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Balloon Dilation of the Eustachian Tube for Dilatory Dysfunction: A Randomized Controlled Trial

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Objectives/Hypothesis: To assess balloon dilation of the Eustachian tube with Eustachian tube balloon catheter in conjunction with medical management as treatment for Eustachian tube dilatory dysfunction.

Study Design: In this prospective, multicenter, randomized, controlled trial, we assigned, in a 2:1 ratio, patients age 22 years and older with Eustachian tube dilatory dysfunction refractory to medical therapy to undergo balloon dilation of the Eustachian tube with balloon catheter in conjunction with medical management or medical management alone.

Methods: The primary endpoint was normalization of tympanogram at 6 weeks. Additional endpoints were normalization of Eustachian Tube Dysfunction Questionaire-7 symptom scores, positive Valsalva maneuver, mucosal inflammation, and safety.

Results: Primary efficacy results demonstrated superiority of balloon dilation of the Eustachian tube with balloon catheter + medical management compared to medical management alone. Tympanogram normalization at 6-week follow-up was observed in 51.8% (72/139) of investigational patients versus 13.9% (10/72) of controls ($P < .0001$). Tympanogram normalization in the treatment group was 62.2% after 24 weeks. Normalization of Eustachian Tube Dysfunction Questionaire-7 Symptom scores at 6-week follow-up was observed in 56.2% (77/137) of investigational patients versus 8.5% (6/71) controls ($P < .001$). The investigational group also demonstrated substantial improvement in both mucosal inflammation and Valsalva maneuver at 6-week follow-up compared to controls. No device- or procedure-related serious adverse events were reported for those who underwent balloon dilation of the Eustachian tube.

Conclusions: This study demonstrated superiority of balloon dilation of the Eustachian tube with balloon catheter- + medical management compared to medical management alone to treat Eustachian tube dilatory dysfunction in adults.

Level of evidence: 1b

Key Words: Eustachian tube dysfunction, balloon catheter, normalization of tympanogram.

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Additional Supporting Information may be found in the online version of this article.

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INTRODUCTION

Eustachian tube dilatory dysfunction (ETDD) is an ubiquitous healthcare problem, affecting children and adults, that can lead to severe consequences including hearing loss, chronic otitis media, and cholesteatoma. Nevertheless, safe and effective treatments have remained elusive.[1] Numerous studies have consistently failed to support the effectiveness of medical management (MM) using systemic decongestants or antihistamines and nasal topical decongestants or steroid sprays for the treatment of otitis media with effusion (OME).[2,3] Surgical widening of the narrow, bony portion of the Eustachian tube (ET) has been unsuccessful and abandoned after injuries to the internal carotid artery (ICA).[4,5] Endoscopic studies found that inflammation within the cartilaginous portion of the ET was the most common finding in ETDD, and removal of the inflamed tissue using lasers or microdebriders produced modest improvement in small, noncontrolled trials.[6–9] More recently, preliminary studies, without controls, using inflation of a noncompressible balloon in the cartilaginous ET reported improvement in clinical outcomes such as tympanogram and Eustachian Tube Dysfunction Questionaire-7 Symptom (ETDQ-7) scores without significant complications.[10,11]

This study was designed to assess the safety and efficacy of balloon dilation of the ET (BDET) using a custom-designed ET balloon catheter (ETBC) (Acclarent, Inc., Irvine, CA) in conjunction with MM compared to MM alone in adult patients with drug-refractory ETDD. Briefly, the balloon catheter has a shaft consisting of dual lumen tubing with an actuator component to enable careful rotation and advancement of the device, a balled tip catheter to restrict advancement to the isthmus, an endoscopic marker for positioning, and a guide catheter with an angled tip and rigid shaft for access guidance to the ET. The present multicenter study is the first randomized controlled trial (RCT) to investigate the outcomes of surgery in the treatment of ETDD.

