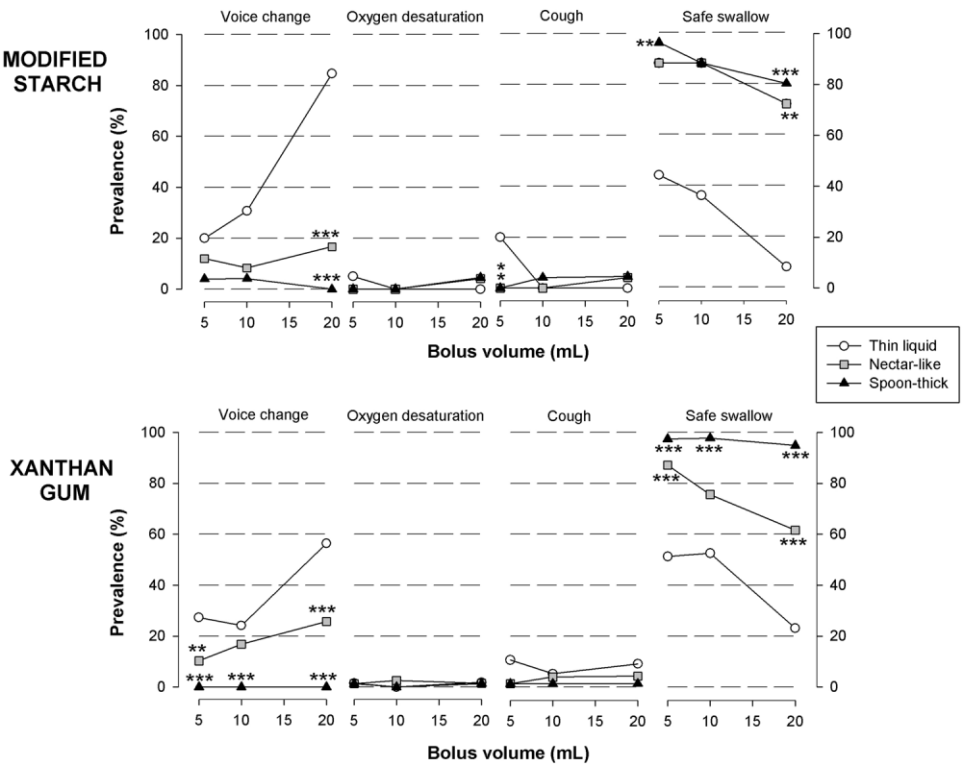

Fig. 2 Prevalence of post-stroke OD patients with clinical signs of impaired safety (V-VST) of swallow and prevalence of safe swallow for each volume, viscosity and thickener. $^{**}P < 0.01$, $^{***}P < 0.001$ versus thin liquid

safety and efficacy of deglutition of increasing bolus viscosity was assessed by Fisher's test. Measurements of the effect of each bolus on oropharyngeal swallow response were calculated during 5 mL swallows of each viscosity during the VFS study. P values <0.05 were considered statistically significant.

Results

Study Population

We included 122 patients (75.13 ± 9.97 years, 59.8 % male) with a previous stroke episode who were screened for chronic OD. MS was used as thickening agent on 46 patients and XG on 76 patients. Demographic and clinical data are shown in Table 1. Differences were detected regarding the time from stroke episode to the screening visit date, which was shorter in the MS group, and the EAT-10 and MNA-sf questionnaire scores, which showed that patients in the XG group reported more clinical complaints of OD and presented poorer nutritional status.

Effect of Thickeners on Clinical OD Signs During the V-VST

Clinical Signs of Impaired Efficacy of Swallow

Prevalence of clinical V-VST signs of impaired efficacy of swallow in OD patients for each thickener, volume and viscosity are shown in Fig. 1. Main clinical signs of impaired efficacy in stroke patients were fractional swallow and oropharyngeal residue. *Modified starch thickener* The prevalence of pharyngeal residue increased with viscosity from 10.96 % at nectar to 28.17 % at spoon-thick viscosity ($P < 0.05$) vs nectar). Prevalence of fractional swallow also increased with viscosity from 4.35 % at thin liquid to 5.48 % at nectar and up to 21.13 % at spoon-thick

Table 1 Demographic, clinical and nutritional patient characteristics plus level of significance (*P*) for group differences (modified starch versus xanthan gum)

