Corticosteroid nasal irrigations are more effective than simple sprays in a randomized double-blinded placebo-controlled trial for chronic rhinosinusitis after sinus surgery

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Background: **Persistent mucosal inflammation in patients with chronic rhinosinusitis (CRS) often results in ongoing symptoms, recurrence of polypoid mucosa, infective exacerbations, and further systemic medication despite surgical intervention. Debate exists as to the most effective topical therapy in CRS.**

Methods: **The objective was to determine if corticosteroid delivered via a nasal irrigation or via a simple nasal spray would be more effective in controlling the symptoms and signs of CRS. A double-blind placebo-controlled randomized trial over 12 months was performed between 3 tertiary rhinologic clinics. After sinus surgery, all patients performed a nasal irrigation followed by a nasal spray once a day for 12 months. Groups were defined by corticosteroid (2 mg mometasone) delivered by either spray or irrigation. The primary outcomes were patient-reported symptoms: visual analogue score (VAS) and 22-item Sino-Nasal Outcome Test (SNOT-22), a global rating of sinonasal function. Secondary outcomes were also recorded from radiology (Lund-Mackay score [LMS]) and endoscopic (Modified Lund-Kennedy score [mLKS]) assessments.**

Results: **A total of 44 patients were randomized (age 50.3 ± 13.0 years; 40.9% female). Overall, patients improved significantly from either intervention. However, the corticosteroid nasal irrigation group had greater improvement in nasal blockage (−69.91 ± 29.37 vs −36.12 ± 42.94; $p = 0.029$), a greater improvement on LMS (−12.07 ± 4.43 vs −7.39 ± 6.94; $p = 0.031$) and less inflammation on mLKS at 12 months (7.33 ± 11.55 vs 21.78 ± 23.37; $p = 0.018$). One-year posttreatment blockage, drainage, fever, and total VAS scores were all lower in the corticosteroid irrigation group.**

Conclusion: **In the setting of diffuse or patchy CRS disease, the use of corticosteroid delivered by nasal irrigation is superior to simple nasal spray in postsurgical patients.** © 2018 ARS-AAOA, LLC.

Key Words:
chronic rhinosinusitis; paranasal sinuses; irrigations; corticosteroid; intranasal spray, nasal polyps

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It is widely accepted that chronic rhinosinusitis (CRS) is a disorder resulting from an abnormal inflammatory response in the upper airway and not simply an infectious

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Public clinical trial registration: Australian New Zealand Clinical Trials Registry (https://www.anzctr.org.au). Trial ID: ACTRN12612000866808. In patients with chronic rhinosinusitis, what is the effect on disease severity of post-operative mometasone irrigation, compared to simple nasal steroid spray.

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disease for most patients.[1,2] Although CRS is a heterogeneous definition that can potentially include disease states such as fungal ball, allergic fungal sinusitis, odontogenic related sinusitis, mucus recirculation, and mucosal disease around benign neoplasms such as osteoma, this is *not* what most clinicians refer to as CRS. In general otolaryngology practice, CRS is a term commonly applied to patients who present with patchy diffuse mucosal changes in the upper airway on endoscopy and/or radiology along with associated symptoms. In this patient group, simple concepts such as "blocked" or "infected" sinus(es) are not supported by research on CRS.[3,4] Many of these patients respond to corticosteroid when given systemically only to have their inflammatory process continue soon after cessation.[5] Many treating physicians seek to modify the disease or suppress it in the same way that maintenance treatment is applied to dermatitis, asthma, or inflammatory bowel disease.

Topical corticosteroid delivered to the upper airway is a widely accepted standard in the medical management of CRS.[1,2,6] However, the response to corticosteroid sprays in randomized controlled trials (RCTs) on patients with CRS has been variable, with many studies demonstrating little or no effect.[7] Systematic review of these trials suggest that heterogeneity exists partly based on the surgical state of the sinus cavity and the method of drug delivery.[7] This supports the wealth of preclinical data that demonstrates the influence of surgery and delivery device on distribution of topical medication to the paranasal sinus cavity.[8]

Delivery of corticosteroids by a high-volume nasal irrigation solution has become very popular with excellent anecdotal experience and uncontrolled trials.[9,10] Despite this, the clinical data for the effectiveness of corticosteroids delivered by nasal irrigation as superior to nasal sprays has been limited by study design, heterogeneity of surgical practice, short follow-up, and underpowered analyses.[11,12] However, there is substantial evidence of effect.[10,13–16]

With the ability to standardize surgical intervention and the target population, the influence of topical corticosteroid delivery in the postsurgical management of CRS was assessed. The primary goal was to evaluate whether corticosteroid delivered by nasal irrigation or by nasal spray achieved greater long-term disease control.

Patients and methods

Study design

In 3 tertiary rhinology clinics, adults with CRS were randomized in a double-blind, randomized, placebo-controlled trial comparing the clinical effectiveness of a corticosteroid nasal irrigation on disease control vs standard practice (corticosteroid nasal spray) between January 2012 and November 2014. Patients were treated over a 12-month period following surgical intervention. The work was performed at the following institutions: University of New South Wales/St Vincent's Hospital, Sydney Australia and Macquarie University, Sydney Australia. The study was approved by the Research Ethics Boards both at the central coordinating center and at each of the participating sites (St Vincents HREC/10/SVH/10 and Macquarie HREC 5201200048). The trial was registered at the Australian New Zealand Clinical Trials Registry (ACTRN12612000866808). Reporting of this trial was done in compliance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines.[17]

Study population

Patients with CRS undergoing endoscopic sinus surgery were assessed for eligibility. CRS, with or without nasal polyps, was defined as the presence of 2 or more symptoms for >12 weeks, 1 of which should be:

either nasal blockage/obstruction/congestion
nasal discharge (anterior/posterior nasal drip)
± facial pain/pressure
± reduction or loss of smell
AND endoscopic or radiographic evidence of mucosal inflammation

Prior to surgery, all patients had to have failed a minimum 6-week period of medical therapy. Medical therapy prior to surgery included at least nasal saline irrigations and a simple corticosteroid spray (either mometasone 200 μg/day or fluticasone 110 μg/day). Patients with nasal polyps all had a course of prednisone for at least 3 weeks. Antibiotics were given preoperatively if there were purulent secretions or a microbiology culture was positive.