MATERIALS AND METHODS

Study Design

The Study of Safety and Efficacy for the Eustachian Tube Balloon Catheter (NCT02087150) is a prospective, multicenter, nonsignificant risk, RCT, sponsored by Acclarent, Inc., conducted between March 31, 2014 and April 11, 2016, and designed to demonstrate the superiority of BDET with ETBC plus MM compared to MM alone for the treatment of ETDD. Two interim and one final analyses were planned based on BDET:MM ratio of evaluable patients: 54:27, 108:54, and 162:81. After each investigator performed three successful BDETs in nonrandomized lead-in patients, patients were randomized (2:1) to BDET with ETBC plus MM or MM alone. Randomization was stratified by baseline tympanogram type such that equal numbers of patients with baseline type B and C tympanograms were assigned to each group. In patients with unilateral symptoms, treatment was confined to the affected ear. When bilateral treatment was indicated and the subject had two different abnormal tympanogram scores, the patient was stratified to type B. Patients completed follow-up visits at 2, 6, 12, 24, and 52 weeks after treatment initiation; as this is the second interim analysis, data from the 52-week visit are not reported. Patients randomized to the control arm were allowed to crossover to BDET after a 6-week follow-up. Crossover patients completed follow-up at 2, 6, and 12 weeks post-procedure. Safety data for crossover patients are included in the overall safety data analysis, but efficacy results, although presented, were not used for the determination of efficacy. Institutional review board approval was obtained from each center. All patients provided written informed consent before enrollment.

Patients

Eligible patients were 22 years and older with persistent ETDD who had failed MM consisting of either a minimum of 4 weeks of continuous daily usage of any intranasal steroid spray or a minimum of one completed course of an oral steroid within 90 days prior to study enrollment. Persistent ETDD was defined by patient-reported symptoms and at least one of the protocol-defined confirmatory indicators for 12 weeks or more prior to enrollment. A positive diagnosis of persistent ETDD was confirmed with both abnormal tympanometry and symptomatic dysfunction as documented by the ETDQ-7[12] mean item score $\geq$2.1 after failed MM. Transnasal endoscopy of the ET was performed and the degree of mucosal inflammation scored with a validated scale. In addition, absence of ICA dehiscence into the ET lumen on both sides was confirmed by a computed tomography (CT) scan including the temporal bone.

Exclusion criteria included the following: 1) anatomy that required an adjunctive surgical procedure; 2) planned concomitant nasal, sinus, or ear procedures during the study; 3) history of major head or neck surgery within 4 months of randomization; 4) history of radiation; 5) diagnosis of patulous ET; 6) fluctuating sensorineural hearing loss; 7) active chronic or acute otitis media; 8) tympanic membrane perforation or presence of a tympanostomy tube; 9) presence of tympanosclerosis; 10) acute upper respiratory infection; 11) active temporomandibular joint disorder; 12) cleft palate or history of cleft palate repair; 13) history of craniofacial syndrome; 14) history of cystic fibrosis; 15) history of ciliary dysmotility syndrome; 16) history of systemic mucosal diseases or immunodeficiency disorders; 17) intolerance of protocol-defined medication regimen; 18) prior surgical ET intervention; and 19) limited dilatory muscular contractions on endoscopy of the ET.

Treatment

Balloon dilation of the ET was performed under general anesthesia in the operating room. Each ET dilation was performed at inflation pressure of 10 to 12 atm, with total dilation time of 2 minutes per ET. On the day of BDET, subjects in the investigational cohort began their triamcinolone acetonide (TA) nasal steroid spray regimen consisting of two sprays to each nostril once per day (220 μg total daily dose). Subjects in the control cohort began this same TA regimen on the day of randomization. After 6 weeks, continuation of medical therapy was at investigator discretion. Throughout the duration of study participation, subjects were permitted to continue any concomitant medications for their ETDD or other medical conditions (i.e., allergic rhinitis, laryngopharyngeal reflux) deemed clinically necessary, per the investigator's discretion. Subjects were not permitted to start any new medications or to increase the dose or frequency for existing concomitant medications.

