In-office balloon sinus dilation versus medical therapy for recurrent acute rhinosinusitis: a randomized, placebo-controlled study

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Background: **A limited number of studies have demonstrated symptomatic improvement for recurrent acute rhinosinusitis (RARS) patients after endoscopic sinus surgery. In this randomized, controlled study we evaluated 24-week outcomes for balloon sinus dilation (BSD) performed in-office (IO) with medical management (MM) as compared with MM only for RARS patients.**

Methods: **Adults diagnosed with RARS were randomized to groups with BSD plus MM (n = 29) or MM alone (n = 30). Patients who received MM alone also received a sham BSD-IO procedure to blind them to group assignment. Patients were followed to 48 weeks posttreatment. The primary outcome was the difference between arms in change in Chronic Sinusitis Survey (CSS) score from baseline to 24 weeks. Secondary endpoints included comparisons of Rhinosinusitis Disability Index (RSDI) score, medication usage, medical care visits, and sinus infections.**

Results: **Change in patient-reported quality of life (QOL), as measured by the CSS total score from baseline to 24 weeks, was significantly greater in the BSD plus MM group compared with the MM-only group (37.3 ± 24.4 [n = 26] vs 21.8 ± 29.0 [n = 27]; $p = 0.0424$).**

Conclusion: **BSD plus MM proved superior to MM alone in enhancing QOL for RARS patients. BSD plus MM should be considered as a viable treatment option for properly diagnosed RARS patients.** © 2018 ARS-AAOA, LLC.

Key Words:
paranasal sinuses; quality of life; endoscopic sinus surgery; balloon dilation

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Recurrent acute rhinosinusitis (RARS) is a chronic condition defined as 4 or more episodes of acute bacterial rhinosinusitis (ABRS) within a 12-month period without signs or symptoms of rhinosinusitis between episodes.[1] In 2005, the annual prevalence of RARS was approximately 0.035% that costed, on average, $1091 per patient-year in total direct health-care costs not including cost of prescriptions.[2] Medical therapy is the first-line treatment for RARS and typically consists of antibiotics, intranasal steroids, and/or saline rinses for relief of congestion. However, systematic reviews regarding the effectiveness of medical therapy for RARS suggest that antibiotics are not effective and there is only limited evidence for an effect of intranasal steroid sprays.[3,4] A recent, nonrandomized, comparative study of medical therapy vs endoscopic sinus surgery (ESS) demonstrated that RARS patients can benefit from medical therapy, but surgical treatment results in greater symptomatic improvement.[5] Improved quality of life (QOL)/productivity, reduced medication usage, and number of sinus infections have been demonstrated in RARS patients after ESS for up to 19 months postoperatively.[6–8]

Balloon sinus dilation (BSD) technology is available as an additional surgical tool in the ear, nose, and throat (ENT)

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armamentarium to enlarge sinus outflow tracts. Compared with traditional ESS, BSD is less invasive, as sinus outflow tracts can be widened without tissue removal. BSD can be routinely and safely performed in a clinic setting.[9–12] Although a growing body of evidence suggests that sinus surgery can be an effective treatment option for RARS patients, the literature lacks prospective, controlled studies with design features minimizing bias, such as randomization or blinding.

In this study we aimed to compare health outcomes and health-care utilization resulting from BSD conducted in-office (IO) plus medical management (MM) vs MM alone for patients with RARS via a patient-blinded, randomized, controlled trial. This study was designed to provide high-quality evidence intended to aid patient and physician evaluation of treatment options for RARS.

Patients and methods

Study overview and treatment arms

This multicenter study (NCT01714687, CABERNET) enrolled patients between January 2013 and April 2015 at 3 centers in the United States after institutional review board (Aspire IRB) approval at all sites. Adult patients with RARS who met study criteria were eligible to enroll and were randomized to either BSD-IO plus MM or to MM alone. The medical regimen for subjects in either arm was dictated by the patient's specific disease process and customized by the treating investigator. To blind patients to treatment arm assignment, those randomized to MM underwent a sham, IO, balloon procedure. Patients were followed through 48 weeks postprocedure, with the primary endpoint being the difference in the change in Chronic Sinusitis Survey (CSS) score from baseline to 24 weeks between the 2 cohorts.[13] A sinonasal endoscopic examination was performed to document any abnormal finding and/or sinus infections at 2-, 8-, 24-, and 48-week follow-up. Concomitant medications, nonstudy medical care for sinusitis, and adverse events were evaluated and documented at this time as well. In addition, during follow-up visits at weeks 8, 24, and 48, subjects completed the following questionnaires: the CSS; the Rhinosinusitis Disability Index (RSDI); and a sinus infection/medication survey. At weeks 16, 32, and 40 postprocedure, subjects completed the CSS and sinus infection/medication survey by mail. If applicable, any potential adverse events were also reported by the patient at this time. For subjects randomized to the MM arm, open-label crossover to receive a true BSD procedure was allowed after 24 weeks. All subjects were followed to 48 weeks posttreatment.