	Modified starch group	Xanthan gum group	*P* value
Subjects	46	76	
Sex (% men)	65.22	56,58	0.446
Age (years)	75.63 ± 8.40	74.83 ± 10.86	0.952
Time from stroke episode to evaluation visit (months)	7.45 ± 8.97	27.32 ± 72.04	0.0001
Barthel index	83.26 ± 22.64	72.92 ± 26.32	0.160
Charlson index	3.28 ± 1.34	3.76 ± 1.58	0.077
0	0 % (0)	0 % (0)	
1–2	26.09 % (12)	25.00 % (19)	
3–4	60.87 % (28)	40.79 % (31)	
≥5	13.04 % (6)	34.21 % (26)	
Nutritional status (MNA-SF)	11.78 ± 2.08	9.47 ± 2.60	<0.0001
Malnourished (0–7)	6.67 % (3)	22.37 % (17)	
At risk (8–11)	26.67 % (12)	53.95 % (41)	
Well nourished (12–14)	66.67 % (30)	23.68 % (18)	
Nutritional status (BMI)	27.59 ± 4.60	26.97 ± 4.13	0.605
<18.5 kg/m^2 (underweight)	0 % (0)	2.63 % (2)	
18.5–24.9 kg/m^2 (normal weight)	33.33 % (15)	25.00 % (19)	
>25.0 kg/m^2 (overweight)	66.67 % (30)	72.37 % (55)	
Swallowing symptoms (EAT-10)	4.82 ± 5.58	12.34 ± 10.37	<0.0001
EAT-10 < 2	33.33 % (15)	15.63 % (10)	
EAT-10 ≥ 2	66.67 % (30)	84.37 % (54)	
Type of stroke			0.428
Ischemic	42.35 % (36)	68.42 % (52)	
Hemorrhagic	5.88 % (5)	15.79 % (12)	
Not specified	5.88 % (5)	15.79 % (12)	
Stroke lateralization			0.366
Right hemisphere	21.74 % (10)	34.20 % (26)	
Left hemisphere	45.65 % (21)	43.42 % (33)	
Not specified	32.61 % (15)	22.37 % (17)	

MNA-sf Mini Nutritional Assessment short form, *BMI* body mass index, *EAT-10* Eating Assessment Tool-10

viscosity ($P < 0.05$ vs thin liquid; $P < 0.01$ vs nectar). *Xanthan gum thickener* Prevalence of pharyngeal residue increased with viscosity from 2.23 % at thin liquid to 5.33 % at nectar and 11.26 % at spoon-thick viscosity ($P < 0.001$ vs thin liquid; $P < 0.05$ vs nectar). Prevalence of fractional swallow increased from 10.06 % at thin liquid to 18.18 % at spoon-thick viscosity ($P < 0.05$).

Patients included in the MS group presented higher prevalence of pharyngeal residue symptoms at thin liquid ($P < 0.01$) and spoon-thick ($P < 0.01$) viscosities compared with XG group.

Clinical Signs of Impaired Safety of Swallow

Prevalence of clinical V-VST signs of impaired safety of swallow in post-stroke OD patients considering each thickener, volume and viscosity are shown in Fig. 2. Voice changes after swallow were the most prevalent clinical sign. *Modified starch thickener* Prevalence of patients with safe swallow increased with viscosity. Prevalence of safe swallow was 47.83 % at thin liquid, 84.93 % at nectar ($P < 0.001$ vs thin liquid) and up to 92.96 % ($P < 0.001$ vs thin liquid) at spoon-thick viscosity. Increasing bolus viscosity to nectar and to spoon-thick viscosities with MS thickeners significantly reduced voice changes after deglutition. *Xanthan gum thickener* XG thickeners also strongly increased the safety of swallow. Prevalence of safe swallow was 55.31 % at thin liquid, 77.78 % at nectar ($P < 0.001$ vs thin liquid) and increased to 97.84 % ($P < 0.001$ vs thin liquid; $P < 0.001$ vs nectar) at spoon-thick viscosity.