Endpoints and Assessments

The primary effectiveness endpoint was normalization of tympanometry at 6-week follow-up. Investigators and a blinded, independent evaluator, unaffiliated with the patients' care, reviewed all tympanograms. When findings between investigator

TABLE I.
The Eustachian Tube Dysfunction Questionnaire–7 Symptom.*

Over the past 1 month, how much has each of the following been a problem for you?	No Problem		Moderate Problem				Severe Problem
1. Pressure in the ears.	1	2	3	4	5	6	7
2. Pain in the ears?	1	2	3	4	5	6	7
3. A feeling that your ears are clogged or "under water"?	1	2	3	4	5	6	7
4. Ear symptoms when you have a cold or sinusitis?	1	2	3	4	5	6	7
5. Crackling or popping sounds in the ears?	1	2	3	4	5	6	7
6. Ringing in the ears.	1	2	3	4	5	6	7
7. A feeling that your hearing is muffled.	1	2	3	4	5	6	7

*From McCoul et al.[12]

and evaluator were inconsistent, a second independent evaluator conducted a tie-breaking assessment. Each patient served as the unit of analysis; for a bilaterally treated patient, both ears had to normalize for that patient to be considered a success. An ad hoc analysis was performed to evaluate normalization of ETDQ-7 scores (<2.1) (Table I)[12] considering the secondary effectiveness endpoint, minimally important difference level change of 0.5, was not highly sensitive. Positive modified Valsalva maneuver (nose-blow + swallow) performed before tympanograms and mucosal inflammation were also assessed (Fig. 1). For additional information on secondary and exploratory endpoints see Supporting Tables SI and SII in the online version of this article.

Patients were assessed using otoscopy (baseline, 2-, 6-, 12-, and 24-week follow-up), nasal endoscopy (baseline, procedure, 2-, 6-, and 24-week follow-up), and tympanometry (baseline, 6-, 12-, and 24-week follow-up).

Statistical Analysis

A sample size of 243 evaluable patients (162 in the investigational arm and 81 in the control arm) was estimated to provide 80% power to detect a difference between 45.0% in the control arm and 65.0% in the investigational arm using a one-sided test at an α of .025 in a fixed sample design. These estimates were made based on the available balloon dilation literature and a study of the effectiveness of nasal steroids in treating ETD.[13]

O'Brien-Fleming α spend algorithm was used to enable early stopping when superiority of the investigational arm was demonstrated.[14] Effectiveness of BDET was established via a superiority hypothesis using a one-sided Fisher Exact Test at an α of .025 on the primary analysis cohort (PAC) (i.e., all intent-to-treat [ITT] patients who received study treatment for which they were randomized and who completed their primary analysis visit). The investigational device in conjunction with MM was considered superior to MM when the one-sided P value from the statistical testing of the primary effectiveness endpoint was less than or equal to the required P value necessary to reject the null hypothesis, 0.00026 and 0.00706 for the first and second interim analyses, respectively.

Safety of the device/procedure was assessed in all patients who underwent the procedure, including the lead-in cohort. Sensitivity analyses were performed to test the robustness of the efficacy results and the impact of missing data in the ITT versus PAC cohorts.

RESULTS

Demographics and Baseline Characteristics

Four hundred twenty-one patients across 21 centers in the United States provided written informed consent and were screened. Three hundred twenty-three patients (462 ears) were enrolled, including 81 lead-in (115 ears),