Crossover subjects

Subjects were allowed the option to elect BSD after completion of the 24-week follow-up visit. Because subjects were blinded, this population may have included MM subjects who crossed over to BSD plus MM, or subjects who received a BSD procedure who thought a second BSD procedure was needed (such as if those who did not demonstrate improvement or believed that they had not received a BSD procedure on day 0). Subjects who elected to cross over were then unblinded to inform their decisionmaking.

All MM subjects who elected to cross over and receive a BSD-IO procedure after the 24-week visit were followed at 2, 8, and 24 weeks after the crossover procedure (with additional survey administration at 16 weeks) and then exited from the study. Therefore, MM subjects who crossed over were enrolled for a total of up to 48 weeks and 7 postenrollment follow-up visits (at maximum 2, 8, and 24 weeks postenrollment, crossover procedure, and 2, 8, and 24 weeks after crossover procedure). Subjects in the BSD plus MM arm who elected a second BSD-IO procedure were followed according to their original follow-up schedule to 48 weeks.

Changes in QOL for MM subjects who elected to cross over were evaluated. If crossover subjects completed QOL questionnaires (CSS, RSDI) and then missed work/medication subject questionnaire 4 weeks or less before the crossover procedure, the results were used as baseline preprocedure results to evaluate change after procedure. If the crossover procedure occurred at least 4 weeks after completion of the questionnaires, one additional unscheduled visit was completed to evaluate preprocedure subject QOL. MM subjects who crossed over to receive BSD were analyzed separately.

Inclusion/exclusion criteria

The study included adult patients aged 19 years or older with a diagnosis of RARS, defined by the 2007 AAO-HNS Rhinosinusitis Task Force as having 4 or more episodes of ABRS within the previous 12 months.[1] ABRS was characterized by signs or symptoms of acute rhinosinusitis (ARS) 10 or more days beyond the onset of upper respiratory symptoms, or within 10 days after initial improvement (double worsening). For each subject, at least 1 episode was confirmed by the study physician via endoscopic evaluation, documenting evidence of purulent drainage and edema during an acute exacerbation. All qualifying ABRS episodes not directly evaluated by the study physician were corroborated with referring or primary care physician records to ensure consistent diagnoses meeting the ABRS criteria. Evidence of sinus or osteomeatal complex disease during an acute episode from a computed tomography (CT) scan was required. The purpose of the CT evaluation during an acute ABRS episode is to aid in confirming sinus involvement in the patient's disease. All patients were screened as appropriate candidates for an BSD-IO procedure (ie, concomitant procedures were not required to permit sinus access). All patients could read and understand English.

Patients were excluded if they had: a diagnosis of chronic rhinosinusitis (CRS); previous sinus surgery (not including rhinoplasty or septoplasty); physician-determined need

for ethmoidectomy, polypectomy, septoplasty, or turbinate reduction or incision; known immune deficiency, ciliary dysfunction, and/or autoimmune disease; not suitable for an office-based BSD procedure; clinically significant illness that could interfere with the evaluation of the study; involvement in other clinical studies 6 months before start of the study; pregnant or lactating; or inability to adhere to a follow-up schedule or protocol requirements. Ethmoid disease, allergic rhinitis, and rhinitis were not exclusionary conditions.

Baseline assessments

Eligible patients provided written informed consent for the study participation after discussion with study physicians regarding potential risks and benefits of a BSD-IO procedure, their 50:50 chance of receiving a real or sham sinus surgery procedure, and the option to have a true procedure after 24 weeks if randomized to the MM arm without satisfactory improvement. A CT scan collected during an acute episode of ABRS within the previous 3 months was evaluated and scored according to Lund-Mackay (score range, 0-24).[14] Endoscopic findings were graded using the Lund-Kennedy scoring system (score range, 0 to 20).[15] The endoscopic exam was performed during the screening visit (up to 30 days before the procedure). At this time, patients also completed the CSS and RSDI surveys, and a questionnaire regarding sinus infections, medical care visits, and medication usage (ie, days on oral antibiotics, oral steroids, topical intranasal steroid sprays, and "atypical" topical steroids [drops or respules]).[16]