XG thickeners significantly reduced the prevalence of voice changes and cough after deglutition at nectar and spoon-thick viscosities. Both thickeners presented similar therapeutic capacity to clinically improve safety of swallow. Figure 3

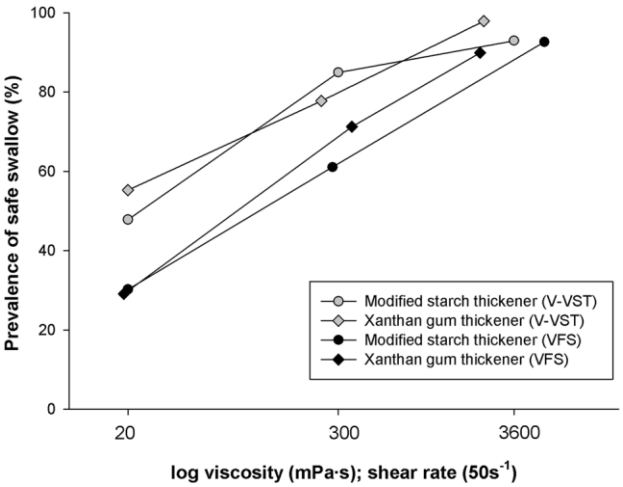

Fig. 3 Prevalence of post-stroke patients with safe swallowing in V-VST and VFS with respect to bolus viscosity

Effect of Thickeners on VFS Signs

VFS Signs of Impaired Efficacy of Swallow

Prevalence of clinical VFS signs of impaired efficacy of swallow in OD patients considering each thickener, volume and viscosity are shown in Fig. 4. The main signs of impaired efficacy of swallow were the presence of oropharyngeal residue and fractional swallow. *Modified starch thickener* Prevalence of oral residue ranged from 24.16 % at thin liquid to 24.06 % at nectar and 28.47 % at spoon thick. Impaired labial seal remained practically undetected for all the viscosities ($P > 0.05$). However, prevalence of pharyngeal residue increased with viscosity from 25.0 % at thin liquid to 33.83 % at nectar and up to 51.83 % at spoon-thick viscosity ($P < 0.001$ vs thin liquid; $P < 0.01$ vs nectar). Fractional swallow also increased with viscosity, from 17.50 % at thin liquid to 18.80 % at nectar and 29.20 % at spoon-thick viscosity ($P < 0.05$ vs thin liquid; $P < 0.05$ vs nectar). *Xanthan gum thickener* In contrast to MS thickeners, the prevalence of pharyngeal residue or fractional swallow did not increase at any of the viscosities tested with XG. Prevalence of pharyngeal residue reached around 9 % at thin liquid, nectar and spoon-thick viscosities while fractional swallow remained at 25.27 % at liquid, 23.32 % at nectar and 24.56 % at spoon thick ($P > 0.05$). Moreover, increasing bolus viscosity to spoon thick reduced the prevalence of labial seal impairments from 3.85 % at thin liquid to 0 % at spoon-thick viscosity ($P < 0.001$ vs thin liquid). Prevalence of oral residue significantly increased from 8.79 % at thin liquid to 17.10 % at spoon-thick viscosity ($P < 0.05$ vs thin liquid).

MS thickener showed significant higher prevalence of oral and pharyngeal residue at thin liquid-, nectar- and spoon-thick viscosities in comparison with XG. However, higher prevalence in labial seal impairments was detected in the XG group at liquid and nectar viscosities.

VFS Signs of Impaired Safety of Swallow

Prevalence of VFS signs of impaired safety of swallow in stroke patients with OD considering each thickener, volume and viscosity are represented in Fig. 5. *Modified starch thickener* Prevalence of patients with safe swallow (without penetrations and/or aspirations) increased from 30.25 % at thin liquid series to 61.07 % at nectar ($P < 0.001$ vs thin liquid) and up to 92.54 % at spoon thick ($P < 0.001$ vs thin liquid). *Xanthan gum thickener* Prevalence of patients with safe swallow increased from 29.12 % at liquid viscosity series, to 71.30 % ($P < 0.001$ vs liquid) at nectar viscosity and to 89.91 % ($P < 0.001$ vs thin