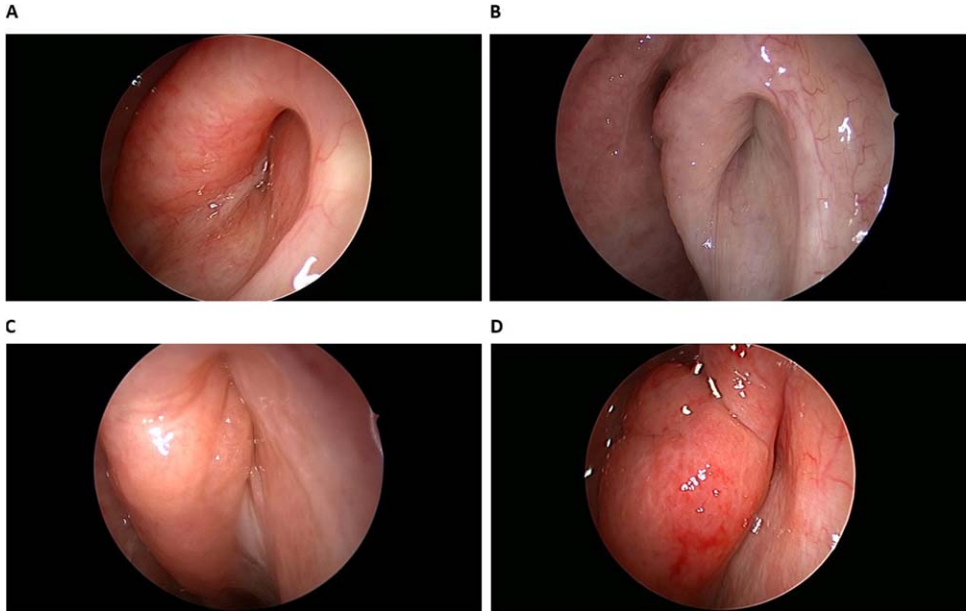

Fig. 1. Mucosal inflammation rating scale. (A) Normal. (B) Mild edema or erythema. (C) Moderate inflammation compromise of dilation. (D) Severe inflammation, inability to dilate lumen open.[15] [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

