

Research

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Prospective Study of Upper Esophageal Sphincter Assist Device for Treating Extraesophageal Reflux

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ABSTRACT

Background: Extraesophageal reflux (EER) is a heterogeneous disease, caused by the regurgitation of gastroduodenal contents into the larynx. The Upper Esophageal Sphincter (UES) Assist Device is a novel medical device designed to prevent gastroduodenal reflux into the laryngopharynx.

Objective: A multicenter prospective study assessing safety and effectiveness of the UES Assist Device in patients with EER.

Methods: Patients with Reflux Symptom Index (RSI) >13 were enrolled. The device was fit and adjusted to at least 20 mmHg applied external cricoid pressure. The primary effectiveness end-point was reduction in RSI at 4-weeks compared to baseline. 36-Item Short Form Health Survey or SF-36® Health Survey (SF-36), patient and physician satisfaction, and Functional Outcomes of Sleep Questionnaire (FOSQ) were secondary end-points. Safety was based on reported adverse reactions.

Results: Eighty-nine of 95 patients completed the study [mean(Standard Deviation (SD)) age=48.8(+/-13.7); mean(SD) Body Mass Index (BMI)=25.5(+/-4.2); 69.5% female, 81.1% Caucasian]. Most common troublesome symptoms included chronic cough (21.3%) and excess mucus/post nasal drip (20.2%). There was a significant ($p<0.0001$) reduction in median (Intelligence Quotient (IQ)) RSI at 2- and 4-weeks [12.5(8.0-20.0) and 10.0(5.8-16.5), respectively] compared to baseline [25.6(21.0-30.0)]. Eighty-two percent (82%) reported improvement greater than 25% with 30.1% having an improvement of 75% or more. 84.7% of patients and 95.2% of providers reported satisfaction. Adverse events were generally mild and transient with no withdrawals due to adverse events.

Conclusion: The UES Assist Device is a safe and effective for the treatment of extraesophageal symptoms and may be an alternative for the many patients that do not respond to Proton Pump Inhibitors (PPI) therapy.

KEYWORDS: GERD; Reflux; Extraesophageal reflux (EER); Laryngopharyngeal reflux (LPR).

ABBREVIATIONS: EER: Extraesophageal reflux; UES: Upper Esophageal Sphincter; RSI: Reflux Symptom Index; FOSQ: Functional Outcomes of Sleep Questionnaire; SD: Standard Deviation; IQ: Intelligence Quotient; PPI: Proton Pump Inhibitors; UES: Upper Esophageal Sphincter; IRB: Institutional Review Board; CPAP: Continuous Positive Airway Pressure; ICD: Implanted Cardioverter Defibrillator; ITT: Intent to treat; QoL: Quality-of-Life; ANOVA: Analysis of Variance; SAS: Statistical Analysis System; BMI: Body Mass Index.

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INTRODUCTION

Extraesophageal reflux (EER) disease represents a wide spectrum of manifestations, mainly related with the upper and the lower respiratory system, such as laryngitis, asthma, chronic obstructive pulmonary disease, cough, hoarseness, postnasal drip disease-sinusitis, otitis media, recurrent pneumonia and laryngeal cancer.^{1,2} Evaluation and management of EER is often resource intensive with significant economic burden. In the US, the cost of caring for this group of patients exceeds \$50 billion.³ The main driver of this cost is the use of Proton Pump Inhibitors (PPI's), which are often over-utilized and in many, do not result in symptomatic improvement. PPI therapy results in reduction of gastric acidity but does not affect reflux of weakly acidic or non-acidic material. Studies have shown that in many patients with EER, incompetence of the Upper Esophageal Sphincter (UES) plays an important role in allowing reflux of gastric content into the pharynx.^{4,5}

The Upper Esophageal Sphincter (UES) Assist Device is a novel medical device designed to prevent the reflux of gastric contents into the laryngopharynx.⁶ It is a non-pharmacologic non-surgical medical device worn while sleeping and applies a standardized external pressure to the cricoid cartilage in order to decrease retrograde reflux of gastroduodenal contents (Figure

1). Physiologic studies with this device have shown that application of 20-30 mmHg cricoid pressure by an external UES Assist Device, significantly increases the UES intraluminal pressure and prevents pharyngeal reflux induced by esophageal slow liquid infusion.⁶

Outside initial important physiologic tests, there are currently no clinical data regarding the efficacy and safety of the UES Assist Device in patients with EER. Thus, the aim of this multi-center prospective cohort study was to employ validated tools to evaluate clinical benefit and safety of the UES Assist Device in patients with chronic EER symptoms.