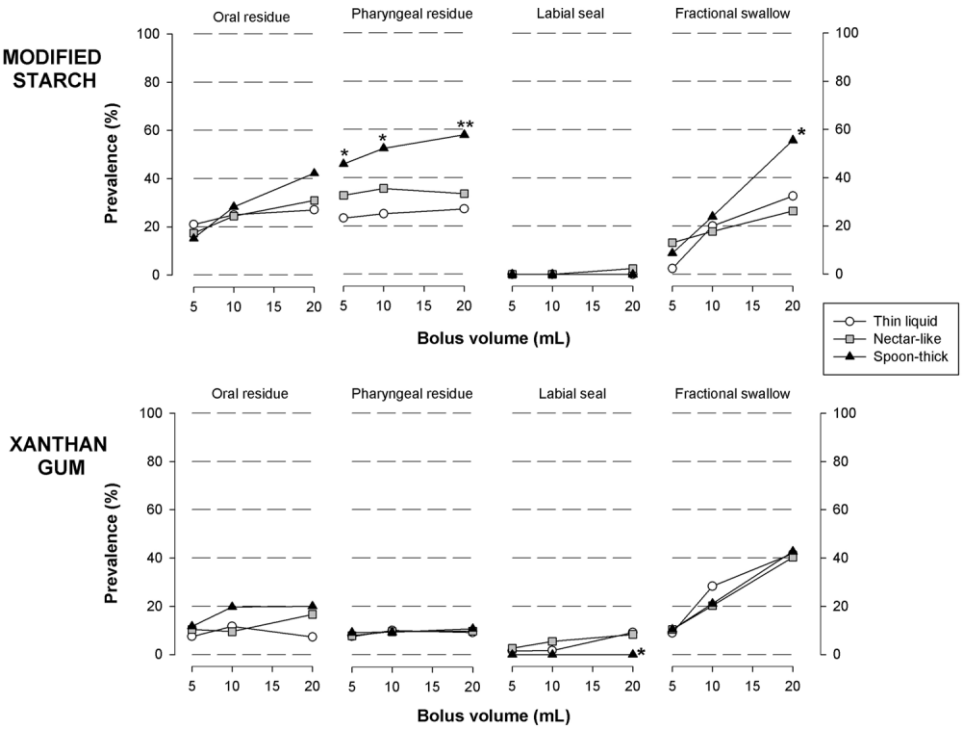

Fig. 4 Prevalence of post-stroke OD patients with VFS signs of impaired efficacy of swallow for each volume, viscosity and thickener. $*P < 0.05$, $**P < 0.01$ versus thin liquid