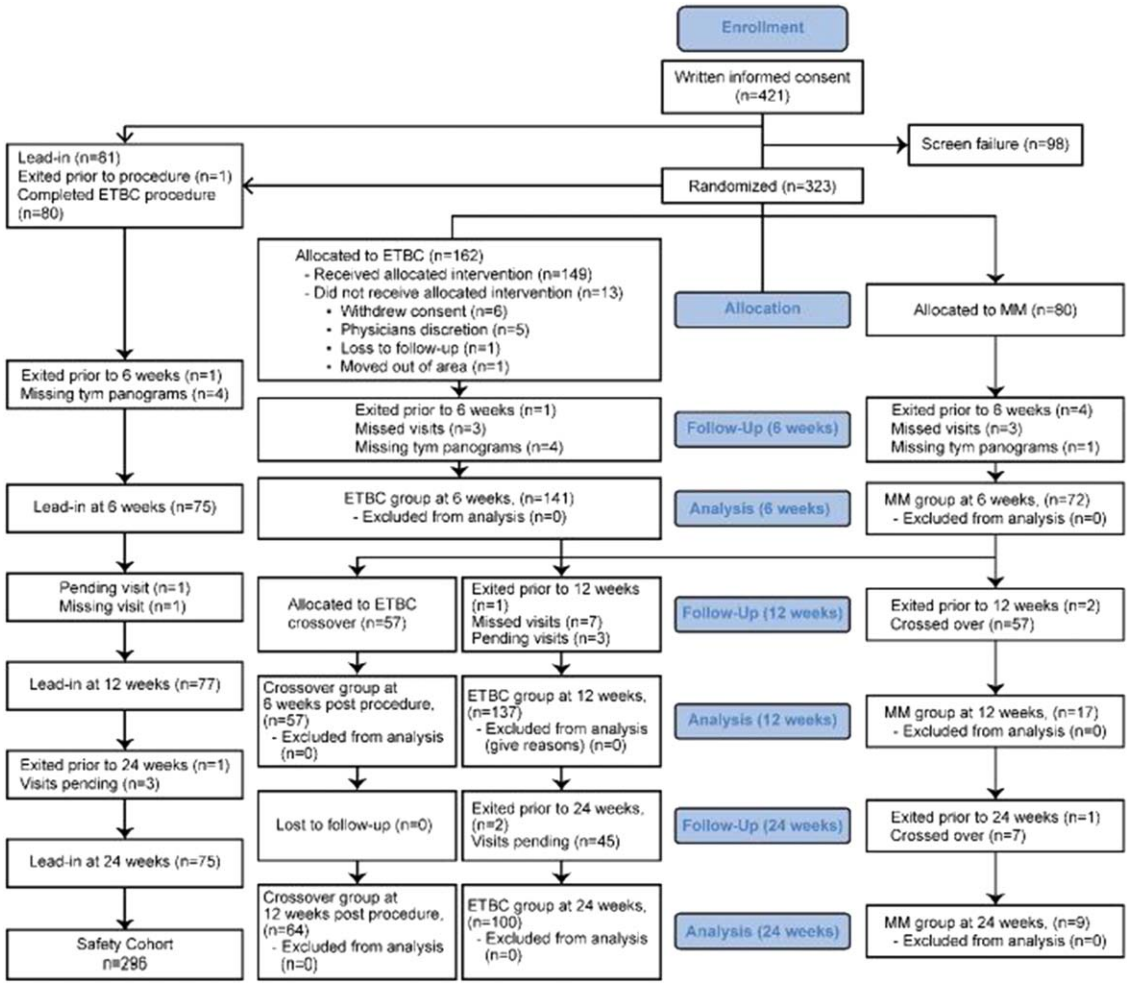

Fig. 2. Consolidated Standards of Reporting Trials flow diagram. ETBC = Eustachian tube balloon catheter; MM = medical management. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

162 randomized BDET (234 ears), and 80 MM patients (117 ears) (Fig. 2). Three patients were removed from analysis considering they were treated with BDET despite having a normal tympanogram at baseline. Patient demographics and baseline characteristics were comparable among the lead-in, control, and investigational cohorts (Table II) although the MM cohort had a trend toward more female patients (60%) compared to the lead-in (37%) and BDET (47.5%) cohorts ($P = .0763$). The majority of the MM patients who completed the 6-week follow-up (82%, 59/71) underwent BDET before their 12-week follow-up (Fig. 2). Criteria for stopping the trial were met with the second interim analysis.

Effectiveness of Treatment

Significantly more patients in the investigational arm compared to the control arm had a normal tympanogram at 6-week follow-up (51.8% [72/139] vs. 13.9% [10/72]; $P < .0001$). The crossover group also experienced an increase in tympanogram normalization 6-weeks postprocedure (data not shown). The treatment effect at 6-week follow-up remained significant ($P < .0001$) after controlling for sex ($P = .2162$) and the interaction between sex and treatment ($P = .1781$). Sensitivity analyses did not reveal a large source of uncertainty in the outcomes interpretation because no tipping point was identified. At 24 weeks postoperatively, tympanogram normalization in the treatment group was 62.2%, but the majority of failed control group subjects had crossed over, so no statistical comparison could be made.

The majority of ears in the investigational arm (128/202; 63.4%) showed improvement in tympanogram (i.e., B to C, B to A, or C to A; note that a C tympanogram is still indicative of negative pressure, < -100 daPa) from baseline to 6-week follow-up compared to only 25.7% of patients in the control arm (27/105) (Fig. 3). Tympanograms remained unchanged in 32.7% of ears in the investigational arm (66/202) compared to 68.6% in the control arm (72/105). A low percentage of ears in both the investigational (8/202; 4%) and control arm (6/105; 5.7%) showed worsening tympanograms at 6-week follow-up.

Improvement in ETDQ-7 Scores

Improvement in tympanometry was associated with normalization of ETDQ-7 at 6-week follow-up; significantly more patients in the investigational (77/137;

TABLE II.
Patient Demographics and Baseline Characteristics.