METHODS

The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. Each investigational site obtained Institutional Review Board (IRB) approval prior to initiating the study.

Study Population

The study was a non-randomized, prospective, open label trial of 95 patients at 5 investigational sites in the United States to assess the safety and effectiveness of the Reza Band®



Figure 1A: Overview of the UES Assist Device. Cushion is placed at the patient's cricoid with the Comfort Band attached to the frame body, by a magnetic Clasp. Physician fit the patient according to pressure required and patient comfort, by adjusting the Comfort Band. Patient is allowed some adjustment to the pressure, using the Comfort Dial.



Figure 1B: UES Assist Device positioned at the cricoid on a patient while sleeping.



Figure 1C: The UES Assist Device is fit by the physician, using the External Manometer connected by a luer lock to the Pressure Sensor. As the UES Assist Device is adjusted, the pressure being applied in mmHg, is displayed in real time. Once the device fitting has been completed, the Pressure Sensor is disconnected, as each Pressure Sensor is a one-time use component.

Upper Esophageal Sphincter (UES) Assist Device for the treatment of esophagopharyngeal reflux with extra-esophageal symptoms (i.e., chronic cough, choking, aspiration, chronic post nasal drip, globus, sore throat, throat clearing). The study population consisted of subjects that were 18 years of age or older, clinically diagnosed with esophagopharyngeal reflux with extra-esophageal symptoms and had a Reflux Symptom Index (RSI)⁷ score >13. Patients were excluded if they were currently receiving treatment for sleep apnea with Continuous Positive Airway Pressure (CPAP), were female and of child bearing potential and is not using an acceptable method of birth control, or was pregnant or breast feeding, had undergone previous head or neck surgery or radiation, had been diagnosed with carotid artery disease, thyroid disease, or history of cerebral vascular disease, was suspected of esophageal or nasopharyngeal cancer, had either a pacemaker or Implanted Cardioverter Defibrillator (ICD) or had undergone Nissen Fundoplication.

Protocol and Study Design

As part of the inclusion requirement, and prior to being fit with the UES Assist Device by the investigator, patients completed the RSI. All subjects had to achieve a RSI score of >13 to be included in the study. Patient demographics and medical history were obtained, including procedural history, relating to the condition over the last 2 years. Once fitted with the device (Figure 1A), patients were instructed as to how to apply the device, and to wear it when sleeping at home (Figure 1B). The fitting process included the UES Assist Device being set to apply external cricoid pressure to above 20 mmHg (Figure 1C). Patients were required to complete a diary and return it to the investigator at the follow-up visits. RSI, SF-36, and Functional Outcomes of Sleep Questionnaire (FOSQ)⁸ were measured at baseline, 2- and 4-weeks post-enrollment. The patient and physician satisfaction scores were measured at 4-weeks post-enrollment. The investigator documented all adverse events as noted in the diary, as well as upon examination for both the 2 and 4 week visit. Reduction in RSI comparing baseline to post intervention was the study primary endpoint and reductions in SF-36, FOSQ and patient and physician satisfaction scores were the secondary endpoints. Intent to treat (ITT) analysis conducted post intervention.

pH testing was not employed in this study since the sensitivity of pH monitoring is about 50% in the proximal esophagus and 40% in the hypopharynx in detecting true reflux events. Patients were diagnosed with esophagopharyngeal reflux based on laryngeal exam and symptom presentation, had been poorly responsive to PPI therapy, and had continued on pursuing treatment for their condition.

Investigators and patients were asked about their satisfaction with the UES Assist Device at the conclusion of the study based on a 7-point Likert Scale (1=extremely satisfied; 2=very satisfied; 3=satisfied; 4=somewhat satisfied; 5=dissatisfied; 6=very dissatisfied; 7=extremely dissatisfied). The FOSQ is a self-reported measure designed to assess the impact of

disorders of excessive sleepiness on multiple activities of everyday living that includes areas of physical, mental and social functioning. The SF-36 is a multidimensional, health-related, Quality-of-Life (QoL) questionnaire, which measures 8 health related parameters (physical function, social function, physical role, emotional role, mental health, energy, pain, general health perceptions). Each parameter is scored from 0 to 100. The SF-36 also includes a list of 18 self-reported chronic conditions.