Patients did not get systemic corticosteroid or antibiotics in the 4-week period prior to surgery and the commencement of the study.

All patients had the same extent of endoscopic sinus surgery. A complete sphenoethmoidectomy and wide antrostomy was performed on all patients. Draf3 frontal sinusotomy was performed when there was concern that the frontal sinusotomy might be less than 10 mm, otherwise a complete Draf2a was performed. The intent of the endoscopic sinus surgery was to establish a neo-sinus cavity that could be managed with topical medications. Septal surgery was performed when deviations impaired access to the sinus cavity, at the time of surgery or potentially in the postoperative period. A typical patient example and the surgery applied is shown in Figure 1.

Patients were excluded if they had prior sinus surgery, unilateral sinus changes (including fungal ball, allergic fungal sinusitis, odontogenic-related disease, mucus recirculation and any local neoplasm associated with sinus disease), or sinus disease associated with systemic conditions such as immunodeficiency, Churg-Strauss (eosinophilic angiitis), Wegener's granulomatosis, autoimmune disease, and connective tissue disease. Patients taking immunosuppressive medication were excluded. Patients with clinically significant caudal or anterior septal deviations were excluded. Other exclusions included those patients under the age of 18 years, pregnant women, history of sensitivity to mometasone, and patients unable to give informed consent.

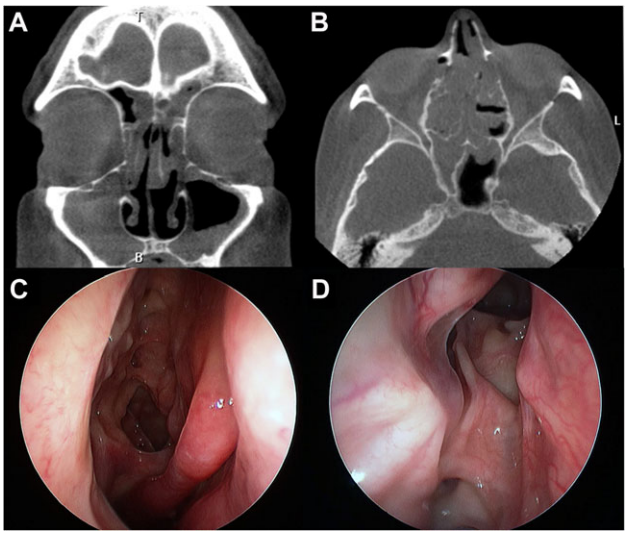

FIGURE 1. Typical CT and postsurgical cavity of patients treated during the trial. The coronal (A) and axial (B) CT images demonstrate a typical patchy and diffuse process. The mucosal changes are not limited to 1 sinus cavity or functional group (ie, frontal, maxillary, and anterior ethmoid). The style of endoscopic sinus surgery was to create a simple sinus cavity or neosinus cavity (C) including a frontal sinus connection (D). The example from (C) and (D) was from a 12-month assessment for a patient in the active or corticosteroid irrigation group. CT = computed tomography.

Disease characteristics

The following population characteristics were collected: age, gender, asthma, aspirin-exacerbated respiratory disease (AERD), smoking status, sinus mucosal eosinophilia, and allergy status.

Asthma status required the additional criteria of either a 15% change in forced expiratory volume in 1 second (FEV1) on spirometry from challenge testing or β-agonist use, or if using regular inhaled bronchodilator/corticosteroid therapy. Patients were determined to have a diagnosis of AERD if they had a history of aspirin or nonsteroid anti-inflammatory drug (NSAID) exacerbation or positive oral aspirin provocation test performed by an immunologist, presence of multiple nasal polyps on endoscopy, and a diagnosis of asthma (as defined at the beginning of this paragraph). Smokers were defined as any patient currently smoking or who had ceased within the last 12 months.

For mucosal eosinophilia, sinus mucosal specimens were obtained intraoperatively and placed in formalin. These were then processed with standard hematoxylin and eosin (H&E) staining and assessed by pathologists blinded to the clinical data. Eosinophilic CRS (eCRS) was defined by histopathological assessment showing >10 eosinophils/high-power field (HPF) (magnification × 400) on 2 separate HPFs.[18,19]

Allergen sensitization was determined by either epicutaneous testing or serological assessment.

Patients refrained from antihistamines for at least 72 hours prior to testing. Epicutaneous testing was performed using allergens in a 50% glycerin solution. Allergens were applied to the volar forearm with a Multi-test II device (Lincoln Diagnostics, Inc., Decatur, IL, USA). The aeroallergen panel used comprised of dust mites (*Dermatophagoides farina*, *D. pteronyssinus*), molds (*Penicillium*, *Cladosporium* sp. mix [*Cladosporium cladosporioides*, *C. herbarum*], fungus (*Aspergillus* sp. mix [*Aspergillus fumigatus*, *A. nidulans*, *A. niger*, *A. alternata*]), animal epithelium (cat, dog), and grass (7-grass mix [Kentucky Blue/June, meadow, rye, sweet vernal, cocksfoot, Timothy], Bermuda grass, Bahia grass, Rye grass). Glycerin was used as negative control and histamine 10 mg/mL as positive control. The wheal size was measured after 15 minutes of application. A positive skin test result was defined as a wheal of more than 3 mm to any one of the allergens with a nonreactive negative control. Serum specific immunoglobulin E (IgE) toward 4 allergen mixes that corresponded to the epicutaneous test panel were evaluated (house dust, mold, animal, and grass) by automated immunoassay. A serum specific IgE value of 0.35 kU/L or more for any of the mixed airborne antigen mixes was considered positive. Patients were grouped as allergen sensitized if either serology or epicutaneous test was positive.