	Lead-In, N = 81 Patients, 115 Ears	Randomized BDET, N = 162 Patients, 234 Ears	Medical Management, N = 80 Patients, 117 Ears	All Enrolled, N = 323 Patients, 466 Ears	*P* Value*
Age, yr, mean (SD)	53.7 (14.1)	55.6 (14.3)	57.7 (13.4)	55.6 (14.1)	
Sex, female, no. (%)	30 (37.0)	77 (47.5)	48 (60.0)	155 (48.0)	
Race, white or Caucasian, no. (%)	77 (95.1)	147 (90.7)	67 (83.8)	291 (90.1)	
Indicated sides, unilateral, no. (%)	47 (58.0)	88 (54.7)	43 (53.8)	178 (55.3)	
Tympanogram type by ear, no. (%)					.0855
Type A	0 (0)	1 (0.4)	4 (3.4)	5 (1.1)	
Type B	48 (41.7)	81 (34.6)	42 (35.9)	171 (36.7)	
Type C	67 (58.3)	152 (65.0)	71 (60.7)	290 (62.2)	
Average ETDQ-7, mean (SD)	4.6 (1.2)	4.7 (1.1)	4.8 (1.3)	4.7 (1.2)	
Allergic rhinitis, yes, no. (%)	36 (44.4)	73 (45.3)	30 (37.5)	139 (43.2)	
Endoscopy findings by side: adenoid hypertrophy, no. (%)					1.0000
None	99 (86.1)	203 (87.5)	102 (87.9)	404 (87.3)	
Mild	7 (6.1)	23 (9.9)	12 (10.3)	42 (9.1)	
Moderate	9 (7.8)	5 (2.2)	2 (1.7)	16 (3.5)	
Severe	0 (0)	1 (0.4)	0 (0)	1 (0.2)	
Endoscopy findings by side: mucosal inflammation, no. (%)					.1276
None	47 (40.9)	91 (39.2)	55 (47.4)	193 (41.7)	
Mild	50 (43.5)	106 (45.7)	52 (44.8)	208 (44.9)	
Moderate	17 (14.8)	29 (12.5)	9 (7.8)	55 (11.9)	
Severe	1 (0.9)	6 (2.6)	0 (0)	7 (1.5)	
Prior ear tube surgeries, no. (%)					.8579
None	28 (34.6)	63 (39.1)	36 (45.0)	127 (39.4)	
One	33 (40.7)	67 (41.6)	33 (41.3)	133 (41.3)	
Two	18 (22.2)	26 (16.1)	9 (11.3)	53 (16.5)	
Three	1 (1.2)	2 (1.2)	1 (1.3)	4 (1.2)	
Four or more	1 (1.2)	3 (1.9)	1 (1.3)	5 (1.6)	

*Fisher exact test used for categorical variables. *P* value compares randomized BDET and MM groups only.
BDET = balloon dilation of the Eustachian tube; ETDQ-7 = Eustachian Tube Dysfunction Questionaire-7 Symptom; MM = medical management; SD = standard deviation.

56.2%) versus control (6/71; 8.5%; $P < .001$) arm had normal ETDQ-7 scores (i.e., <2.1) (Fig. 3). At 12- and 24-week follow-up, more patients in the investigational arm continued to have less, though not significantly different, symptomatic dysfunction than those in the control arm (Fig. 3). However, this comparison is likely biased (see Limitations below). Similar to tympanogram normalization, 6 weeks postprocedure, crossover subjects showed significant improvement in ETDQ-7 scores (data not shown). For additional analysis on ETDQ-7 scores see Figures S1 and S2 in the online version of this article.

Change in Mucosal Inflammation

There was a marked increase (22.0 percentage points) in the number of patients from the investigational group demonstrating normal mucosal inflammation scores at 6 weeks compared to baseline (Fig. 4A). In the MM group, there was a slight decrease (4.6 percentage points) in the number of patients demonstrating normal mucosal inflammation at 6 weeks compared to baseline. Normal levels of mucosal inflammation at 6 weeks were significantly higher in the investigational group ($P < .001$).

Positive Modified Valsalva Maneuver

In comparison to baseline, there was a 32.8 versus 3.1 percentage point increase in number of ears with positive modified Valsalva maneuver in the investigational arm compared to the control arm at 6-week follow-up, respectively (Fig. 4B). The percentage of patients that could perform a positive modified Valsalva maneuver at 6-weeks was significantly higher in the investigational group ($P < .001$).

Primary Safety

No device- or procedure-related serious adverse events (SAEs) were reported for the 296 patients (444 ears), including crossover patients, who underwent BDET. No medication-related SAEs were reported in the MM group. Five SAEs unrelated to device, procedure, or medications were reported (n = 4 events in the BDET group; n = 1 event in the MM group).

