Squeeze bottle versus saline spray after endoscopic sinus surgery for chronic rhinosinusitis: A pilot multicentre trial

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ABSTRACT

Background: *There is a need for controlled trials to guide the perioperative management of patients undergoing endoscopic sinus surgery (ESS). The authors performed a pilot multicenter trial to compare two types of saline delivery devices in this population.*

Methods: *Patients were randomized to high volume saline irrigation with a squeeze bottle and low volume saline spray after ESS in patients with chronic rhinosinusitis (CRS). Surgeons were blinded to treatment, and one-month postoperative scores for sinonasal outcomes [Sinonasal Outcome Test-22 (SNOT-22)] scale, nasal and sinus symptom score (NSS), and perioperative sinus endoscopy (POSE) scale were compared with preoperative scores.*

Results: *Nine centers provided data for 86 patients. All three outcomes measures improved significantly for both groups. Saline spray: SNOT-22 48.8 versus. 23.7, treatment effect 25.1 (95% confidence interval [CI], 17.9–32.2), POSE 21.1 versus. 8.4, treatment effect 12.7 (95% CI, 9.2–16.1), and NSS 8.2 versus 5.0, treatment effect 3.1 (95% CI, 1.4–4.9) pre- and postoperatively, respectively (all $p < 0.0001$). Squeeze bottle: SNOT-22 49.5 versus 23.6, treatment effect 25.9 (95% CI, 20.3–31.6), POSE 18.6 versus 9.2, treatment effect 9.3, (95% CI 6.7–12.0), and NSS 9.0 versus 5.7, treatment effect 3.3 (95% CI, 2.3–4.3) pre- and postoperatively, respectively (all $p < 0.0001$). Analysis of variance did not identify a difference between the two treatment groups. Subgroup analysis based on preoperative disease severity did not change the nonassociation of saline bottle with outcome measures. Post hoc sample size calculation determined that 176 patients is required to detect an 8.9-point difference in SNOT-22 scores.*

Conclusion: *In this pilot multicenter trial examining patients with chronic rhinosinusitis undergoing ESS, both squeeze bottle and saline spray showed significant improvement in SNOT-22, POSE, and NSS scores at one-month postoperatively. Because the study was nonpowered, we cannot rule out a potential difference between the two treatment groups.*

(Am J Rhinol Allergy 29, e13–e17, 2015; doi: 10.2500/ajra.2015.29.4125)

Chronic rhinosinusitis (CRS) is a common inflammatory condition of the upper respiratory tract lasting more than 12 weeks. CRS has an estimated prevalence of 5% in the Canadian population,[1] and up to 16% in some adult populations in the United States.[2] Sinusitis is associated with a major societal health care burden, costing billions of dollars a year in North America.[3,4]

The medical treatment of CRS includes topical saline and corticosteroid sprays, systemic steroids, and antimicrobials. Specifically, saline nasal irrigation (SNI) is a safe, nonpharmacologic treatment and is an important and effective treatment option in CRS management.[5,6] SNI can vary by concentration (*e.g.*, hypertonic, isotonic, and hypotonic) and device (*e.g.*, bulb syringe, nasal mist, and squeeze bottle).

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Presented at the 67th Annual Canadian Society Otolaryngology, Head and Neck Surgery meeting in Banff, Alberta, Canada, June 2, 2013

The authors have no conflicts of interest to declare pertaining to this article

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Despite a lack of controlled trials, there is an overall consensus agreement for the use for SNI in the CRS population.[7] Three studies, all more than 15 years old, examined saline formulations that are currently unavailable in North America.[8–10] Harvey *et al.* explored how irrigation is delivered and retained in the sinuses, using more common devices.[11,12] In a cadaveric model, they compared squeeze bottle with saline spray devices and found a greater sinus cavity delivery ($p < 0.02$) in the former. More recently, an Australian prospective trial randomized 74 postsurgical CRS patients to various saline formulations. They found that irrigation with Ringer's solution resulted in improved quality of life measures and endoscopic mucosal appearances, compared with normal and hypertonic saline.[13]

Examples of popular high-volume low-pressure and low-volume formulations include squeeze bottle (NeilMed Pharmaceuticals, Inc., Santa Rosa, CA) and saline spray (Salinex, Sandoz, QC, Canada), respectively. These are positive pressure treatments[11] that are used globally, despite insufficient evidence demonstrating safety or efficacy. This is likely in part because topical saline sprays are considered safe, they do not require a prescription, and they are heavily marketed. To date, there are no studies comparing high-volume, low-pressure devices with low-volume devices in the postoperative CRS patient.