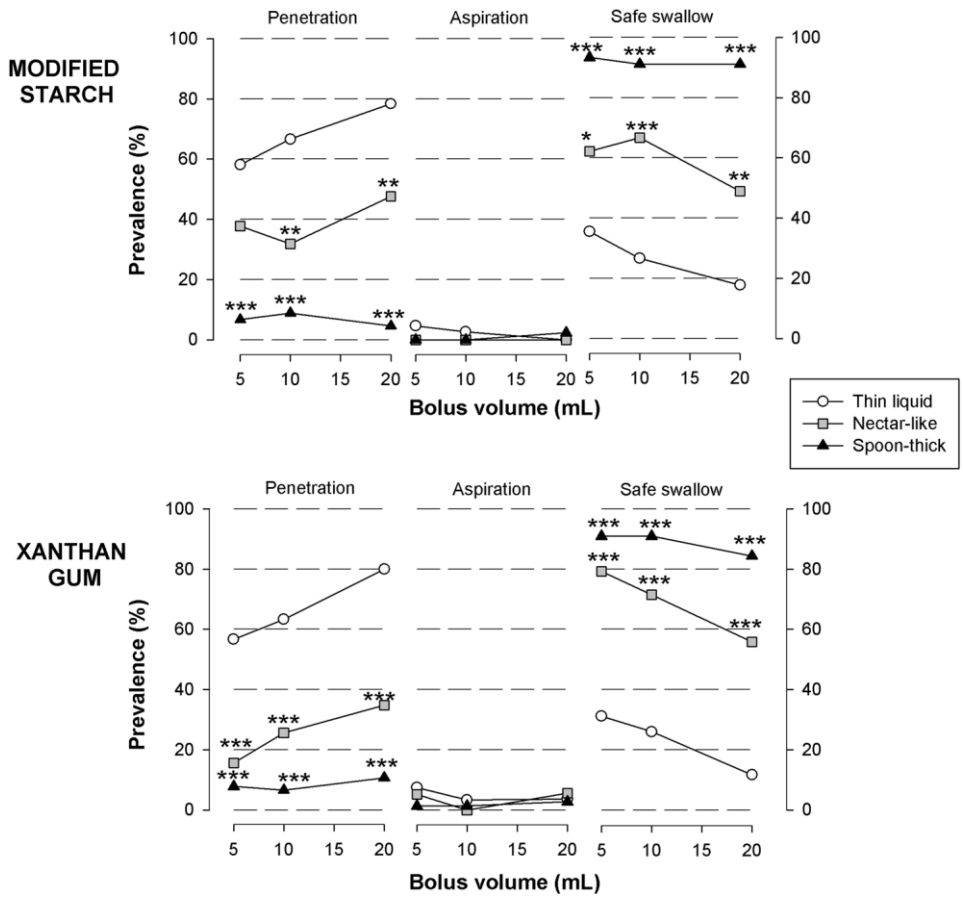

Fig. 5 Prevalence of post-stroke OD patients with VFS signs of impaired safety of swallow for each volume, viscosity and thickener. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ versus thin liquid

liquid) at spoon-thick viscosity series. PAS score for each thickener and viscosity are shown in Fig. 6. For both thickeners, prevalence of swallows with clinically relevant penetrations (PAS scores from 3 to 5) and aspirations (PAS scores from 6 to 8) decreased significantly as bolus viscosity increased. For MS thickener, the prevalence was reduced from 69.05 % at thin liquid to 44.0 % at nectar ($P < 0.05$ vs thin liquid) and to 11.11 % at spoon thick ($P < 0.001$ vs thin liquid; $P < 0.01$ vs nectar) and for XG thickener, the prevalence was reduced from 50.0 % at thin liquid to 19.48 % at nectar ($P < 0.001$ vs thin liquid) and 11.69 % at spoon thick ($P < 0.001$ vs thin liquid).

Comparing both thickeners, the level of protection achieved at spoon-thick viscosity was similar, but the XG thickener offered a greater therapeutic effect at nectar viscosity ($P < 0.01$ vs MS).

Effect of Thickeners on Oropharyngeal Physiology

Timing of Swallow Response

Modified starch thickener Total duration of swallow response (time from GPJ opening to LV opening) at 5-mL thin liquid boluses was 998.14 ± 187.81 ms and was not affected by increasing bolus viscosity to nectar (1022.61 ± 183.14 ms) or spoon-thick viscosities (983.48 ± 181.96 ms) ($P > 0.05$ vs thin liquid). Time of airway closure (LV closure) using MS was 413.02 ± 132.30 ms at thin liquid, 416.52 ± 130.25 ms at nectar and 400.0 ± 166.96 ms at spoon-thick viscosity. No significant differences were found ($P > 0.05$ vs liquid). *Xanthan gum thickener* Patients on XG presented a LV opening time of 952.0 ± 187.51 ms at thin liquid, also not modified with viscosity: 955.26 ± 174.41 ms at nectar and 965.33 ± 234.47 ms at spoon-thick viscosity ($P > 0.05$ vs liquid). Time of LV closure of patients on XG did not present significant differences as viscosity increased: LV closure time was 365.6 ± 139.5 ms during 5-mL thin liquid swallows, 347.9 ± 107.3 ms during 5 mL nectar swallows and 371.9 ± 185.5 ms at 5 mL spoon-thick swallows ($P > 0.05$).

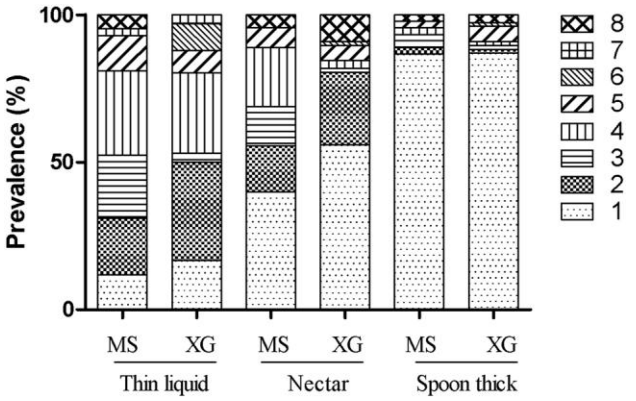

Fig. 6 Prevalence of penetration–aspiration scale scores for each thickener and viscosity

Bolus Kinematics

Modified starch thickener In the MS group, the final velocity of 5-mL thin liquid bolus (0.52 ± 0.20 m/s) was not significantly modified at nectar (0.45 ± 0.18 m/s) nor spoon-thick viscosity (0.47 ± 0.19 m/s) ($P > 0.05$). *Xanthan gum thickener* The final velocity in the XG group was neither affected as bolus viscosity increased: bolus velocity was 0.55 ± 0.20 m/s at thin liquid, 0.51 ± 0.20 m/s at nectar viscosity and 0.49 ± 0.21 m/s at spoon-thick viscosity. No significant differences were detected in the final bolus velocity between thickeners comparing all the viscosities tested ($P > 0.05$).