Study interventions

Adult patients with CRS were randomly assigned from day 1 postsurgery to receive either a corticosteroid nasal irrigation with a placebo nasal spray OR a placebo nasal irrigation and corticosteroid nasal spray. All patients performed both nasal irrigation followed by a nasal spray.

Routine perioperative intervention

Postsurgery, patients received a 3-week course of daily prednisone (25 mg for 1 week, 12.5 mg for 1 week, then 5 mg for 1 week). Antibiotics were given postsurgery for 10 days as amoxicillin 875 mg and clavulanic acid 125 mg twice a day. Patients with penicillin allergy were given 7 days of clindamycin 150 mg twice a day. All patients had microbiology cultures at surgery and antibiotics were adapted to culture and sensitivity if necessary. No course of antibiotics or prednisone course exceeded 3 weeks. Routine postsurgical care was provided at 1 week, 6 weeks, and 3 months.

The randomized topical corticosteroid intervention

From the first postoperative day, all patients performed a 240-mL nasal irrigation with a placebo or corticosteroid (performed as one 240 mL irrigation for both sides via NeilMed Sinus Rinse bottle (Santa Rosa, CA, USA)), followed by a single 0.1-mL nasal spray to each side of the nose with a placebo or corticosteroid. Patients were free to use simple saline irrigations in addition to the once per day medicated nasal irrigation.

The corticosteroid used was mometasone and was compounded in suspension to a white viscous base and was odorless. The placebo was an identical base solution

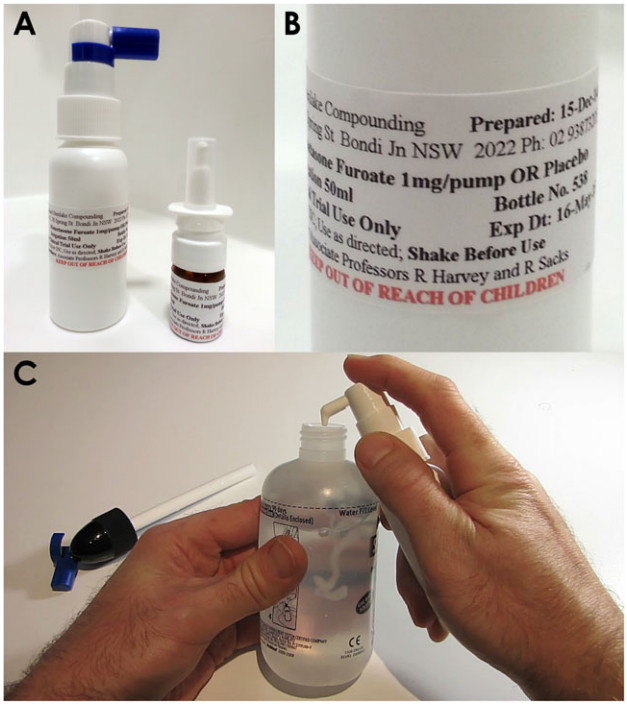

FIGURE 2. The study medication. All patients performed a once per day 240-mL nasal irrigation across both sides followed by a nasal spray with 1 spray (0.1 mL) per side. The nasal irrigation solution was prepared with 2 pumps of the mometasone or placebo via a metered pump (A) and mixed with the saline solution prepared as per commercial guidelines (C). The nasal sprays were prepared and delivered 1 mg mometasone per spray. (B) The patient and investigators were blinded to which device had the active agent or placebo.

without the mometasone. For the nasal irrigation the corticosteroid/placebo was delivered into a 240-mL saline nasal irrigation as metered pump to deliver a 2-mg dose (1-mg per pump with 2 per irrigation bottle) (Fig. 2). For the nasal spray, the bottle contained the corticosteroid/placebo to give a single spray (0.1 mL) delivering 1 mg per side (Fig. 2). All patients received a 2-mg mometasone dose either via the nasal irrigation or via nasal spray. The once-daily topical care of nasal irrigation followed by spray was performed for 12 months postsurgery.

Concomitant therapy

During the treatment period of 12 months, patients were treated in a real-world scenario. If exacerbations or secondary infections occurred in either the upper or lower airway, patients were treated accordingly. All systemic medications except for systemic immunosuppressive agents were allowed during the treatment period. However, only additional saline irrigations were used topically. No other additives or other topical therapies were allowed during the study period.

Maintenance

All patients were reviewed in the same protocol postsurgery at 1 week, 6 weeks, 3 months, 6 months, and 12 months. Compliance with medication, assessment for adverse events, and concomitant therapy was recorded at each visit. Noncompliance was defined as patient self-reported medication use of less than 5 days in a week. Primary and secondary outcomes were assessed at baseline and 12 months postsurgery.