The authors hypothesized that there is an advantage of squeeze bottle over saline spray. The mechanical effect of high volume (240 mL) irrigation debrides and cleans a larger surface area of sinonasal mucosa. A saline spray bottle contains 30 mL, a small portion of which is expelled with each actuation and therefore may not have the same cleansing effect.

There is growing interest to establish a collaborative Canadian Rhinology group to perform multicenter clinical trials. In addition to

Table 1. **Study inclusion/exclusion criteria**

Inclusion Criteria	Exclusion Criteria
Documented diagnosis of unilateral or bilateral CRS	Pregnant
Documented failed medical treatment of CRS	Cystic fibrosis
18–85 years of age	Diagnosed immotile cilia syndrome
Planned ESS for the treatment of CRS	Diagnosed immunodeficiency syndrome
Able to read and understand English	Diagnosed fungal sinusitis
	Sinonasal tumors or obstructive lesions

CRS = chronic rhinosinusitis.

addressing the above clinical question, this pilot study was performed to determine the feasibility of performing such trials.

METHODS

The authors conducted a prospective, multicenter, single blind, randomized trial evaluating symptom and endoscopic outcomes of squeeze bottle versus saline spray in patients who had endoscopic sinus surgery (ESS) for CRS. One-month postoperative scores were compared with preoperative scores.

Initial contact for center study participation was made to 19 practicing Canadian otolaryngologists who had an interest in rhinology. The standard initial information package explained the purpose and protocol of the study. Surgeons who agreed to participate were then guided for study initiation at their center. Each surgeon could enlist the aid of one resident or research assistant.

Because this was a pilot study to determine the feasibility of performing collaborative multicenter trials, effort was made to design a short, feasible trial with a reasonable number of patients. As such, no sample size calculation was performed, and each center was asked to enroll 10 patients who were offered ESS for CRS. The inclusion and exclusion criteria are listed in Table 1.

The primary outcome was successful study completion, with at least 10 participating surgeons each contributing final data on 80% of enrolled patients (total of 80 patients). Secondary outcomes included symptom-based and endoscopic questionnaires: the Sinonasal Outcome Test-22 (SNOT-22), the perioperative sinus endoscopy (POSE) scale, and the nasal and sinus symptoms score (NSS). Preoperative computed tomography (CT) scans were graded using the Lund-Mackay (LM) score.[14]

The SNOT-22 survey is a rhinology-specific quality of life instrument, based on 22 items. It is reliable, valid, responsive, and easy to use.[15] The POSE scoring system has been used to endoscopically assess the sinonasal cavities in ESS patients and compares well with the Lund-Kennedy endoscopy staging system.[16] Each sinonasal cavity site is graded from 0 to 2, based on the degree of inflammation and/or purulence observed, with a total possible score of 20. For our purposes, an adjusted scale with a denominator of 40 was generated for comparison of the two treatment groups. This calculation has been previously described and allows for comparison between patients with varying extent of sinus surgery.[16]

The NSS was developed at McGill University by DesRosiers and colleagues. It is a five-item scale for patients to rate the perceived disability from 0 (no symptoms) to 3 (as bad as it can be). The items include congestion, pain, headache, need to blow nose, and postnasal drip.

Treatment Allocation

Randomization was performed independently for each center with a computer software program, with patients allocated to either "A" or "B." Equally weighted boxes were prepared by NeilMed Pharmaceuticals, and five boxes of bottle A and five boxes of bottle B were sent by mail to each participating surgeon. Only the designated representative at NeilMed Pharmaceuticals and the administrative assistant for the senior author (I.J. Witterick) were aware of treatment allocation. In this way, surgeons were blinded to bottle allocation.

On the day of the surgery, patients were provided with their allocated box and instructed to use the device "two sprays in each nostril twice daily for one month." The directions were the same for both devices. No other specific instructions were given to participating surgeons, and they were free to treat the patient with other medications as per their usual perioperative protocol.

The trial was registered through ClinicalTrials.gov, Unique Identifier NCT01575223. Because NeilMed Sinus Rinse is considered a natural product (NPN 800271420), and not a medication, Health Canada approved the usage of this product for our study, without a formal Clinical Trial Application. The trial qualified as a phase IV trial. (See Health Canada website for more information.)

Statistical Analysis

Primary analysis was performed according to an intention-to-treat analysis. To encourage surgeon participation, there was no attempt to determine a potential center-by-treatment interaction, and instead, data were grouped together.