Randomization, procedure, and blinding

Patients were randomized at time of procedure to BSD plus MM or MM only in a 1:1 ratio. Randomization was conducted in block assignments by investigational sites using sequentially numbered, sealed, and masked envelopes. All procedures were conducted using transnasal wire-based BSD instruments (Acclarent, Inc, Irvine, CA). Study investigators prepared both BSD plus MM and MM patients for the BSD-IO procedure in an identical fashion according to the surgeon's usual practice. Typical procedure preparations included aerosolized local anesthetic and decongestant, followed by topical anesthetic on soaked cottonoids or pledgets. Infiltration of local anesthetic and/or oral anxiolytics was allowed. Those randomized to the BSD plus MM arm were treated with BSD tools and standard functional endoscopic surgical instruments as needed to achieve the goal of the treatment. The particular sinuses in which balloon catheter dilation was performed was determined by the investigator based on the subject's disease pattern. All frontal, maxillary, and sphenoid sinuses intended for dilation were dilated using BSD tools. A sham procedure was conducted for MM patients in a manner such that no anatomic structures were mobilized. Device guide catheter tips were introduced into the nasal space, but not within the osteomeatal complex, infundibular space, or advanced such that sinonasal structures (turbinates, uncinate process) were displaced or sinus drainage routes were dilated. This was done to minimize potential risk as well as the potential for unintentional therapeutic benefit from additional opening of the sinonasal airway. The procedure included local anesthesia of the nasal cavity using topical anesthetic and, if needed, local infiltration of anesthesia. The guidewire was introduced to all sinuses suspected of having disease and, if feasible, without generating resistance to anatomic structures. The sham procedure utilized only the 3.5-mm-diameter × 12-mm-length balloon, to ensure that balloon inflation did not result in any displacement of nasal anatomy, whereas the BSD procedure used balloon sizes of 5, 6, or 7 mm in diameter and 16 or 24 mm in length according to investigator discretion and based on patient anatomy. The BSD procedure was replicated only so far as introduction of the devices into the nasal cavity and wire into the involved sinuses with concurrent use of an endoscope for visualization. Procedures excluded irrigation or adjunctive procedures.

Primary and secondary outcomes

The primary effectiveness endpoint was comparison of change in patient-reported QOL as measured by total CSS score, a duration-based survey capturing weeks of sinus symptoms and medication usage over an 8-week recall period,[13] from baseline to 24 weeks for subjects randomized to BSD plus MM vs MM only. The CSS includes 3 questions regarding symptoms and 3 regarding medication usage, yielding a total score as well as symptom and medication subscores evaluated as secondary endpoints. CSS total score ranges from 0 to 100 in which a low CSS score represents greater symptoms and/or medication usage. The CSS was administered every 8 weeks to assess outcomes continuously during the study, as RARS is characterized by symptom-free periods between acute exacerbations. The RSDI, included as a secondary endpoint, is a 30-question survey that includes a total score as well as physical, functional, and emotional subscores, with no specified recall period.[16] RSDI scores range from 0 to 120, where a higher score indicates increased impact of sinus disease. Additional secondary endpoints were assessed via a patient questionnaire administered every 8 weeks, and evaluated the number of sinus infections, medical care visits, and medication usage in the previous 8 weeks. Patients reported severity of their sinus symptoms and sinus infections as either "much improved," "somewhat improved," "neither improved nor worse," "somewhat worse," or "much worse." In addition to the patient questionnaire, at each follow-up visit, the investigator performed a sinonasal endoscopic examination and documented abnormal findings and/or sinus infections at this visit. Concomitant medications, nonstudy medical care for the patient's sinusitis, and adverse events were evaluated and documented. All adverse events were evaluated for seriousness and causal relationship to medication, procedure, or device.

Sample size calculation and statistical analysis

Observed changes reported in the literature were considered for estimating sample size. Smith et al utilized the CSS to compare outcomes for CRS patients after ESS or continued medical therapy and observed a 15.7-point difference between the surgical and medical arm in mean change in CSS score (standard deviation [SD], 23.8) at 24 weeks posttreatment.[17] Poetker et al employed the CSS to evaluate postsurgical outcomes for CRS and RARS patients and showed similar improvements for each group.[7] In considering these reports, the current study was powered to detect a 10-point difference in CSS change between groups, assuming an SD of 25, 80% power, and a 2-sided α of 0.05, yielding a sample size of 99 patients in each arm. A smaller difference than shown in previous studies was assumed due to restriction on adjunctive procedures and anticipated perceived benefit in the placebo-controlled arm. Based on patient retention challenges demonstrated in earlier studies of ESS, up to 50% loss to follow-up was anticipated, allowing up to 400 patients to enroll.[17,18]

Bayesian adaptive design was employed to allow enrollment stopping before accrual of the full 400-patient cohort, thereby minimizing the number of patients randomized to the sham-control arm. Interim analyses were prespecified when approximately 50, 100, and 200 patients completed 24 weeks of follow-up. Enrollment could be stopped early for superiority if the Bayesian predictive probability of superiority was at least 95%, indicating the probability that the observed results would not change if the study were allowed to fully enroll. Conversely, if the Bayesian predictive probability of superiority was below 10%, the enrollment could be stopped early for futility.