Statistical Analysis

Sample size was based on the primary efficacy variable, which was defined as the percent reduction in RSI from Baseline to Week 4. For this efficacy variable it was assumed that the study would be successful if the mean percent reduction of the RSI score when comparing the baseline to the final measure, is significantly greater than 25%. This criterion was based on the average placebo response of placebo-controlled trials using the RSI.^{9,10} Assuming that the UES Assist Device has a 35% reduction in the RSI score, using a power of 80%, and a one-sided significance level of 0.05, it was determined that 85 subjects were required for the study. Allowing for slight departure in the assumptions, and allowing for some subjects having no post-baseline efficacy assessments, up to 100 subjects would be recruited for the study.

Baseline demographic and medical history data were obtained and summarized for all subjects treated. The primary efficacy variable is the percent reduction in total the RSI score when comparing baseline measures to week 4 measures. The mean percent change was compared to the hypothesized response of 25% using a one-sample t-test. A *p*-value of <0.05 was considered significant, with regard to demonstrating efficacy. Subjects who did not complete the study but who had at least one post-baseline efficacy assessment had their four-week assessment imputed by using the last post-baseline assessment. No other special data handling algorithms were used for imputing missing data. Subgroup analysis were conducted including study site, pre-existing comorbidities, gender, race, smoking status, alcohol consumption, Body Mass Index (BMI) group, age range group, applied pressure range group, and most troublesome RSI symptom reported by the subjects at baseline. For subgroups that formed two outcomes (i.e., gender) the subgroups were compared using a two-sample t-test. Subgroups that formed more than two outcomes (i.e., race) the subgroups were compared using an Analysis of Variance (ANOVA).

Safety was based on reported adverse reactions. These events were summarized overall, by severity, and by relationship to the device. If subjects reported the same event several times, the worst reported case of the event was used for the purpose of analysis of severity, and the most related event was used for the purpose of analysis of relationship to the UES Assist Device. The incidence of site reactions, including laryngospasm, choking, pain, cough and hoarseness, is summarized, including the exact 95% confidence intervals.

Continuous data were summarized that included the number of observations analyzed, the mean, the standard deviation, the median, the minimum, and the maximum. Categorical data were described by the number and percent of subjects for each outcome. Statistical significance was declared if the two-sided p -value was <0.05 . No correction for multiple testing was performed. Data were summarized using descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) for continuous variables (e.g., age) and counts and percent for discrete variables (e.g., success vs. failure). Statistical Analysis System (SAS) statistical software, version 9.2, was used for all data analyses. All analysis were performed on data points stored in SAS in the primary datasets (containing data derived directly from Case Report Forms) or on secondary data points stored in temporary datasets created from SAS scripts performing functions on the primary datasets.

RESULTS

Demographics

Ninety-five (95) subjects with esophagopharyngeal reflux with extra-esophageal symptoms (i.e., chronic cough, choking, aspiration, chronic post nasal drip, globus, sore throat, throat clearing), were treated with the UES Assist Device (69.5% female; 81.1% Caucasian; 48.8(\pm 13.1) mean age; 25.5(\pm 4.2) Body Mass Index) (Table 1). There was no significant difference among demographic parameters across the investigational sites. Table 2 outlines the distribution for RSI components by study site and overall. The most common symptom complaints included: troublesome or annoying cough (21.3%), excess mucous or post nasal drip (20.2%), throat clearing (13.5%), hoarseness (9%) and heartburn (9%).