Discussion

The main result of this comparative study is that thickening liquids with both agents (MS and XG) present a strong therapeutic effect on safety of swallow in chronic post-stroke OD patients. The prevalence of safe swallow using MS and XG thickeners increased with bolus viscosity reaching up to 89–92 % of patients with post-stroke OD at spoon-thick viscosity. Regarding this effect, our results agree with a recent review [14] and several previous studies from our group that reported that increasing bolus viscosity using thickeners greatly improved safety of swallow. We also found that this therapeutic effect of thickeners is a purely compensatory mechanism without any major change on the timing of swallow response [11, 24–26].

In this study, swallowing function was assessed by a trained dysphagia team by means of a clinical test (V-VST) and VFS, the latter considered the gold standard to assess swallowing function and physiology [7]. Although reliability was not specifically assessed in this study, internal controls from our unit found high inter-rater reliability of the PAS score for identification of aspiration and assessment ($\kappa = 0.7051$). In addition, good intra-rater (0.9) and inter-rater (0.9) reliability have been previously reported for the laryngeal vestibule closure time, the main quantitative variable of our study, using the same equipment and methodology than that used in our study. This coincided with previous results reporting a similar reliability when the VFS analysis was performed by trained clinicians, as it was in this study [27, 28]. For the clinical and VFS studies, both MS- and XG-thickened boluses were prepared according to their specific methodology in order to obtain similar viscosity levels. It should be emphasized that to

achieve the proper viscosities needed for the VFS, XG boluses were prepared 3 h before starting the test [18].

Regarding efficacy of swallow, the most common signs shown by chronic post-stroke patients were pharyngeal residue and fractional swallow. When evaluated by VFS, increased prevalence of pharyngeal residue and fractional swallow with viscosity were only confirmed with the MS thickener. Previous VFS studies also described increased prevalence of pharyngeal residue associated with increased bolus viscosity obtained with a MS thickener [4, 29, 30]. A recent systematic review mainly considering studies with MS thickeners also highlighted this negative side-effect of thickeners [14]. However, we have seen that the prevalence of pharyngeal residue seems also to be dependent on the composition of the thickening agent used. In the VFS assessment, we observed that the XG thickener did not increase the prevalence of pharyngeal residue despite reporting it in the clinical test. This point gives XG a therapeutic advantage versus MS thickeners, as pharyngeal residue puts patients at risk of post-swallow aspirations when swallow is finished and respiration is resumed [31]. The differences between the reporting of pharyngeal residue in the clinical test and the lack of residue in the VFS study could be attributed to impaired pharyngeal sensitivity presented by most post-stroke patients with OD [32], leading to possible misreporting of pharyngeal residue in the clinical test.

XG thickener improved efficacy of swallow more than MS despite patients in the XG group having worse nutritional status and swallowing complaints. We expected that patients with weakened oropharyngeal musculature would present more difficulties in moving thick boluses, with an increased likelihood of post-swallow residue. Contrary to this hypothesis, patients in the XG group did not present any increase in pharyngeal residue with the thick boluses compared to thin liquid in the VFS study, highlighting again the advantage of XG thickener. This different behaviour observed between both thickeners can in part be explained by the different intrinsic properties of the fluids. While the fluids obtained with both thickeners presented the same levels of viscosity at 50 s^{-1} (which is thought to be a mean oral shear rate), as non-Newtonian fluids their viscosity varies with the force applied [18]. This means that tongue force may play a critical role in changing the shear rate and, depending on how vigorously the bolus moves through the mouth and into the pharynx, the real viscosity of the fluid in the pharyngeal cavity might significantly change. Bolus propulsion forces have been reported to vary depending on sensory properties of the bolus [29, 33], so the difference in taste and texture between the thickeners could induce changes in bolus propulsion forces, which in turn could induce changes in real viscosities of fluids during swallow. Another possible explanation for the effect of the thickeners is that, from the rheological point of view, thickened fluids are classified as complex fluids which cannot be adequately described by single values of viscosity [19]. Therefore, several rheological bolus proprieties such as hardness, gumminess, adhesiveness, cohesiveness and chewiness may also play an important role in swallow physiology. A study identified some food textures with higher risk of aspiration in post-stroke OD patients and described that semisolid foods with high risk of aspiration presented higher gumminess, higher hardness and adhesiveness, and lower cohesiveness than those not aspirated [34]. Whatever the case, the influence of these intrinsic bolus proprieties on safety and efficacy of swallow needs further research.