Categorical data are summarized using number and percent. Continuous data are summarized with mean, SD, and 5-number summaries. The nonparametric two-sided Fisher's exact and Kruskal-Wallis (KW) tests were used for analyzing differences between groups in categorical and continuous variables, respectively. The sign test was used to assess changes between baseline and follow-up time-points within groups. No adjustments for multiplicity or imputations for missing data were made. All available baseline and follow-up data are presented for patients randomized. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Patient flow

A total of 59 subjects were randomized and included in this study. Of those, 29 subjects were randomized to the treatment arm (BSD plus MM) and 30 subjects were randomized to the control arm (MM only) (Fig. 1).

Of the 29 randomized BSD plus MM subjects, 1 subject withdrew consent and was not treated with a BSD procedure. Of the remaining 28 randomized BSD plus MM subjects, 26 completed their 24-week follow-up visit; 2 of 28 subjects missed their 24-week visit but returned for subsequent follow-up. As allowed by the protocol, a total of 4 randomized BSD plus MM subjects chose to have a second procedure. These 4 repeat procedure subjects were then followed according to their original follow-up schedule to 48 weeks. Of the 24 subjects who did not have a second procedure, 2 subjects were lost to follow-up and 22 subjects completed their 48-week visit.

Of the 30 randomized MM subjects, 3 subjects were lost to follow-up before their 24-week follow-up visit. All remaining 27 randomized MM subjects completed their 24-week follow-up visit. One subject was lost to follow-up after the 24-week visit. As allowed by the protocol, 18 subjects elected to have a crossover procedure at their 24-week visit. Two additional subjects chose to have a crossover procedure after the 24-week visit (n = 2). All 20 of these crossover subjects completed follow-up for an additional 24 weeks postprocedure. Of the remaining 6 subjects who did not have a crossover procedure, all 6 completed a 48-week follow-up visit. Two of these 6 subjects chose to have a crossover procedure after the 48-week visit and were then followed for an additional 24 weeks postprocedure.

Baseline characteristics and patient disposition

Female patients comprised 61.0% of the study population with a mean age of 45.4 ± 9.9 years. Baseline characteristics and medical history are shown in Table 1. Patients randomized to BSD plus MM had a higher incidence of septal deviation (41.4%) compared with MM-only patients (16.7%; $p = 0.047$), but otherwise had similar comorbidities. There were no differences in baseline CT scan anatomic findings, endoscopic findings, CSS, or RSDI scores (Table 2). Table 3 presents the frequencies with which individual sinuses were ballooned, combinations of sinuses that were ballooned, and laterality. The majority of patients in both the BSD plus MM and MM-only cohorts had no abnormality in either the right or left anterior and posterior ethmoids (54.8% and 67.7%, respectively). The absence of abnormalities by ethmoid was: right anterior ethmoid (61.3% and 76.5%, respectively); left anterior ethmoid (64.5% and 70.6%, respectively); right posterior ethmoid (80.7% and 94.1%, respectively); and left posterior ethmoid (87.1% and 91.2%, respectively). Postoperative debridements were conducted as needed based on physician exam. There were 29 instances of debridement during follow-up. The 29 instances of debridement occurred in 27 subjects. All were suctioning of the mucus. Of the 27 subjects, 14 were BSD plus MM and 13 were MM. Patient retention was good and similar across groups with 26 of 29 BSD plus MM and 27 of 30 MM patients completing the 24-week assessment.

Safety

There were no device- or sinus medication-related adverse events. Three procedure-related or possibly