Randomization

The research coordinators (EP and JC) assigned patients the codes and stored the allocation codes. For allocation concealment, the research coordinator allocated a unique code to each patient after eligibility screening. This code was associated with a computer-generated randomization schedule performed in blocks of 6. Allocation only occurred once surgery was scheduled. Study investigators, attending care teams, and patients were blinded to treatment allocation. The surgeons were unaware of intervention group, the study assessments were done without knowledge of allocation, and the research coordinator was not involved in assessment or analysis. Patients were blinded to allocation both by placebo, label, bottle, and management (Fig. 2).

Study outcomes

The study outcomes were recorded at baseline and at 12 months postsurgery. Baseline assessment was performed in the week prior to surgery and at least 4 weeks after any systemic medication had been given. The 12-month assessment was within ±4 weeks from the 1-year postsurgery date. Both patient and assessor were blinded to treatment group when recording patient reported outcomes, radiology assessments, and endoscopic evaluations.

The primary outcome was patient-reported symptom scores. Three assessments were made; a visual analogue scale (VAS) assessment of symptoms, a disease-specific quality of life measure (22-item Sino-Nasal Outcome Test [SNOT-22]), and a 13-point Likert score of overall (or global) sinonasal function. The VAS was performed with a 100-mm scale and included questions on 10 symptoms (blockage, drainage, headache, fatigue, hyposmia, ear pain, cough, halitosis, facial pain, fever) and a single combined total VAS representing the average of those symptoms. The VAS was recorded as the status on the day of assessment. The SNOT-22 was used as described.[20] The global sinonasal function score was a 13-point Likert scale from "terrible function" (−6) to "neither good nor bad" (0) to "excellent function" (+6). The global sinonasal function was recorded as the status on the day of assessment.

For secondary outcomes, a radiologic assessment was done at baseline and at 12 months, and a 12-month endoscopic assessment was recorded.

Radiological assessment was performed using a compact, upright volume cone bean volumetric tomography scanner (MiniCAT IQ™ Xoran Technologies, Ann Arbor, MI). The scans were taken during the screening visit (baseline) and at 12 months. The paranasal sinuses were assessed from serial images (0.4-mm slices) on

coronal, axial, and sagittal views. The images were scored using the Lund-Mackay score (LMS) to determine the degree of mucosal disease.[21,22] The effective dose estimate for a 40-second sinus scan with 600 projection frames taken with the MiniCAT^{TM} scanner is ~0.17 mSv. In total, participants were exposed to ~0.34 mSv over the course of 12 months, which is within the dose constraints required by Australian Radiation Protection and Nuclear Safety Agency (ARPANSA).

Endoscopic assessment was scored from archived video at 12 months using a Modified Lund-Kennedy score (mLKS).[23] The endoscopic appearances of all 10 post–endoscopic sinus surgery cavities (left and right maxillary, ethmoid, sphenoid, frontal sinuses, and olfactory fossa) are quantified for mucosal inflammation: (0-6: 0 = normal mucosa; 1 = mild edematous mucosa with patent cavity; 2 = severe edematous mucosa with compromised cavity; 3 = mild polypoid mucosa with patent cavity; 4 = severe polypoid mucosa with compromised cavity; 5 = polyp confined within cavity; 6 = polyp extending beyond cavity), mucus (0-2: 0 = none; 1 = clear and thin; 2 = thick and eosinophilic) and purulent discharge (0-1: 0 = absent; 1 = present). Only a single posttreatment endoscopic assessment was used for comparison. The mLKS is a post-surgical score that attempts to assess the overall burden of inflammation in the entire sinonasal cavity and is not applicable to unoperated sinus cavities.

Statistical analysis

Our primary analysis was conducted using an intent-to-treat approach, and therefore included all randomized adults. Baseline characteristics of patients in the 2 treatment groups were reported using frequency distributions and descriptive statistics including measures of central tendency and dispersion. The chi-square test was used when comparing the proportion of characteristics between each treatment group at baseline. Other continuous data at baseline were both continuous and parametric and was assessed with unpaired Student *t* tests to compare between groups.

The principal analysis of patient reported outcome measures (PROMs) was continuous and assessed with paired Student *t* test within groups and the change scores (baseline to 12 months) were assessed with unpaired Student *t* tests for assessment between treatment groups. The global score was treated as continuous; although strictly an ordinal scale, it was symmetrically assessed from −6 to 0 to +6. The data was normally distributed when converted. Endoscopic and radiology scores were also continuous and normally distributed. Initial sample size analysis was based on the SNOT-22. Assuming SNOT-22 symptom scores follow the norms for patients with CRS (preoperative mean score = 1.9 ± 0.9) and the minimal clinically important difference (MCID) of 0.8, where the power is 0.8 and the alpha level of significance is 0.05, a sample size of 25 per arm was predicted to detect an MCID. Statistical analyses were performed using SPSS v 24.0 (IBM Corp., Armonk, NY). A p value <0.05 was considered significant.

TABLE 1. The baseline patient characteristics between the 2 treatment groups*

	Intervention		
	Active spray	Active irrigation	*p*
n	23	21	
Age (years)	51.6 ± 11.9	48.8 ± 14.1	0.48
Gender (% female)	34.8	47.6	0.39
Asthma (%)	34.8	52.4	0.39
AERD (%)	0.0	14.3	0.07
Smokers (%)	22.7	33.3	0.44
eCRS (%)	73.9	66.7	0.60
Allergy (+RAST) (%)	57.1	56.3	0.96

*Values are mean ± SD or as indicated. The active group refers to corticosteroid over placebo. The 2 groups were similar with only a trend to AERD in the corticosteroid or active irrigation group.
AERD = aspirin-exacerbated respiratory disease; eCRS = eosinophilic chronic rhinosinusitis; +RAST = a positive IgE result on serum ImmunoCAP analysis; SD = standard deviation.