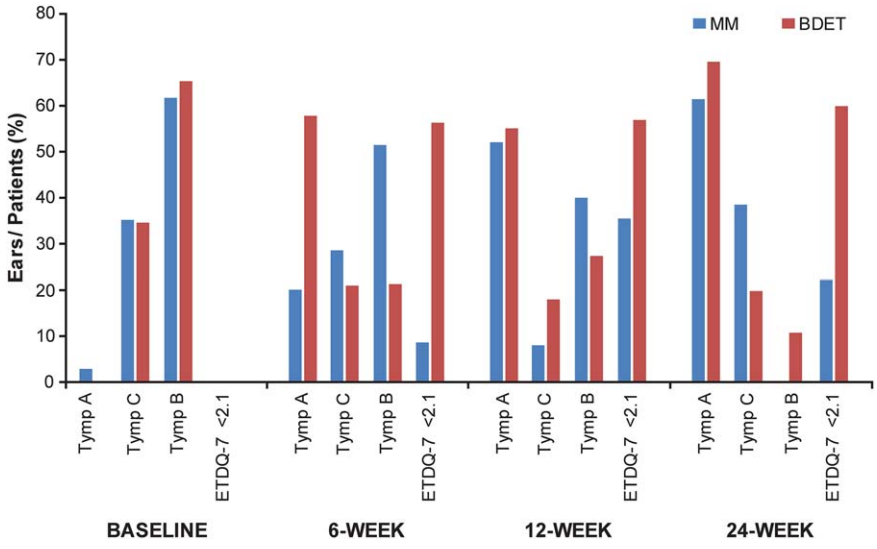

Fig. 3. Correlation of tympanogram and ETDQ-7 normalization. MM group is self-selecting after a 6-week follow-up. Tympanogram is reported by ear and ETDQ-7 is reported by patient. BDET = balloon dilation of the Eustachian tube; ETDQ-7 = Eustachian Tube Dysfunction Questionaire-7 Symptom; MM = medical management; Tymp = tympanogram. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

DISCUSSION

This is the first RCT in which the safety and effectiveness of BDET with ETBC was compared to MM. Results demonstrate that BDET using ETBC with adjunctive MM is superior to MM alone in the treatment of adults with medically refractory ETDD. The primary effectiveness endpoint was met; significantly more patients experienced tympanogram normalization in the investigational cohort at 6 weeks compared to patients in the control cohort. In both randomized cohorts, the proportion of patients with tympanogram normalization (51.8% vs. 13.9%, respectively) was similar to the proportion of patients with normalized ETDQ-7 scores (56.2% vs. 8.5%, respectively) at 6-week follow-up, indicating that BDET also improved symptomatic dysfunction supporting previously published results.[16] Improvements in ETDQ-7 scores were sustained to week 24 in the BDET group and remained greater than those in the MM group (59.8% vs. 22.2%, respectively), although they were not statistically significant.

MM has never been shown to improve ETDD. Short-term benefit in reducing symptoms has been demonstrated, but they fail to adequately address the underlying cause of the mucosal inflammation.[17] In the present study, of the MM subjects who completed a 6-week follow-up and had the option to crossover to the BDET group, 59/72 (82%) patients elected to crossover before their 12-week follow-up, suggesting dissatisfaction with MM. In a recent RCT, the incidence of tympanogram normalization and severity of symptoms were similar among patients treated with nasal topical aqueous triamcinolone or placebo for 6 weeks.[13]

Currently, the most common surgical treatment for treating middle ear ETDD symptoms created by OME is insertion of tympanostomy tubes. Repeated need for tubes occurs commonly,[18] and long-term intubation is associated with increased complications such as infection, perforation, or cholesteatoma.[6]

Preliminary cadaver studies found that BDET could be expected to be a safe procedure with high technical success and short procedure times that effectively widens the functional valve.[19,20] The cartilaginous portion of the ET serves as a functional valve, and ETDD is most commonly associated with inflammatory pathology within that portion. A subsequent pilot clinical trial assessing this procedure for safety and effectiveness reported successful dilation, improvement in tympanogram (if tympanic membrane intact), and positive postoperative modified Valsalva maneuvers in all (n = 11) patients, but they also found a clinically significant reduction in mucosal inflammation scores.[11] In