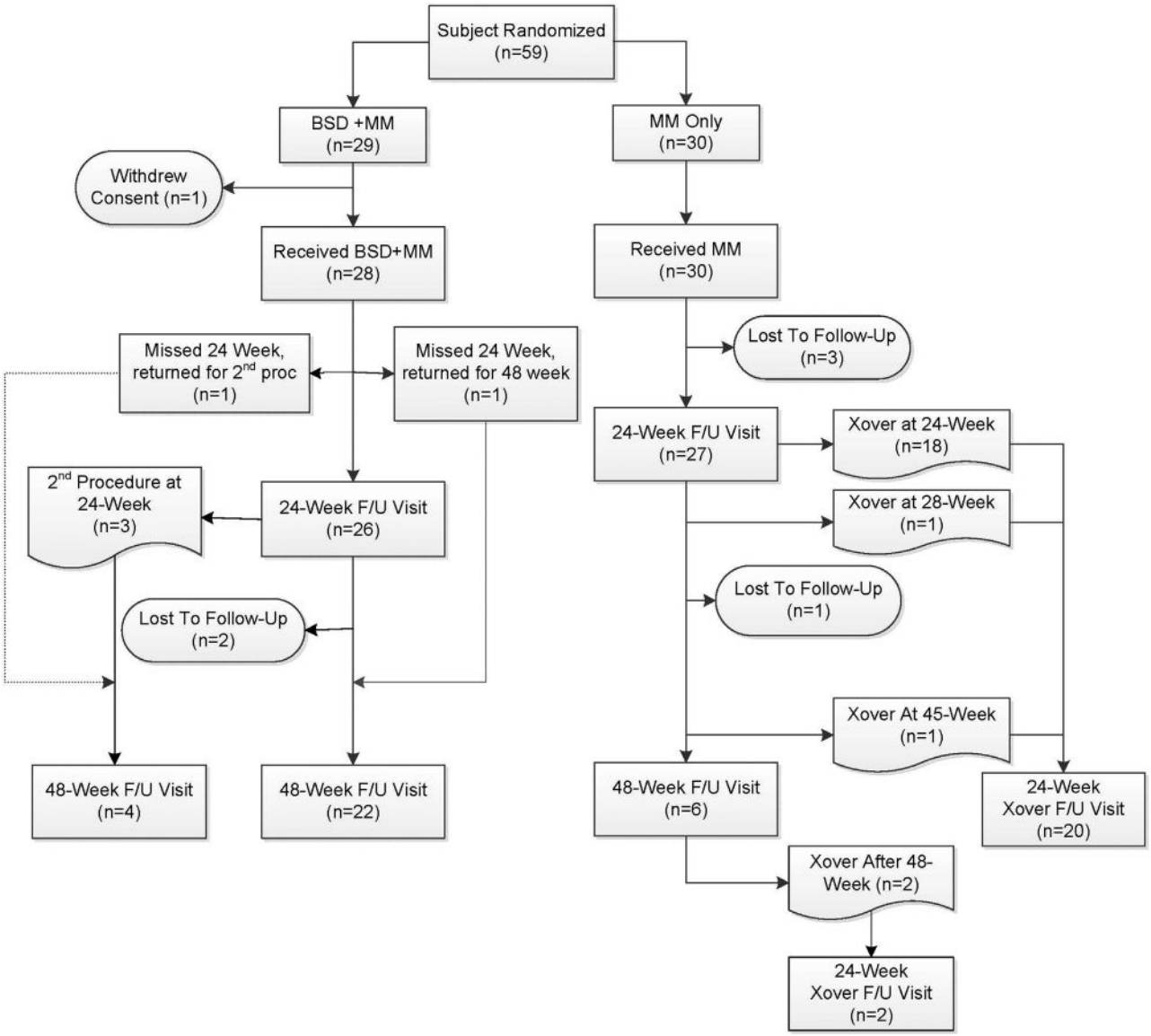

FIGURE 1. Patient flow. BSD = ballooon sinus dilation; F/U = follow-up; MM = medical management.

procedure-related adverse events (of which 1 was considered serious) occurred in the BSD plus MM arm. One patient had headache the evening after the procedure and sought treatment in the emergency room. The patient was admitted to the hospital, treated with narcotic pain medications, and discharged the following day upon resolution of symptoms. This event was considered a procedure-related serious adverse event. A second patient experienced vasovagal response with light-headedness and nausea resulting in procedure discontinuation. Blood pressure normalized after a period of recumbency. A third patient had Eustachian tube dysfunction 3 weeks postprocedure. The latter 2 events were considered possibly procedure-related nonserious adverse events. Incidence of nonserious adverse events did not differ between the BSD plus MM and MM groups (58.6% vs 60.0%, respectively).

Primary and secondary outcomes

The primary outcome, change in patient-reported QOL, as measured by the CSS total score from baseline to 24-week follow-up, was significantly greater in the BSD plus MM group compared with the MM-only group (37.3 ± 24.4 [n = 26] vs 21.8 ± 29.0 [n = 27]; $p = 0.0424$). For a complete summary comparing the 2 cohorts on primary and secondary outcomes refer to Tables 4 and 5, respectively. When comparing the number of postenrollment sinus infections for subjects randomized to BSD plus MM vs MM only, those in the BSD plus MM group had a significantly lower mean number of sinus infections through 24-week follow-up (0.2 ± 0.4 [n = 26] vs 0.9 ± 0.9 [n = 27]; $p = 0.0015$). Similarly, those in the BSD plus MM group had less severe sinus symptoms ($p = 0.0040$) and less severe sinus infections ($p = 0.0266$) at 24 weeks