Preoperative and one-month postoperative SNOT-22, POSE, and NSS scores for the two treatment groups were compared. Patients were stratified according to disease severity using the LM score to determine whether this influenced the association of bottle on outcome measures.

Demographic variables for each bottle type were compared using χ^2 analysis for categorical variables, and paired Student's *t*-test for continuous variables. Analysis of variance was performed to compare the difference in outcome measures between the two treatment groups. Finally, logistic regression models were formulated with the baseline variables included. This was to determine whether controlling for any baseline variables changed the association of bottle type and outcome measure.

95% confidence intervals were calculated, and a *p*-value of 0.05 was set. Results from each center were weighted according to the number of subjects recruited from that center. Based on the variances of the two treatment groups, a sample size calculation was performed for future studies. Analyses were performed with SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Nineteen surgeons were initially approached for study participation. From March 2012 to November 2013, 11 surgeons from nine centers provided data for 86 patients. Each participating surgeon achieved local institutional ethics board approval. Nine surgeons provided data for at least eight patients. Of the eight surgeons who did not participate, three did not respond to the initial request to participate, three agreed to participate but did not proceed with ethics board submission, and two initiated but did not complete ethics approval.

The two treatment groups were similar in age, gender, primary versus revision surgery, and preoperative SNOT-22, POSE, NSS, and LM scores (Table 2), Patients allocated to the saline spray group were significantly more likely to have CRS with polyps (CRSwP) than CRS without polyps: 31 (72%) versus 12 (28%), respectively, compared with those in the squeeze bottle group: CRSwP, 24 (56%) versus CRS without polyps, 19 (44%), $p = .03$, respectively.

There was significant improvement in the three outcome measures for both treatment groups (Fig. 1). All differences were very highly significant. Comparing the two treatment groups, there was no difference in the pre- and postoperative treatment effects (Fig. 2).

Although no individual center results were displayed, each participating site showed the same magnitude of treatment effect (*i.e.*, all

Table 2. **Baseline characteristics by treatment group**

	Saline Spray (n = 43)	Squeeze Bottle (n = 43)	p-value
Age, years	48.1 (43.8–52.3)	44.5 (40.4–48.7)	0.91
Gender, n (%)			
Male	30 (69.8)	25 (58.1)	
Female	13 (30.2)	18 (41.9)	0.12
Surgery, n (%)			
Primary	21 (48.8)	27 (62.8)	
Revision	22 (51.2)	16 (37.2)	0.07
Polyps, n (%)			
CRSsP	12 (27.9)	19 (44.2)	
CRSwP	31 (72.1)	24 (55.8)	0.03
Preop scales			
SNOT-22 (score/110, CI)	48.8 (42.2–55.4)	49.5 (43.2–55.8)	0.89
POSE (score/40, CI)	21.1 (18.2–24.0)	18.6 (15.5–21.7)	0.88
NSS (score/15, CI)	8.2 (7.0–9.3)	9.0 (8.1–9.8)	0.04
LM (score/24, CI)	17 (15.4–18.6)	15.1 (13.3–16.9)	0.79
Missing, n (%)	3 (6.7)	6 (12.2)	

Categorical variables were compared with χ^2 analysis. Continuous variables were compared with t-test. Preoperative scale scores were weighted to the number of patients from each center. CI = confidence interval; CRSsP = chronic rhinosinusitis without polyposis; CRSwP = chronic rhinosinusitis with polyposis; NSS = nasal and sinus symptom scale; LM = Lund-Mackay scale; Preop = preoperative; POSE = perioperative sinus endoscopy scoring system; SNOT-22 = sinonasal outcomes test-22 scale.

outcomes showed improvement postoperatively, with little difference between saline spray and squeeze bottle).

Subgroup Analysis by Preoperative CT, LM Score

The median value for the LM preoperative CT score was 17.0. Those with more severe preoperative disease (LM > 17.0) were compared with those with less severe disease (LM < 17.0). There were 44 patients in the severe group, and 42 in the less severe group. The main outcome effects were the same as in the whole group, with the severe disease group showing no difference between saline spray or squeeze bottle: mean difference in preoperative and postoperative SNOT-22 scores 27.7 (95% CI, 20.0–35.5) versus 33.2 (95% CI, 24.3–42.0), p = .36, in POSE scores 17.5 (95% CI, 13.5–21.6) versus 11.9 (95% CI, 7.4–16.5), p = .07, and in NSS scores 3.2 (95% CI, 1.3–5.2) versus 4.1 (95% CI, 1.9–6.3), p = .54, respectively. Similarly, those with less severe preoperative disease showed no difference between saline spray or squeeze bottle: mean difference in preoperative and postoperative SNOT-22 scores 21.5 (95% CI, 11.1–31.9) versus 20.0 (95% CI, 10.8–29.2), p = .83, in POSE scores 6.0 (95% CI, 2.1–9.9) versus 7.2 (95% CI, 3.8–10.6), p = .64, and in NSS scores 3.0 (95% CI, 0.8–5.1) versus 2.6 (95% CI, 0.7–4.5), p = .81.