Results

Study population

Approximately 950 patients were screened for eligibility during the recruitment period January 2012 and November 2014. Many patients elected not to participate but surgeon preference also led to many patients being recommended a treatment path that was believed to be more optimal than the management offered in the trial. A total of 44 patients (5%) agreed to participate, with an age 50.3 ± 13.0 years and 40.9% female. Of these n = 44 patients, polyps or polypoid thickening of the mucosa was seen in 77%. The disease burden was high with a baseline LMS of 14.00 ± 5.26 for the entire group.

The participant flow and recruitment are demonstrated in Figure 3. The baseline demographics and clinical characteristics were similar between groups (Table 1). Patients with polypoid changes were similar between groups (78.3% vs 76.2%; p = 0.87). Additionally. the burden of disease was similar between the corticosteroid irrigation and corticosteroid spray groups (Table 2). Withdrawals were similar between groups and the 2 participants that withdrew due to progression of their inflammatory disease were evenly distributed. Both patients also had asthma and lower airway involvement that was not well controlled with inhaled corticosteroid. All patients (100%) who remained in the study reported compliance, defined as at least 5 days a week treatment, at the 12-month endpoint. Medication was supplied on a monthly basis and the research coordinator had the opportunity to confirm usage on a regular basis.

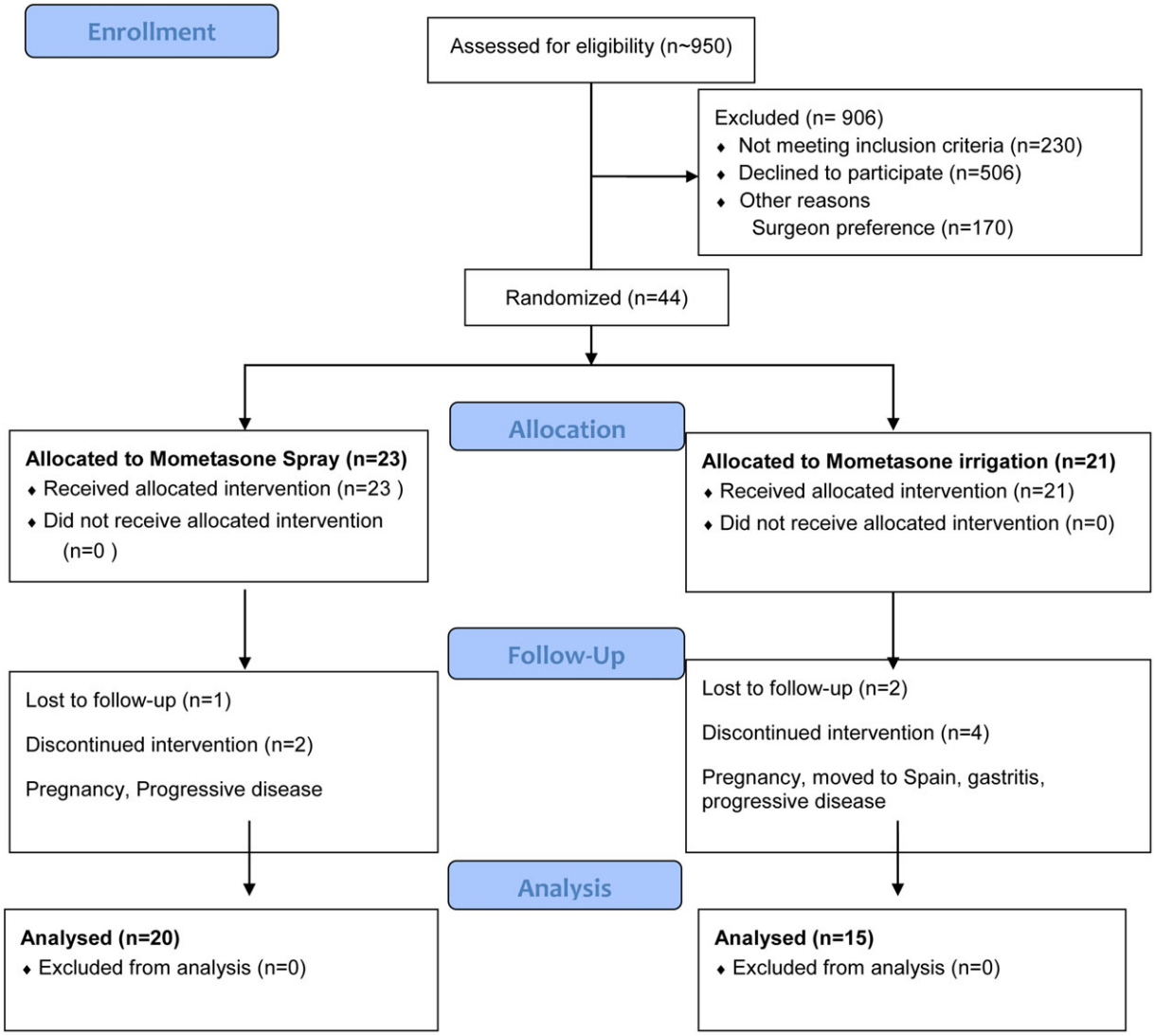

FIGURE 3. The CONSORT patient recruitment and flowchart. All patients who were randomized went on to start the trial. Withdrawals were similar between groups, and importantly to the two patients with difficult to control disease were evenly distributed. CONSORT = Consolidated Standards of Reporting Trials.

