The Upper Esophageal Sphincter Assist Device Is Associated With Symptom Response in Reflux-Associated Laryngeal Symptoms

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Reflux-associated laryngeal symptoms (RALS) is the process in which chronic laryngeal symptoms are related to gastroesophagopharyngeal reflux.[1] Impairment of upper esophageal sphincter (UES) reflexes may predispose to esophagopharyngeal reflux.[1] The novel noninvasive nonpharmacologic UES assist device (UESAD) applies external cricoid pressure to augment intraluminal UES pressure by 20 to 30 mm Hg and reduce esophagopharyngeal reflux events.[2] This study aimed to assess the therapeutic efficacy of the UESAD in a pragmatic clinical setting, and to identify factors associated with symptom response among patients with suspected RALS.

Methods

This prospective single-center pragmatic exploratory clinical trial was conducted from September 2015 to March 2017, approved by the Northwestern Institutional Review Board (STU#00201370), and registered with clinicaltrials.gov (NCT02552966). The study included adult patients experiencing 1 month or more of laryngeal complaints (eg, throat clearing, sore throat, dysphonia, cough, globus) with a reflux symptom index (RSI) score of 13 or higher. Exclusion criteria included pregnancy, inability to consent in English, active imprisonment, altered mental status, and pre-existing conditions preventing UESAD use per the manufacturer's guidelines. Proton pump inhibitor use was permitted if not initiated or modified within 4 weeks of study initiation.

The 20-day study protocol included a baseline assessment, an intervention period during which subjects wore the UESAD for 14 consecutive nights, and a postintervention assessment. At each assessment participants completed 3 validated patient-reported questionnaires (RSI,[3] GerdQ,[4] and the Nocturnal Gastroesophageal Reflux Disease [GERD] Symptom Severity and Impact Questionnaire [N-GSSIQ][5]) and provided 3 consecutive fasting salivary samples that were analyzed via Peptest (RD Biomed, Ltd, Hull, UK) to quantify pepsin concentration.[6]

The primary outcome was symptom response measured by the RSI. Participants were categorized into 3 responder groups (complete responder, >50% reduction from baseline RSI and postintervention RSI < 13; partial responder, reduction from baseline RSI, not meeting criteria for complete response; and nonresponder, no reduction from baseline RSI). The secondary outcomes included a change in GerdQ, N-GSSIQ, and salivary pepsin level.

This was an exploratory per-protocol analysis without a predetermined sample size. Outcomes at baseline and postintervention were compared via two-tailed paired t test. Variability in factors among the responder groups were assessed via one-way analysis of variance for continuous variables and by chi-square analysis for categoric variables. P values less than .05 were considered statistically significant. All statistical analyses were conducted using STATA 14.2 (College Station, TX).

Results

Of 20 enrolled subjects, 3 withdrew because of poor tolerance, 2 were lost to follow-up evaluation, leaving 15 who were included in the final analysis (mean age, 45.7 ± 13.4 y; 60% female; and 60% on continued proton pump inhibitor therapy).

Compared with baseline, mean questionnaire scores significantly decreased after intervention (RSI: 26.0 ± 7.8 vs 19.4 ± 8.5, $P < .01$; GerdQ: 10.4 ± 2.1 vs 8.6 ± 2.4, $P < .01$; and N-GSSIQ: 43.4 ± 20.1 vs 26.8 ± 20.8, $P < .01$). The mean salivary pepsin concentrations did not significantly differ (146.5 ± 172.7 vs 158.4 ± 150.2 ng/mL, $P = .61$).

