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The Upper Esophageal Sphincter Assist Device is Associated with Symptom Response in Reflux Associated Laryngeal Symptoms

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Introduction

Reflux associated laryngeal symptoms (RALS) is the process where chronic laryngeal symptoms are related to gastro-esophago-pharyngeal-reflux.¹ Impairment of upper esophageal sphincter (UES) reflexes may predispose to esophagopharyngeal reflux.¹ The novel non-invasive non-pharmacologic UES assist device (UESAD) applies external cricoid pressure to augment intraluminal UES pressure by 20–30 mmHg and reduce esophagopharyngeal reflux events.² This study aimed to assess the therapeutic efficacy of

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Specific Author Contributions

RY: Study oversight; study concept and design; acquisition of data; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content; finalization of manuscript.

JC: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content; finalization of manuscript.

CA: study concept and design; acquisition of data; critical revision of the manuscript for important intellectual content; finalization of manuscript.

JEP: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content; finalization of manuscript.

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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 9/2015–3/2017, approved by the Northwestern Institutional Review Board (STU#00201370;8/24/2015), and registered with clinicaltrials.gov (NCT#02552966). The study included adult patients experiencing 1 month of laryngeal complaints (e.g., throat clearing, sore throat, dysphonia, cough, globus) with a reflux symptom index (RSI) score ≥ 13 . Exclusion criteria included pregnancy, inability to consent in English, active imprisonment, altered mental status and preexisting conditions preventing UESAD use per manufacturer 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 over 14 consecutive nights, and a post-intervention assessment. At each assessment participants completed three validated patient-reported questionnaires (RSI³, GerdQ⁴, and the Nocturnal GERD Symptom Severity & Impact Questionnaire [N-GSSIQ]⁵) and provided three consecutive fasting salivary samples which were analyzed via Peptest™ (RD Biomed Ltd) to quantify pepsin concentration.⁶

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

This was an exploratory per-protocol analysis without a predetermined sample size. Outcomes at baseline and post-intervention 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 chi-square analysis for categorical variables. P-values <0.05 were considered statistically significant. All statistical analysis was conducted using STATA 14.2 (College Station, TX).

Results

Of 20 enrolled subjects: 3 withdrew due to poor tolerance, 2 were lost to follow-up, and 15 were included in the final analysis (mean age: 45.7 ± 13.4 years, 60% female, and 60% on continued PPI).

Compared to baseline, mean questionnaire scores significantly decreased following intervention (RSI: 26.0 ± 7.8 vs 19.4 ± 8.5 , $p < 0.01$; GerdQ: 10.4 ± 2.1 vs 8.6 ± 2.4 , $p < 0.01$; and N-GSSIQ 43.4 ± 20.1 vs 26.8 ± 20.8 , $p < 0.01$). Mean salivary pepsin concentrations did not significantly differ (146.5 ± 172.7 vs 158.4 ± 150.2 ng/mL, $p = 0.61$).

Responder type distribution was as follows: 29% complete responders, 58% partial responders, and 14% non-responders. Reduction in salivary pepsin was significantly greater among complete responders ($p<0.01$). While not statistically significant, mean age and body mass index were lower and baseline salivary pepsin higher among complete responders. [Table 1]

Among all participants, following intervention 100% planned to continue using the UESAD, 93% would recommend the UESAD to others; mean tolerability was rated as 4.4 (scale of 1–5, 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 demonstrated a partial symptom response. Additionally, symptom improvement was associated with reductions in salivary pepsin.

These results suggest that the UESAD is an effective non-invasive therapeutic option for RALS. Furthermore, the salivary pepsin data is thought provoking. Reductions in pepsin appear to track with symptom response, and in this study significant reductions in salivary pepsin were only seen among complete responders. This suggests that patients with complete response and reduction in pepsin likely had RALS and derived an actual benefit with the UESAD whereas patients reporting symptom response without a reduction in pepsin may be experiencing a placebo effect. Although the sample size in this study is small, particularly when comparing responder groups, the sample size is 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

N-GSSIQ	Nocturnal GERD Symptom Severity & 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

	Non-Responder (no reduction in RSI) (n=3)	Partial Responder (reduction in RSI, not meeting criteria for complete response) (n=8)	Complete Responder (post- intervention RSI < 13 and 50% reduction from baseline) (n=4)	P- value
Age (years)	54.5 ± 20.5	47.4 ± 14.4	41.0 ± 8.5	0.53
Body mass index (kg/m ²)	31.8 ± 10.2	29.6 ± 8.5	23.9 ± 1.1	0.39
Female sex	1 (33%)	5 (63%)	3 (75%)	0.52
Baseline Reflux symptom index	19.0 ± 1.4	30.1 ± 7.6	22.0 ± 7.0	0.09
Baseline GerdQ	9.0 ± 0.0	11.4 ± 1.5	9.8 ± 2.9	0.22
Baseline N-GSSIQ	35.5 ± 9.2	51.1 ± 23.3	33.5 ± 15.7	0.35
Baseline salivary pepsin (ng/ml), mean	22.3 ± 2.4	139.9 ± 179.2	221.6 ± 190.8	0.44
Proton pump inhibitor use	1 (33%)	4 (57%)	3 (75%)	0.53
Post-intervention GerdQ	9.5 ± 3.5	9.1 ± 1.7	7.0 ± 2.9	0.31
Post-intervention N-GSSIQ total	29.5 ± 10.6	32.4 ± 25.2	14.3 ± 7.2	0.39
Post-intervention salivary pepsin (ng/ml), mean	41.0	164.1 ± 158.1	182.5 ± 169.4	0.74
Delta (baseline minus post-intervention) salivary pepsin (ng/ml), mean	-17.0	-24.2 ± 35.9	+110.3 ± 14.5	<0.01
Additional data available				
Hernia on upper gastrointestinal endoscopy	0/1 (0%)	4/6 (67%)	1/4 (25%)	0.27
Elevated acid exposure on 96 hour wireless pH monitoring	0/1 (0%)	0/2 (0%)	1/3 (33%)	0.64
Reduced UES resting pressure on manometry	1/1 (100%)	1/2 (50%)	0/1 (0%)	0.37
Posterior erythema on laryngoscopy	1/1 (100%)	1/4 (25%)	0/2 (0%)	0.19

Nocturnal GERD Symptom Severity & Impact Questionnaire (N-GSSIQ); Upper esophageal sphincter (UES). Data presented as mean ± standard deviation or n (%) as appropriate. Data analyzed via one-way analysis of variance or chi square as appropriate.