TABLE 2. The burden of disease for both symptoms and objective assessments between groups was similar*

	Intervention		
	Active spray	Active irrigation	*p*
n	23	21	
VAS	46.23 ± 21.12	40.23 ± 13.46	0.291
SNOT-22	52.93 ± 26.22	47.79 ± 17.62	0.454
Global	−2.78 ± 3.42	−3.47 ± 1.78	0.431
Radiology (LMS)	13.67 ± 6.15	13.10 ± 4.32	0.729
Withdrawals, n (%)	3 (13.0)	6 (28.6)	0.202

*Values are mean ± SD or as indicated. The active group refers to corticosteroid over placebo.
LMS = Lund-Mackay radiology scores; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test; VAS = visual analogue score (total).

PROMs

Overall, patients who completed the trial improved significantly across all domains. The total VAS improved (41.27 ± 18.35 vs 17.35 ± 17.19; Δ −23.90 ± 15.76; $p < 0.001$), SNOT-22 decreased (49.45 ± 23.25 vs 18.84 ± 15.53; Δ −30.62 ± 18.66; $p < 0.001$), and the global sinonasal function score (assessment of overall sinonasal function) also improved (−3.19 ± 2.50 vs +3.56 ± 2.82; Δ +6.74 ± 3.44; $p < 0.001$).

Even with such a large improvement in both treatment groups, the corticosteroid irrigation group had a greater improvement compared to the corticosteroid spray group for nasal blockage (−69.91 ± 29.37 vs −36.12 ± 42.94; $p = 0.029$) (Table 3). At the 12-month conclusion, all patients in the corticosteroid irrigation group had improved VAS scores; however, several patients in the corticosteroid spray group had relapsed or had progression of disease (Fig.4). One year posttreatment, the blockage, drainage,

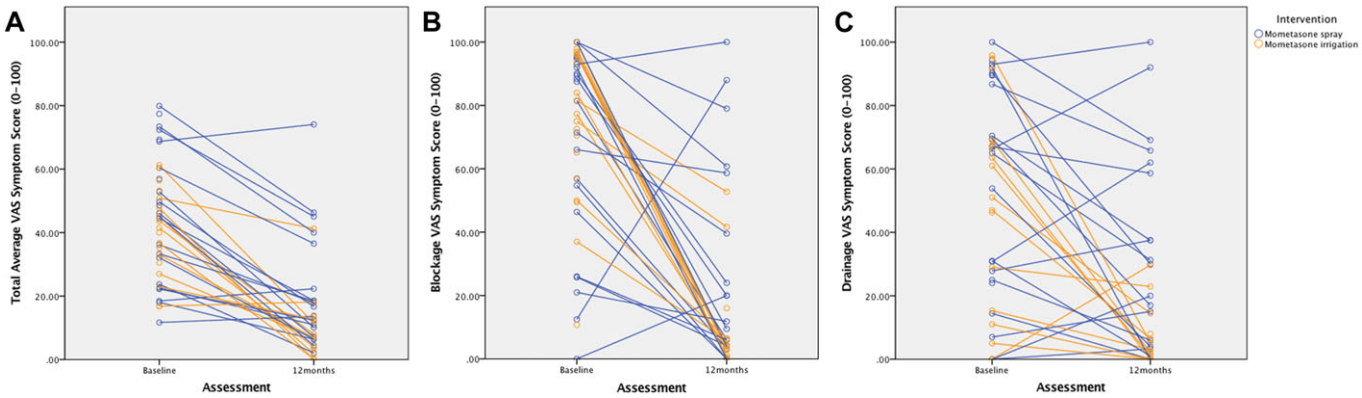

FIGURE 4. The VAS values from total or average (A), nasal blockage (B), and mucus drainage (C) show significant differences at the 12-month assessment. Most striking is the deterioration seen in some patients in the nasal spray (blue) compared to the nasal irrigation (orange) groups. VAS = visual analogue score.

TABLE 3. The comparison of results between baseline and 12 months*

	Intervention		
	Active spray	Active irrigation	*p*
n	23	21	
Δ VAS	−21.14 ± 14.75	−28.67 ± 17.00	0.213
Δ Blockage VAS	−36.12 ± 42.94	−69.91 ± 29.37	0.029[a]
Δ SNOT-22	−31.62 ± 21.95	−29.26 ± 13.65	0.725
Δ Global	+6.07 ± 3.94	+7.31 ± 2.68	0.347
mLKS endoscopy	21.77 ± 23.37	7.33 ± 11.55	0.018[a]
Δ Radiology (LMS)	−7.39 ± 6.94	−12.07 ± 4.43	0.031[a]

*Values are means ± SD or as indicated. The active group refers to corticosteroid over placebo. Although a statistical difference could not be demonstrated in all symptoms, there was a clear separation between treatment arms.
[a]Significant at $p < 0.5$.
Δ = baseline to 12 month change; LMS = Lund-Mackay radiology scores; mLKS = modified Lund-Kennedy endoscopy score; SD = standard deviation; SNOT-22 = Sino-Nasal Outcome Test; VAS = visual analogue score (total).

TABLE 4. One year after surgical intervention and medical therapy there was a clear difference between symptoms*

	Intervention		
VAS at 12 months	Active spray	Active irrigation	*p*
Blockage	28.14 ± 32.79	10.89 ± 16.76	0.06*
Drainage	34.22 ± 31.87	7.31 ± 9.46	<0.01[a]
Headache	20.10 ± 31.29	9.21 ± 14.42	0.20
Fatigue	24.80 ± 28.16	12.93 ± 22.88	0.20
Hyposmia	49.08 ± 38.70	26.43 ± 39.94	0.12
Ear pain	11.81 ± 17.51	10.18 ± 14.21	0.76
Cough	15.61 ± 24.84	6.12 ± 9.17	0.14
Halitosis	7.81 ± 9.38	6.11 ± 12.61	0.69
Facial pain	18.18 ± 26.71	5.90 ± 6.63	0.07
Fever	5.73 ± 8.47	1.13 ± 1.30	0.03[a]
Total VAS	21.55 ± 18.68	9.90 ± 10.93	0.05[a]

*Values are mean ± SD. The active group refers to corticosteroid over placebo. Although an absolute change in drainage VAS could be demonstrated, mucus production at 12 months was 1 of the most significant findings (see Fig. 4).
[a]Significant at $p < 0.5$.
SD = standard deviation; VAS = visual analogue score.

fever, and total VAS scores were all lower in the corticosteroid irrigation group (Table 4).