	Site 1	Site 2	Site 3	Site 4	Site 5	All
	N=44	N=22	N=14	N=1	N=14	N = 95
AGE (Years)						
Mean	47.0	51.5	43.9	68.0	53.6	48.8
Standard deviation	13.1	15.8	10.8	N/A	13.0	13.7
<i>p</i> -Value						0.13
BMI						
Mean	24.8	27.3	23.4	25.8	27.0	25.5
Standard deviation	3.5	4.1	3.6	N/A	5.6	4.2
<i>p</i> -Value						0.06
GENDER						
Female	65.9%	77.3%	71.4%	0.0%	71.4%	69.5%
Male	34.1%	22.7%	28.6%	100.0%	28.6%	30.5%
<i>p</i> -Value						0.13
RACE						
African American	4.5%	9.1%	0.0%	0.0%	0.0%	4.2%
Caucasian	75.0%	81.8%	78.6%	100.0%	100.0%	81.1%
Hispanic	5.0%	0.0%	21.4%	0.0%	0.0%	8.4%
Asian	0.0%	4.5%	0.0%	0.0%	0.0%	1.1%
Other	2.3%	0.0%	0.0%	0.0%	0.0%	1.1%
Not reported	6.8%	4.5%	0.0%	0.0%	0.0%	4.2%
<i>p</i> -Value						0.53

Table 1: Patient demographics by study site and overall.

Most Troublesome RSI	Site 1 N=42(n/%)	Site 2 N=21(n/%)	Site 3 N=12(n/%)	Site 4 N=1(n/%)	Site 5 N=13(n/%)	All Sites N=89(n/%)
Q1 – Hoarseness	3(7.1)	1(4.8)	1(8.3)	1(100.0)	2(15.4)	8(9.0)
Q2 – Clearing throat	7(16.7)	4(19.0)	1(8.3)	0(0.0)	0(0.0)	12(13.5)
Q3 – Excess mucus/post nasal drip	9(21.4)	3(14.3)	4(33.3)	0(0.0)	2(15.4)	18(20.2)
Q4 – Difficulty swallowing	1(2.4)	1(4.8)	0(0.0)	0(0.0)	1(7.7)	3(3.4)
Q5 – Coughing after eating/lying down	1(2.4)	1(4.8)	0(0.0)	0(0.0)	1(7.7)	3(3.4)
Q6 – Breathing difficulties	3(7.1)	2(9.5)	1(8.3)	0(0.0)	0(0.0)	6(6.7)
Q7 – Troublesome or annoying cough	6(14.3)	7(33.3)	3(25.0)	0(0.0)	3(23.1)	19(21.3)
Q8 – Lump in throat	4(9.5)	0(0.0)	1(8.3)	0(0.0)	2(15.4)	7(7.9)
Q9 – Heartburn	4(9.5)	1(4.8)	1(8.3)	0(0.0)	2(15.4)	8(9.0)
Invalid ¹	4(9.5)	1(4.9)	0(0.0)	0(0.0)	0(0.0)	5(5.6)

¹3 patients cited 2 most troublesome RSI symptoms. These responses were classified as an invalid.

Table 2: Reflux symptom index (RSI) component distribution by study site and overall.

Primary Effectiveness Endpoint

The median (IQ) RSI score for the study population at baseline was 25.6(21.0-30.0). Median (IQ) RSI scores at the 2- and 4-weeks post study enrollment were significantly (<0.0001) improved; 12.5(8.0-20.0) and 10.0(5.8-16.5), respectively (Table 3) (Figure 2). Thirty percent (30%) of participants reported $>75\%$ improvement in their RSI while 82% had $>25\%$ improvement. The severity of the baseline RSI score did not impact the percentile improvement of the 4-week RSI score ($p=0.11$) (Table 4). Demographic variables were not predictors of the RSI outcome. The most improved symptom component of RSI (Table 5) included heartburn (78%), difficulty swallowing (64%), cough after eating (63%) and hoarseness (62%). The best predictor of success among all RSI components was the presence of heartburn, chest pain, indigestion, or stomach acid coming up.

Baseline RSI	% Improvement
13-15	45%
16-20	61%
21-25	52%
26-30	58%
31-35	48%
>35	32%
<i>p</i> -Value	0.11

Table 4: Percentage RSI improvement as a function of baseline RSI score. Improvement in RSI occurred at all baseline levels.

Secondary Effectiveness Endpoints

Investigators rated their satisfaction as Satisfied, Very Satisfied or Extremely Satisfied 91.7% of the time. There were no reports of the investigators being Very Dissatisfied or Extremely Dissatisfied. The investigator satisfaction was not significantly different across the study sites ($p=0.26$). Similar to the investigator satisfaction reporting, the majority of patients also reported that they were satisfied to some degree (75.4%). The patient satisfaction results were also found not to be different across the investigational sites ($p=0.10$).