Multivariate Analysis Controlling for Presence of Polyps

As shown in Table 1, patients in the saline spray group were significantly more likely to have CRSwP than those in the squeeze bottle group. To determine the effect that the presence of polyps may have on the outcomes for saline spray and squeeze bottle, logistic regression analysis was performed, controlling for the presence of polyps. Three analyses were run, with difference in pre- and postoperative SNOT-22, POSE, and NSS scores as outcomes. For all three outcome measures, the presence of polyps was not found to be a significant predictor. Similarly, whether the presence of polyps variable was in the model, there was still no significant association between bottle type and outcome measure (all $p > 0.05$, all 95% confidence intervals overlapping 0) (data not shown).

Sample Size Calculation

To help guide future studies, variances from the differences in preoperative and postoperative SNOT-22 scores were used to perform a sample size calculation. The authors agreed on a minimally clinically important difference in SNOT-22 of 8.9.[17] A total of 176 (88 in each arm) patients would be required to detect this difference, with a significance level (α) of 0.05 and 80% power, using a two-sided two-sample t-test.

DISCUSSION

This group of Canadian rhinologists was successful in carrying out a multicenter trial. A similar United States trial with three centers enrolled 302 CRS patients who had ESS.[18] With an average follow-up of 17.4 months, most patients improved across multiple quality of life outcomes. Another United States collaborative trial enrolled 31 otolaryngologists and 117 patients having either medical or surgical therapy for CRS, with 12-month follow-up.[19] Again, quality of life measures improved significantly postoperatively. The authors here concluded, "This study demonstrated the feasibility of multicenter outcome studies in chronic rhinosinusitis and generated testable hypotheses for future investigation."

Despite the limitations of a pilot study, our patient numbers and results compare well with the two multicenter trials above. We achieved impressive recruitment of surgeons and patients, with nine surgeons recruiting at least 80% of the required number of patients. Interestingly, our sample size calculation determined that doubling the enrollment would have sufficiently powered the data.

Similar to previous studies on ESS for CRS, patients in both groups improved significantly postoperatively.[18–22] Because our sample was not powered to detect a difference, we cannot make conclusions on the nonassociation between bottle type and outcome improvement, without risk of a type II error (not detecting a difference when there really is one).

We gained knowledge for the successful conduct of future multicenter trials. A longer follow-up period would help determine a clinically meaningful difference between the two treatment arms. To minimize residual confounding and increase generalizability, we could include more covariates, such as the extent of surgery, middle meatal stenting, prescribed medications such as oral steroids and antibiotics, postoperative infections,[23] frequency of postoperative debridement, and measures of patient compliance.

In general, surgeons who worked with a research assistant or resident were more likely to complete the study. Although at times burdensome and time consuming, all local institutional ethics board applications were