Radiology and endoscopic endpoints

The overall change in LMS was significant for the entire group (13.82 ± 5.29 vs 4.30 ± 4.75; Δ −9.51 ± 6.30; $p < 0.001$). However, the corticosteroid irrigation group had a much larger improvement (−12.07 ± 4.43 vs −7.39 ± 6.94; $p = 0.031$) (Fig. 5). Similarly, the 12-month endoscopic assessment demonstrated greater disease suppression with a lower mLKS in the corticosteroid irrigation group (7.33 ± 11.55 vs 21.78 ± 23.37; $p = 0.018$) (Fig. 6).

Treatment-related adverse events

There were no medication reactions observed in either group. One patient developed a gastritis during the study period, withdrew from the trial, and proceeded with gastroscopy and biopsy that revealed a cytomegalovirus (CMV)-related condition, which gastroenterology assessment determined to be unrelated to study treatment.

Discussion

In the treatment of CRS, where the condition is bilateral and a diffuse or patchy process, the delivery of a topical corticosteroid via a nasal irrigation was superior to that of nasal corticosteroid spray. When combined with surgery this effect was large in both groups, but it is the ongoing ability to suppress disease that is demonstrated in this trial. The population evaluated in this study were CRS patients with an etiology that is likely to be an inflammatory airway

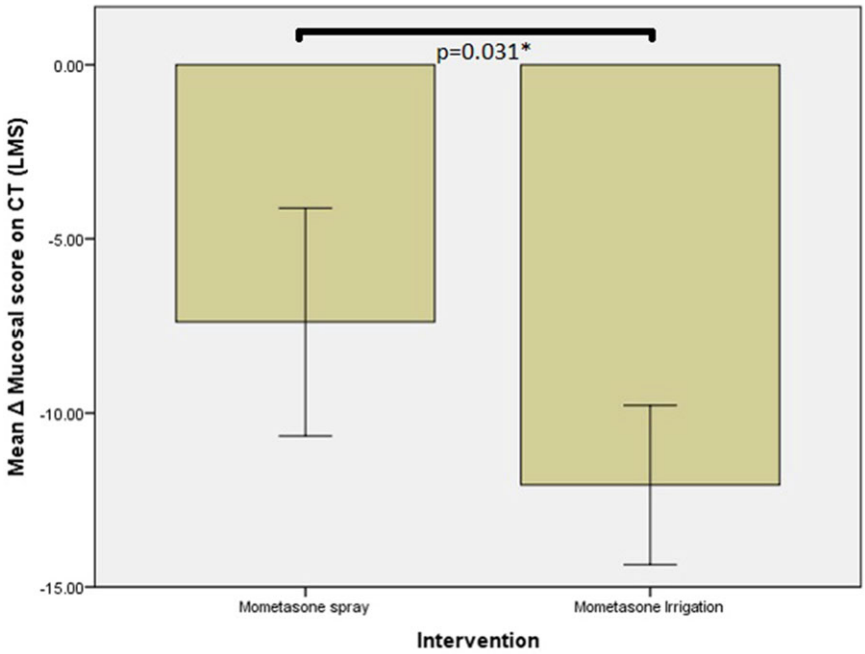

FIGURE 5. Blinded objective assessment of baseline and 12-month radiology performed via cone bean volumetric tomography demonstrated a significant benefit in the corticosteroid nasal irrigation groups with a greater reduction in mucosal disease. Error bars are ±2 SE. Δ = baseline to 12-month change; CT = computed tomography; LMS = Lund-Mackay radiology score; SE = standard error.

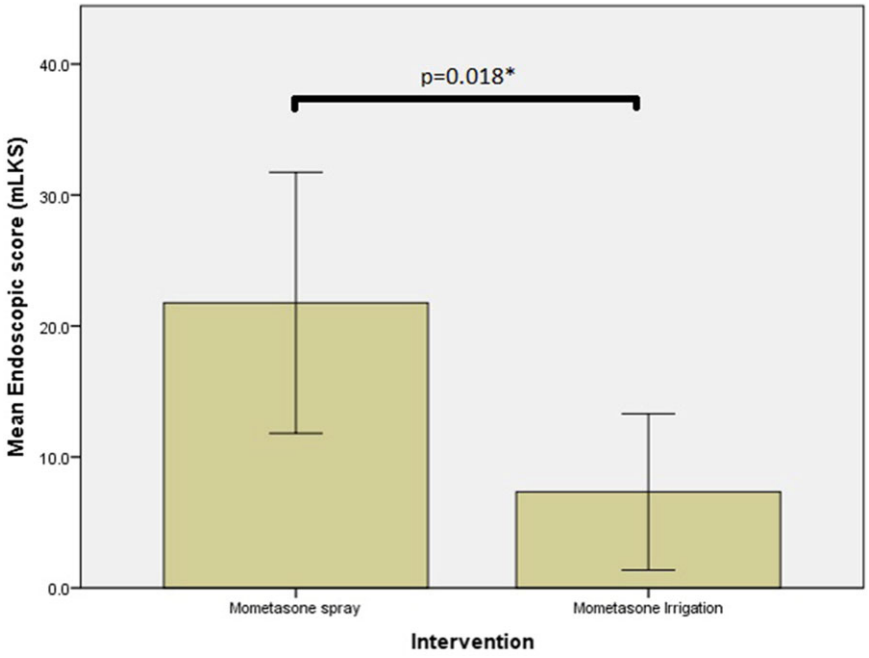

FIGURE 6. Endoscopic evaluation of the surgical cavity/paranasal sinus demonstrated a lower inflammatory burden in the corticosteroid nasal irrigation group at 12 months. Error bars are ±2 SE. mLKS = modified Lund-Kennedy endoscopy score; SE = standard error.