	Reflux Symptom Index		<i>p</i> -Value
	Median	Interquartile (25%-75%)	
Baseline	25.6	21.0-30.0	
2 nd Week	12.5	8.0-20.0	<0.0001
4 th Week	10.0	5.8-16.5	<0.0001

Table 3: Reflux Symptom Index (RSI) at baseline and post UES Assist Device at 2- and 4-weeks.

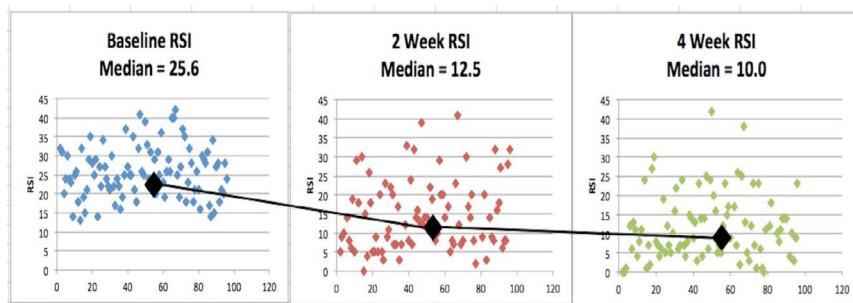


Figure 2: Median reflux symptom index (RSI) for the study population at baseline and at 2- and 4- weeks. There was a significant ($p<0.0001$) reduction of the RSI as compared to baseline.

Most Troublesome Symptom	Mean RSI % Improvement
Hoarseness	62.7
Throat clearing	50.2
Post nasal drip	45.6
Difficulty swallowing	64.2
Coughing after eating/lying down	63.1
Breathing difficulties	42.5
Troublesome/annoying cough	57.6
Lump in throat	49.2
Heartburn	78.1

Table 5: Reflux symptom index (RSI) improvement as a function of individual reported symptoms.

There was no difference in mean (SD) or median (IQ) FOSQ scores at 2-weeks ($p=0.5$) and 4-weeks (0.15), when compared to baseline. Similarly, there was no difference in the mean (+SD) overall SF-36 scores comparing the baseline [115.5(+6.8)] to 4-weeks [116.0(+7.3)] post study enrollment ($p=0.46$).

Primary safety endpoint: The safety of the UES Assist Device was evaluated by assessing the incidence, type, duration and severity of adverse events observed in all subjects. The reported adverse events were generally mild, short in duration, not related to the device and were typically related to the subjects becoming accustomed to the wearing the device (Table 6). The primary reports included soreness, hoarseness, mild skin reaction and a

transient choking sensation. There was one report of laryngospasm. It is important to note that the success of all the categories of adverse events were consistent with overall population. There were no deaths in the study and none of the subjects withdrew from the study due to an adverse event.

DISCUSSION

This is the first report on the effectiveness and safety of a novel UES Assist Device in patients presenting with suspected extraesophageal reflux symptoms. This multicenter study found that the UES Assist Device, when worn for 2-4 weeks at night, resulted in the significant reduction in RSI score among patients

Event	N	Mean Duration in Days (Range)	Mean RSI % Improvement
Soreness	8	6.8(0-32)	38.4%
Laryngospasm	1	0.0(0-0)	86.2%
Transient choking sensation	10	7.6(0-32)	55.3%
Hoarseness	9	2.0(0-7)	46.7%
Skin reaction	9	1.0(0-8)	51.8%

Table 6: Device safety data by complaint, duration and RSI improvement.

with extraesophageal symptoms. There was high degree of satisfaction by both providers and patients and the device use was safe. Among the participants, 30% reported >75% improvement in their RSI, and over 80% had more than 25% improvement.