Regarding the safety of swallow, similar effects were registered for both thickeners in the clinical test: a strong and significant increase in safe swallowing as bolus viscosity increased shown by the reduction in the prevalence of voice changes. These results were confirmed in the VFS study: both thickeners showed a significant reduction in the prevalence of unsafe swallows as viscosity increased, which was linked with a significant reduction in PAS score. These results correlate with results of previous studies that highlight the compensatory effect of thickeners in improving swallow safety [4, 10, 35, 36]. Maximum therapeutic effects and similar levels of protection were obtained at the highest viscosities of MS and XG. However, at nectar viscosity, the levels of protection obtained with XG were higher than the ones obtained with MS. This result agrees with the study of Leonard et al. who suggested that XG thickeners present higher rates of protection of the safety of swallow than MS thickeners. In this study, the involvement of different MS and XG thickener's rheological properties were considered and hypothesized to play a role in safety of swallow [19]. To achieve high levels of protection with intermediate or low viscosity levels is a relevant point in terms of treatment compliance, as the lower the viscosity, the greater the patient acceptance [15]. Another important aspect related to thickener compliance is to ensure an adequate level of hydration. Highly thickened liquids have been shown to reduce patient's daily total fluid intake with the consequent risk of severe dehydration [37, 38]. This point emphasizes the importance of maintaining a proper level of safety with the minimum amount of thickener possible.

To study the mechanism of action of both thickeners during the VFS study, the timing of swallow response and bolus kinematics were analysed. Post-stroke patients included in the study presented a delayed total swallow response in comparison with timing previously described in healthy volunteers [4]. In contrast to data reviewed by Steele et al. concluding that thickened liquids increase the duration of swallowing events and transit time

measurements [14], we found that increasing bolus viscosity with either thickener did not change total duration of swallow response (LV opening time), nor the time of airway protection (LV closure time). So, the impaired physiology of swallow in post-stroke OD is not affected by viscosity and we can conclude that thickeners act through a compensatory mechanism. A trend was detected in the reduction of bolus velocity with the increase of viscosity. A reduction in the bolus velocity through the pharynx has been commonly accepted as the mechanism of action of thickeners [11]. However, in our study, we did not observe any significant effect on bolus velocity to explain the strong therapeutic effect of both thickeners. So, intrinsic bolus properties may play an important role in increasing safety of swallow in thickened liquids without any changes in bolus velocity or the timing of swallow response. It has been previously described that a moderate level of viscosity improves airway protection without modifying bolus velocity or swallow response timing [4, 10].

The main limitation of our study comes from its retrospective design that led to some differences in the basal status between the groups studied. Patients screened using XG thickener were chronic post-stoke patients, with a worse basal situation related to swallow symptoms and nutritional status compared to the MS group. However, as mentioned above, despite the worse status of patients, the XG thickener presented better results than the MS thickener. A prospective study evaluating both thickeners in two matching groups should be performed to confirm these results.

Moreover, we should take into account that bolus velocity was indirectly measured using the VFS images. Measurement of bolus flow using other technologies, for instance, automatic impedance manometry, could add new information on the effects of thickeners on bolus flow. In the study of Leonard et al., the authors reported similar results to ours regarding the safety of swallow, but they do not offer any information related to the effect of both thickeners on the efficacy of swallow neither their effects on swallow physiology. As we have shown, these aspects are important and need investigation. Future studies should be prospective, the effect of both thickeners should be assessed on the same patients, and rheological properties should be measured with the same method and equipment.

Studies have found that the swallow response can be improved by bolus supplementation with agonists of the transient receptor potential (TRP) channels such as acid [36], menthol [39], piperine [40, 41] and capsaicin [30]. Therefore, future research in the development of new OD treatment strategies should combine the demonstrated intrinsic effect of XG thickeners with these active substances.

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Compliance with Ethical Standards

Conflict of interest The company that partially financed the study had no influence on or involvement in the results or the writing of the article.

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