TABLE 1. Baseline demographics and medical history

	BSD (N = 29 subjects)	Sham (N = 30 subjects)	*p* value
Age (years)			0.1897
Mean (SD) [n]	47.1 (10.0) [29]	43.8 (9.7) [30]	
Gender			0.7925
Male	41.4% (12 of 29)	36.7% (11 of 30)	
Race			0.0995
White or Caucasian	79.3% (23 or 29)	93.3% (28 of 30)	
Ethnicity			0.6120
Non-Hispanic	96.6% (28 or 29)	90.0% (27 of 30)	
Medical history			
Asthma	17.2% (5 or 29)	10.0% (3 or 30)	0.4716
Allergic rhinitis	75.9% (22 or 29)	76.7% (23 or 30)	>0.9999
Polyps	3.4% (1 or 29)	0.0% (0 or 30)	0.4915
Number of sinus infections in the last 12 months			
Mean (SD) [n]	4.8 (1.1) [29]	4.6 (1.0) [30]	0.5266

BSD = balloon sinus dilation; SD = standard deviation.

TABLE 2. Baseline CT, endoscopic findings, and QOL scores

	BSD	MM	*p* value
Lund-Mackay	7.9 ± 3.4 [29] (2.0-18.0)	6.7 ± 3.1 [30] (2.0-13.0)	0.1083
Endoscopic findings			
Lund-Kennedy endoscopy score	4.9 ± 1.8 [29] (2.0-8.0)	5.5 ± 1.6 [30] (3.0-10.0)	0.2334
CSS scores			
Total	38.4 ± 20.0 [29]	43.1 ± 17.7 [30]	0.2870
Symptom subscore	26.4 ± 23.7 [29]	35.8 ± 23.1 [30]	0.1296
Medication subscore	50.3 ± 24.2 [29]	50.3 ± 25.6 [30]	0.9453
RSDI scores			
Total	55.2 ± 23.3 [29]	48.3 ± 22.4 [30]	0.2987
Emotional subscore	15.4 ± 8.8 [29]	13.0 ± 8.8 [30]	0.2549
Functional subscore	16.7 ± 7.9 [29]	14.4 ± 7.7 [30]	0.3348
Physical subscore	23.1 ± 8.3 [29]	20.9 ± 8.9 [30]	0.3869

Data expressed as mean ± standard deviation [n] (range).
CSS = Chronic Sinusitus Survey; CT, computed tomography; QOL, quality of life; RSDI = Rhinosinusitus Disability Index.

compared with those in the MM group. Postprocedure return to normal activity assessed at 2 weeks postprocedure was comparable between the BSD plus MM and MM groups (1.8 ± 1.6 [n = 28] vs 1.3 ± 1.3 [n = 29]; $p = 0.1976$). Of those patients randomized to the MM group, 60% (18 of 30) elected to undergo BSD when allowed by the protocol. The crossover nature of this study limited the ability to perform meaningful comparisons between groups after 24-week follow-up; however, evaluation of this larger cohort demonstrated durability of outcome measure differences at 48-week follow-up (Table 5). It is important to note that we did not ask the reason for electing crossover. Of those who crossed over at 24 weeks, 10 reported no change or worsening of symptoms, 3 reported

TABLE 3. Summary of sinuses that were ballooned

		Left			Right				
Randomized Treatment	Laterality	Frontal	Maxillary	Sphenoid	Frontal	Maxillary	Sphenoid	N	%
Balloon sinus dilation	Bilateral	NO	YES	NO	NO	YES	NO	8	27.59
					YES	YES	Not provided	1	3.45
							NO	3	10.34
				YES	NO	YES	YES	1	3.45
					YES	YES	NO	1	3.45
		YES	YES	NO	YES	NO	NO	1	3.45
						YES	NO	12	41.38
				YES	YES	YES	YES	1	3.45
	Unilateral	NO	YES	NO	NO	NO	NO	1	3.45
All								29	100

TABLE 4. Summary of primary outcomes: change in CSS scores from baseline to 24-week follow-up by cohort

Endpoint	BSD	MM	*p* value
CSS total score	37.3 ± 24.4 [26]	21.8 ± 29.0 [27]	0.0424
CSS medication subscore	26.0 ± 26.6 [26]	16.4 ± 24.0 [27]	0.2607
CSS sinusitis subscore	48.7 ± 28.7 [26]	27.2 ± 40.1 [27]	0.0484

Data expressed as mean ± standard deviation [n].
BSD = balloon sinus dilation; CSS = Chronic Sinusitus Survey; MM = medical management.

improved symptoms but still used nasal sprays at high rates, 4 had improved symptoms to varying degrees but were not eliminated, and 1 reported a sinus infection just before their 24-week visit and crossover procedure. Four additional patients elected a BSD procedure during later follow-up after having improved but continuing symptoms.