The question of why an externally applied device, such as UES Assist Device, would result in improvement of extraesophageal symptoms must be addressed based on pathophysiological mechanisms suspected in patients with extraesophageal reflux symptoms. The two proposed mechanisms include the reflux and reflex hypotheses. The latter operates on the principal that embryologically, the esophagus and bronchial tree share similar origin and neural innervation *via* the vagus nerve. With reflux, acidification of the distal esophagus can stimulate acid-sensitive receptors, which can lead to extraesophageal symptoms.¹¹ The reflux hypothesis refers to direct retrograde reflux of gastric (acid and pepsin) and duodenal (bile acids and pancreatic enzyme trypsin) into the esophagus with subsequent aspiration into the lungs; or even higher up in the setting of dental erosions or laryngitis.¹² This leads to direct mucosal injury by gastroduodenal contents leading to extraesophageal symptoms. For example, direct aspiration into lungtissue causes chronic inflammation, which can lead to impaired gas exchange and airway obstruction.^{13,14} In addition, exogenous exposure of larynx to gastroduodenal ingredients can result in significant laryngeal inflammation¹⁵ that may lead to chronic throat symptoms.

An important component of the reflux theory is the incompetence of the UES not preventing the passage of esophageal refluxate into the pharynx.^{4,5} For example, Szczesniak et al⁴ studied 11 patients with extraesophageal reflux symptoms with documented abnormal pH parameters, and found that all reflux of acid into the hypopharynx was associated with relaxation of UES, classified as transient, in 91% of subjects. The authors concluded that UES relaxation is the essential permissive mechanism involved in regurgitation of gastroduodenal contents into the hypopharynx. The same group also showed that in 14 patients with posterior laryngitis, the threshold for esophageal distention induced UES relaxation, was reduced compared to 21 healthy volunteers.⁵ They suggested that up-regulation of the UES relaxation response might be an important pathophysiological mechanism in reflux laryngitis.

An essential mechanism involved in exposure of the larynx to gastroduodenal contents, is the pressure generated by the volume of refluxate. Intraesophageal pressure increases during a reflux event, which eventually leads to relaxation of UES and subsequent reflux into the larynx. However, the pressure generated within the esophagus is often less than 20 mmHg.¹⁶ Thus, could an externally applied pressure of 20-30 mmHg on the cricoid cartilage prevent relaxation of UES and prevent laryngeal exposure to esophageal contents? This question was addressed in a recent physiologic study by Shaker et al in 14 patients with extraesophageal symptoms and 12 healthy volunteers.⁶ The authors reported that slow esophageal liquid infusion resulted in UES incompetence with subsequent laryngeal reflux

events. However, reflux events were significantly reduced by application of a sustained predetermined externally applied cricoid pressure between 20-30 mmHg. The utility of cricoid pressure has been previously recognized in several other settings; for example, cricoid pressure has been used in acute life threatening situations to prevent aspiration of gastric content, and during ventilator assistance of cardiopulmonary resuscitation to prevent air-induced gastric distention.^{17,18} Thus, externally applied pressure on the UES may prevent reflux which might reduce patients symptoms. However, no prior study had systematically addressed the impact of this therapy in a large group of patients with laryngeal symptoms. Therefore, our data are unique and provide impetus for continued evaluation of this alternative therapy in this difficult to treat group of patients.

The strengths of our study includes the large sample size multi-institution nature of the trial, employing validated questionnaires to assess impact on patient symptoms, quality of life as well as sleep and in-depth evaluation for possible unexpected side effects to ensure safety of the employed device. Limitations might include the uncontrolled and non-randomized nature of the study. However, plans are in place to address these limitations with in future trials. Overall, our findings are unique and provide alternative treatment options for patients with suspected extraesophageal reflux based on physiologically confirmed mechanisms. The UES Assist Device resulted in significant symptom improvement within 2-weeks which was sustained for the duration of the study at 4-weeks.

In conclusion, our study showed that the UES Assist Device is a safe and effective non-invasive method for the treatment of extraesophageal symptoms. Given the poor response to PPI therapy in many such patients this device may serve as a potential alternative for this difficult to treat group of patients. Future controlled studies will further validate the importance of this device in this group of difficult to treat patient population.

CONSENT

The subjects provided written permission for publication of case details. The Informed Consent document that was reviewed and approved by the IRB, and signed by all subjects prior to enrolling into the study.

FINANCIAL DISCLOSURES

Dr. Silvers has provided scientific input regarding study design under a consultant agreement for Somna Therapeutics who markets the device used in this study.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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