process. Asthma was prevalent in this group (43%) and tissue eosinophilia was present in most (70%). It is not likely that ostial occlusion or ventilation dysfunction plays a significant role in the pathogenesis of this patient group.[3,4] Thus, the most effective intervention in these patients, after the initial removal of polyps and inflammatory tissue, will be ongoing disease suppression. An enormous amount of data demonstrate that the surgical state of the sinuses and method of drug delivery greatly affects the ability of medication to reach the sinus mucosa.[8] However, attempts to demonstrate this benefit have been impaired by studies that performed corticosteroid irrigations in patients with incompletely opened sinuses[12] or used small-volume irrigations in patients with adequate surgery but an

endpoint too close to surgery and/or completion of systemic corticosteroid.[11]

This study intentionally did not attempt to separate the treatment into surgery or the medications used. The treatment strategy presented for patients with diffuse CRS is to establish a sinus cavity that can be accessed by local therapy (neo-sinus) and then deliver topical therapy effectively to avoid reliance of systemic medication. There is a large heterogeneity of surgical techniques applied to patients with CRS. This study benefits from standardizing the surgical approach. All 3 surgeons agreed to create the same neo-sinus cavity for these patients and all have similar surgical training. The decision by the authors to perform a complete sphenoethmoidectomy and frontal sinus procedure was based on evidence that topical distribution is greatly enhanced by this style of surgery.[8,24] Additionally, where limited frontal sinus distribution was likely, a Draf3 frontal sinusotomy was performed.[25] The purpose of surgery was simply to create a paranasal sinus cavity that could be managed by local topical therapies.

The use of a 240-mL nasal irrigation bottle has been shown to be the most effective in delivering medication to the postsurgical sinus cavity.[26] The effective dose of mometasone retained by the patient is likely to be only 100 to 200 μg (5-8% of 2 mg), with the remaining medication (92-95%) representing run off and discarded.[27] This contrasts with the 2-mg mometasone dose delivered by the nasal spray group. A large amount of this is likely to be retained in the upper airway (30%) with the remaining amount being swallowed.[28] There is a very low bioavailability for mometasone (<1%) and thus systemic effects are likely to be minimal, but the local dose is much greater (30% vs 5–8%). However, the poorer performance of the corticosteroid nasal spray group, despite the higher dose retained, is due to the medication simply not reaching the paranasal sinus cavity effectively.[24,29] As the trial recruitment proceeded, primary care physicians began to utilize corticosteroid nasal irrigations in CRS patients who had surgery many years ago and with great anecdotal success. Many patients needed to be screened in order to convince a few to join the trial. This became more difficult with the widespread use of corticosteroid irrigations, as patients were often advised against the trial by their primary care physician in favor of using a corticosteroid irrigation.

Simply performing a comprehensive surgery for a CRS patient or giving a corticosteroid irrigation to an unoperated CRS patient or a patient with a sinus cavity full of polypoid changes, after previous limited surgery many years ago, represents a flawed interpretation of the treatment strategy presented in this trial. It is the combination of an anatomically remodeled sinus cavity (neo-sinus) and the effective delivery of corticosteroid (nasal high-volume irrigation) that brings about the optimal context for disease control. The patient selection here is critical. The patients recruited had bilateral nasal symptoms and bilateral sinus changes. This is almost certainly an inflammatory process. Unilateral or anatomically discrete sinus disease, where ostial occlusion might be a primary factor, was excluded. The numbers were too small to do a meaningful subgroup analysis on eCRS patients or on other endotypic features, but this remains an area for future research.

There is considerable benefit seen by surgical intervention followed by topical therapies in the management of CRS. Corticosteroid irrigations were superior in blind placebo controlled assessments in VAS, radiology, and endoscopy at 12 months. However, not all outcomes demonstrated improvement. SNOT-22 improvement was similar between groups (-31.62 ± 21.95 vs -29.26 ± 13.65; $p = 0.725$) and at 12 months (19.87 ± 17.63 vs 17.43 ± 12.62; $p = 0.66$). However, these scores demonstrated a wide dispersion of data and include many domains, such as psychosocial and ear/facial, which may not be sensitive enough to demonstrate the difference between groups among a strong effect of the overall intervention.

Considering that many adult patients manage their CRS over several years, this study is limited by small numbers and a follow-up of only 12 months. Resources precluded a longer maintenance period as the study was investigator-initiated and funded. There was little appetite among pharmaceutical companies to support the trial as the outcome does not lead to a commercially protected (patented) intervention. Additionally, in Australia, no intranasal corticosteroid spray is indicated for CRS, but they are registered for rhinitis treatment and used extensively off-label for CRS. However, despite those limitations, there is significant separation between the 2 treatment groups in this RCT that supports the anecdotal and uncontrolled experience with corticosteroid nasal irrigations in the postsurgical management of CRS.

Conclusion

In the setting of diffuse or patchy CRS disease, the use of corticosteroid delivered by nasal irrigation is superior to simple nasal spray in postsurgical patients.

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