Discussion

A small number of studies have evaluated health outcomes of RARS patients after ESS. These studies have shown the clinical benefits of ESS, including improvements in health utility,[19] improvements in QOL,[7,8] reduction in sinus medication usage,[7] reduction in symptoms,[5,10] and reduction in health-care utilization (eg, number of antibiotic course, homebound days, physician visits, and acute infections).[10] Gaps across the various studies include: (1) lack of comparator group; (2) lack of randomization to reduce selection bias; and (3) inability to blind patients to control for placebo effect associated with postsurgical patient-reported outcomes. Our study has addressed these limitations by employing a randomized, sham-controlled study design, thereby providing high-level evidence regarding the relative benefit of BSD plus MM compared with MM alone for RARS patients. Results demonstrate BSD plus MM patients had significantly greater improvement in QOL scores compared with patients randomized to the sham procedure and continued medical therapy. QOL results are consistent with study findings of significantly fewer sinus infections and sinus-related medical care, less severe sinus symptoms, and less severe sinus infections for BSD plus MM patients through 24 weeks postprocedure (Table 4). Importantly, these outcomes were sustainable throughout the 48-week follow-up (Table 5).

Currently, there are 2 options for the treatment of RARS: medical therapy and surgery. Although MM has been shown to clinically benefit a certain subset of this population, one study showed that approximately 33% of patients who began on MM had to undergo surgery after having a significant escalation of symptoms within the first 6 months.[5] Crossover patients in the Costa et al study had significant clinical improvement after surgery. Another study sought to assess when surgical treatment is recommended over MM.[19] Using a health economics model of lost productivity, the results of the study suggest that those patients with more than 3.7 RARS episodes per year would be good candidates for surgery in terms of when a balance is reached between lost productivity, as a surrogate for QOL, from MM and postoperative recovery from surgery. Given that RARS is defined as 4 or more episodes of ABRS within a 12-month period without signs or symptoms of rhinosinusitis between episodes,[1] Leung et al indicated that most patients would meet this suggested threshold for surgery.

The recent Clinical Consensus Statement for Balloon Dilation of the Sinuses has also attempted to address this gap by providing recommendations on patient criteria, perioperative conditions, and outcomes.[20] Among other statements, an expert panel of otolaryngologists reached consensus that there is a role for balloon sinus dilation in

TABLE 5. Summary of secondary outcomes by cohort

Endpoint	BSD [n]	MM [n]	*p* value
Change from baseline to 8-week follow-up			
CSS total score	33.6 ± 27.5 [28]	18.2 ± 26.4 [28]	0.0480
CSS medication subscore	27.7 ± 27.4 [28]	12.2 ± 22.9 [28]	0.0308
CSS sinusitis subscore	39.6 ± 33.7 [28]	24.1 ± 39.6 [28]	0.1208
RSDI total score	−32.9 ± 26.8 [28]	−17.9 ± 30.9 [28]	0.0119
RSDI physical subscore	−14.5 ± 11.2 [28]	−8.6 ± 12.4 [28]	0.0194
RSDI functional subscore	−9.8 ± 8.2 [28]	−5.3 ± 9.4 [28]	0.0181
RSDI emotional subscore	−8.6 ± 8.9 [28]	−4.0 ± 11.2 [28]	0.0126
Change from baseline to 24-week follow-up			
RSDI total score	−35.6 ± 28.2 [26]	−18.7 ± 27.4 [27]	0.0089
RSDI physical subscore	−15.4 ± 10.8 [26]	−9.1 ± 12.1 [27]	0.0174
RSDI functional subscore	−10.4 ± 9.6 [26]	−5.7 ± 7.9 [27]	0.0363
RSDI emotional subscore	−9.8 ± 9.2 [26]	−3.9 ± 9.1 [27]	0.0037
Oral antibiotic usage	0.7 ± 2.3 [26]	2.9 ± 6.6 [27]	0.1261
Oral steroid usage	0.6 ± 2.8 [26]	1.0 ± 3.1 [27]	0.6610
Nasal steroid spray usage	10.5 ± 19.0 [26]	21.5 ± 24.0 [27]	0.1083
Unscheduled medical care visits due to sinusitis	0.2 ± 0.8 [26]	0.9 ± 1.3 [27]	0.0035
Change from baseline to 48-week follow-up			
CSS total score	42.2 ± 17.9 [22]	30.6 ± 24.2 [6]	0.1869
CSS medication subscore	30.7 ± 22.0 [22]	27.8 ± 30.6 [6]	0.6717
CSS Sinusitis subscore	53.8 ± 24.6 [22]	33.3 ± 25.9 [6]	0.1435
RSDI total score	−36.9 ± 21.1 [22]	−17.2 ± 14.9 [6]	0.0409
RSDI physical subscore	−15.1 ± 9.3 [22]	−8.5 ± 6.3 [6]	0.0823
RSDI functional subscore	−11.4 ± 7.1 [22]	−5.0 ± 4.9 [6]	0.0285
RSDI emotional subscore	−10.4 ± 7.3 [22]	−3.7 ± 5.6 [6]	0.0379
Oral antibiotic usage	0.5 ± 2.1 [22]	2.0 ± 3.1 [5]	0.0344
Oral steroid usage	0.7 ± 2.4 [22]	0 [5]	0.4921
Nasal steroid spray usage	10.3 ± 19.8 [21]	24.0 ± 29.4 [5]	0.3458
Unscheduled medical care visits due to sinusitis	0.2 ± 0.9 [22]	0.2 ± 0.4 [5]	0.5292