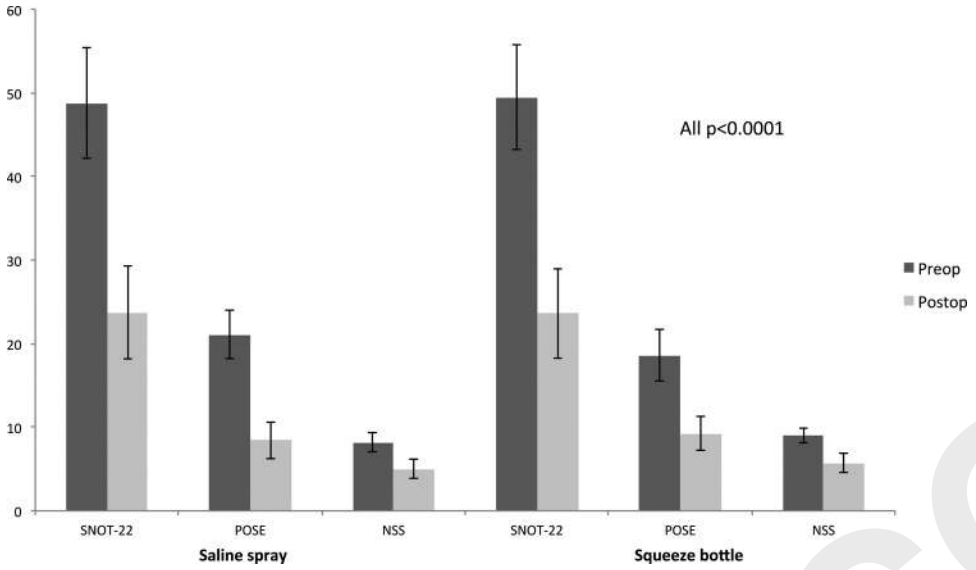

Figure 1. Preoperative versus postoperative scale scores by saline bottle. Preop = preoperative; Postop = postoperative. Error bars represent 95% confidence intervals; p-values were very highly significant for all preoperative versus postoperative scale scores, using a t-test comparing means. Scale scores were weighted to the number of patients from each center.

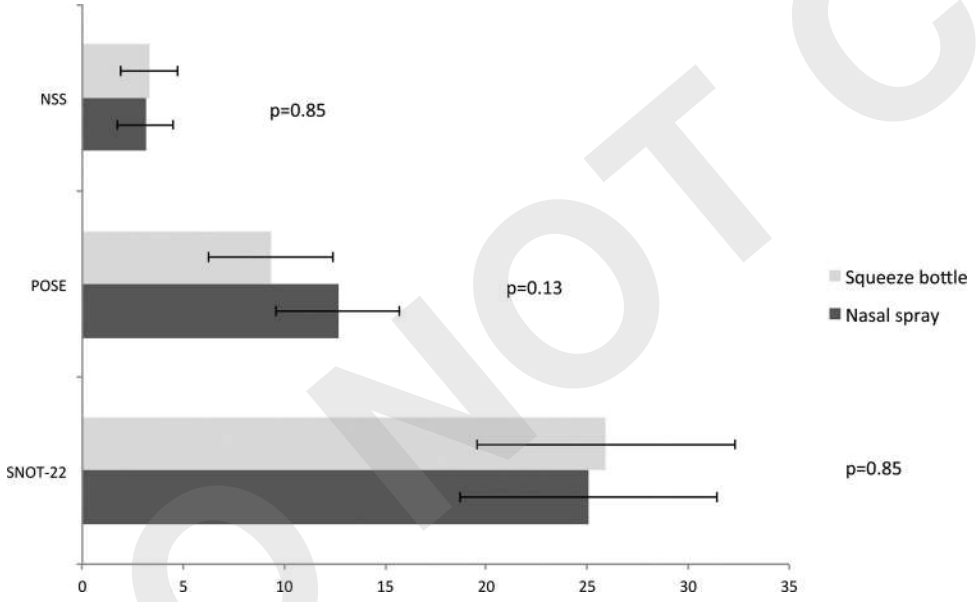

Figure 2. *Postoperative improvement in scale scores. Mean changes in postoperative versus preoperative scores were compared between saline spray and squeeze bottle using analysis of variance (ANOVA). Scale scores were weighted to the number of patients from each center. Error bars represent 95% confidence intervals. The study was not powered to detect a difference between the two-treatment arms.*

successful. A national and uniform ethics board approval for all participating centers would immensely improve efficiency.

A potential disadvantage of our results is selection bias, for both the surgeon and the patient. Surgeons were instructed to recruit consecutive patients to help minimize this bias. Patients who agreed to participate in the trial may have had more or less severe disease than patients who usually have ESS for CRS, which could bias the results toward or away from the null hypothesis. Another potential disadvantage is that patients were not blinded to treatment allocation, which may have influenced their responses on the subjective forms. However, postoperative changes in SNOT-22 and NSS scores were similar to changes in POSE scores, which were rated by blinded surgeons. In addition, these potential disadvantages, selection bias, and lack of blinding are common obstacles to performing randomized surgical trials.[24,25]

The authors of this study are ideally situated for multicenter trials. These are for the most part surgeons at academic centers, who are fellowship trained with a special interest in rhinology, experienced in clinical trials, and have access to CRS patients in all the major Canadian cities. This pilot study demonstrates our capacity to effectively collaborate, and the lessons learned will help ensure success in future trials.

CONCLUSION

This study demonstrated the feasibility of multicenter trials with this group of Canadian rhinologists. Both treatment groups of squeeze bottle and saline spray, in patients having ESS for CRS, showed significant improvement in SNOT-22, POSE, and NSS scores at one-month postoperatively. Because this was a nonpowered pilot study, we could not rule out a difference between in outcomes between the two treatment groups.

ACKNOWLEDGMENTS

The saline bottles used in this study were donated by NeilMed Pharmaceuticals.

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