Responder type distribution was as follows: 29% complete responders, 58% partial responders, and 14%

Abbreviations used in this paper: **N-GSSIQ, Nocturnal GERD Symptom Severity and Impact Questionnaire; RALS, reflux-associated laryngeal symptoms; RSI, reflux symptom index; UES, upper esophageal sphincter; UESAD, upper esophageal sphincter assist device.**

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Table 1. Comparison of Factors by Responder Group

	Nonresponder (no reduction in RSI) (n = 3)	Partial responder (reduction in RSI, not meeting criteria for complete response) (n = 8)	Complete responder (postintervention RSI < 13 and 50% reduction from baseline) (n = 4)	*P* value
Age, *y*	54.5 ± 20.5	47.4 ± 14.4	41.0 ± 8.5	.53
Body mass index, kg/m^2	31.8 ± 10.2	29.6 ± 8.5	23.9 ± 1.1	.39
Female sex	1 (33%)	5 (63%)	3 (75%)	.52
Baseline RSI	19.0 ± 1.4	30.1 ± 7.6	22.0 ± 7.0	.09
Baseline GerdQ	9.0 ± 0.0	11.4 ± 1.5	9.8 ± 2.9	.22
Baseline N-GSSIQ	35.5 ± 9.2	51.1 ± 23.3	33.5 ± 15.7	.35
Mean baseline salivary pepsin concentration, *ng/mL*	22.3 ± 2.4	139.9 ± 179.2	221.6 ± 190.8	.44
Proton pump inhibitor use	1 (33%)	4 (57%)	3 (75%)	.53
Postintervention GerdQ	9.5 ± 3.5	9.1 ± 1.7	7.0 ± 2.9	.31
Postintervention N-GSSIQ total	29.5 ± 10.6	32.4 ± 25.2	14.3 ± 7.2	.39
Mean postintervention salivary pepsin concentration, *ng/mL*	41.0	164.1 ± 158.1	182.5 ± 169.4	.74
Mean delta (baseline - postintervention) salivary pepsin concentration, ng/mL	-17.0	-24.2 ± 35.9	110.3 ± 14.5	<.01
Additional data available				
Hernia on upper gastrointestinal endoscopy	0/1 (0%)	4/6 (67%)	1/4 (25%)	.27
Increased acid exposure on 96-hour wireless pH monitoring	0/1 (0%)	0/2 (0%)	1/3 (33%)	.64
Reduced UES resting pressure on manometry	1/1 (100%)	1/2 (50%)	0/1 (0%)	.37
Posterior erythema on laryngoscopy	1/1 (100%)	1/4 (25%)	0/2 (0%)	.19

NOTE. Data are presented as means ± SD or n (%) as appropriate. Data were analyzed via one-way analysis of variance or the chi-square test as appropriate.

nonresponders. The reduction in salivary pepsin was significantly greater among complete responders ($P < .01$). Although not statistically significant, mean age and body mass index were lower and baseline salivary pepsin level was higher among complete responders (Table 1).

Among all participants, after the intervention 100% planned to continue using the UESAD and 93% would recommend the UESAD to others; mean tolerability was rated as 4.4 (scale, 1–5, with 1 being least tolerable).

Discussion

Current treatment options for RALS are limited and often ineffective. In this pilot clinical trial of 15 patients with suspected RALS, use of the UESAD was associated with significant symptom improvement. Overall, the majority showed a partial symptom response. In addition, symptom improvement was associated with reductions in salivary pepsin.

These results suggest that the UESAD is an effective noninvasive therapeutic option for RALS. Furthermore, the salivary pepsin data are thought provoking. Reductions in pepsin concentration appear to track with symptom response, and in this study significant reductions in salivary pepsin were seen only among complete responders. This suggests that patients with a complete response and a reduction in pepsin concentration likely had RALS and derived an actual benefit with the UESAD, whereas patients reporting symptom response without a reduction in pepsin concentration may be experiencing a placebo effect. Although the sample size in this study was small, particularly when comparing responder groups, the sample size was similar to other previously published studies and abstracts, and trends seen in this study are sufficiently hypothesis-generating.[2,7,8] Future work is needed to assess the long-term physiologic responses to the UESAD and the potential placebo response to the UESAD.

In conclusion, the UESAD is a potentially effective therapeutic tool for RALS, and salivary pepsin may be a reliable diagnostic and prognostic biomarker of RALS. The UESAD should be considered and further examined as a treatment tool for this difficult-to-manage patient population.

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Conflicts of interest
The authors disclose no conflicts.

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