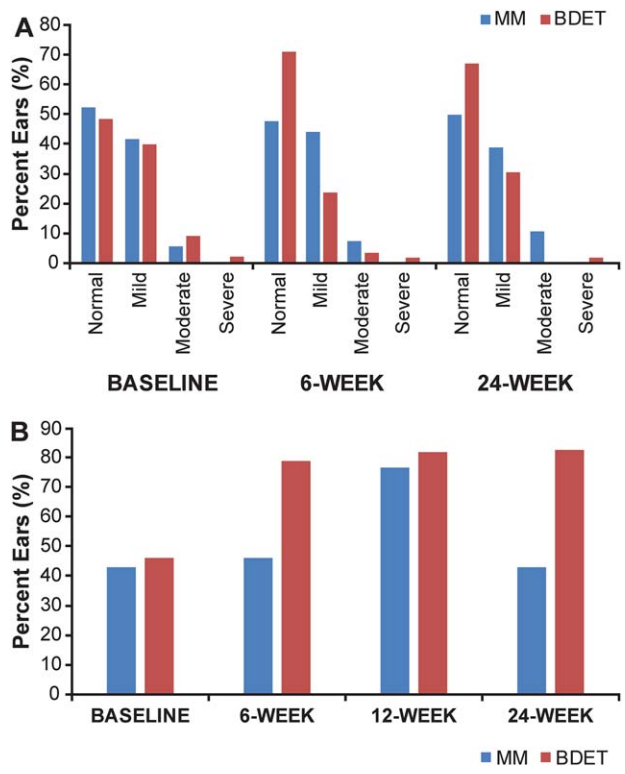

Fig. 4. Change in assessment parameters. (A) Mucosal inflammation. (B) Positive Valsalva maneuver. MM group is self-selecting after 6-week follow-up. BDET = balloon dilation of the Eustachian tube; MM = medical management. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

their continuation report, Silvola and colleagues reported similar results, but with a mean follow-up time of 2.5 years, and again, BDET significantly reduced mucosal inflammation rating scores.[21] A histological study on the effects of balloon dilation suggested that balloon-mediated crushing of irreversibly injured mucosa, submucosal inflammatory lymphoid infiltrate, and follicular hyperplasia may allow for a replacement layer of normal mucosa and submucosal tissue. In effect, it is possible that the noncompressible balloon accomplishes benefits similar to adenoidectomy within the lumen of the ET where conventional techniques would not be accessible. The histological changes might account for the durability of the results.[22] In this study, there was a 22% increase in patients with normal mucosal inflammation scores in the investigational cohort compared to a 4.6% decrease in patients in the control cohort at 6-week follow-up. Importantly, patients who underwent ET dilation had significantly lower non-work activity impairments than patients who underwent MM (see Supporting Figure S3 in the online version of this article). Overall, these results show anatomical and functional benefits of BDET, which may be clinically meaningful to patients.

Limitations

One-third of the study patients were randomized to continue MM, which had previously failed to improve ETDD. Risk of low enrollment was mitigated by providing patients the option to receive BDET after a 6-week follow-up visit. The majority of patients in the control arm (59/72; 82%) did opt to crossover and receive BDET before their 12-week follow-up. Therefore, 6 weeks post-randomization, the MM group became relatively small and self-selecting in nature, likely biasing any statistical comparison between treatment groups. Similarly, the 6-week post-treatment follow-up is rather short; therefore, longer follow-up is needed to properly evaluate the durability of these effects. The use of general anesthesia only in the BDET group added a potential confounding factor, but numerous studies of intranasal interventions under general anesthesia have failed to show improvement in ETDD. Lastly, patients were not blinded to treatment due to the nature of study design comparing MM to surgical procedure. The use of a quantitative primary endpoint, evaluated in a blinded fashion, minimized the risk of a placebo effect.

CONCLUSION

Results from this prospective, multicenter, RCT evaluating BDET using ETBC in the treatment of adults 22 years and older with medically refractory ETDD point to BDET, in conjunction with MM, as a superior treatment option compared to MM alone. A strong safety profile, characterized by the absence of device- or procedure-related SAEs, supports a favorable risk-benefit ratio. The second interim stopping period was met, and study results support the proposed indication for BDET plus MM in this population.

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