Data expressed as mean ± standard deviation [n].
BSD = balloon sinus dilation; CSS = Chronic Sinusitus Survey; MM = medical management; RSDI = Rhinosinusitus Disability Index.

managing patients with RARS. However, the panel also noted that there is currently not enough high-level evidence (ie, randomized, controlled trials) available, so the evidence was considered inadequate to support the statement that sinus ostial dilation is effective in reducing the frequency of episodes or the number of antibiotic courses in this patient population.

The present study has addressed this need for randomized, controlled trials assessing BSD plus MM vs a different procedure (in this case, MM) and provides high-level evidence that RARS patients who have undergone a BSD-IO procedure plus MM demonstrate significantly greater improvement in symptoms and reduced sinus infection frequency and health-care utilization compared with patients receiving medical therapy alone. Although this is the first multicenter, prospective, randomized, controlled trial to evaluate the safety and efficacy of BSD plus MM vs MM through 24 weeks (and through 48 weeks for those who received treatment), our findings are comparable to those previously reported.[7] In the case-control

study performed by Poetker et al, RARS patients exhibited significant improvements in QOL postoperatively. Specifically, the mean change in CSS total score pre- to postoperatively was 30.4 ± 23.0 in the Poetker et al study compared with 33.6 ± 27.5 (8 weeks postprocedure) in the present study. Change in RSDI total score was also similar between studies (-29.3 ± 15.5 in the Poetker et al study vs -32.9 ± 26.8 in the present study). Mean changes in subscores were also similar. It is important to note, however, that the Poetker et al study did not define the follow-up time postoperatively.

Despite design features implemented to minimize bias, our study is not without limitations, including lack of double-blinding, implementation of standardized postenrollment medication regimen, limited ability to perform meaningful comparisons between groups after 24-week follow-up due to 60% crossover in the MM arm, lack of an objective measure to assess staging of the disease, lack of properly validated instruments for RARS, high number of frontal sinuses performed, and conflicts of interest among the investigators. Furthermore, the predictive probability of BSD plus MM superiority for the primary endpoint was below the 95% benchmark established for early stoppage. Instead, the study was stopped when the Bayesian analysis indicated 90% confidence that the primary endpoint would remain the same if the study progressed to full enrollment. After careful review of the totality of the evidence, including strong secondary outcome results, which indicated superiority of BSD plus MM to MM only across all endpoints, the sponsor, with the support of the investigators, made the decision to discontinue enrollment so that further eligible patients would not be subject to sham surgery. There were no standardized methods to determine which sinuses to dilate; rather, this was determined by surgeon discretion. Individual surgeons used a combination of CT, endoscopic findings, and patient symptoms to determine which sinuses to dilate. For example, if the patient described bilateral facial pressure and dental dysesthesia bilaterally and CT findings correlated with maxillary sinusitis, bilateral maxillary BSD was performed.Last, per the protocol, the following ancillary procedures were excluded from the office-based BSD procedure: septoplasty; ethmoidectomy; uncinectomy; turbinectomy or turbinate reduction; resection of concha bullosa; and/or irrigation. This was done to maintain the minimally invasive nature of the procedure and for effective blinding of subjects. Two BSD plus MM patients underwent collapsing reduction of concha bullosa, but no tissue was removed. Even so, it is difficult to determine the extent to which these patients benefited from BSD plus MM, the reduction of concha bullosa, or a combination of the two.

Conclusion

Results from this randomized, placebo-controlled trial show RARS patients who have undergone a BSD-IO procedure plus MM had significantly greater improvement in symptoms, reduced sinus infection frequency, and lower health-care utilization compared with patients receiving MM alone, indicating that BSD-IO plus MM is an effective treatment option for RARS patients. These results were sustained through 48 weeks of follow-up.

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