Randomized clinical trial to evaluate mometasone lavage vs spray for patients with chronic rhinosinusitis without nasal polyps who have not undergone sinus surgery

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Background: **There is no consensus regarding the best route of intranasal delivery of corticosteroids in the treatment of chronic rhinosinusitis (CRS). The study objective of this work was to compare the impact of mometasone furoate nasal spray (MFNS) vs mometasone nasal irrigation in the management of CRS patients who have not undergone sinus surgery.**

Methods: **A double-blind, placebo-controlled, randomized clinical trial was conducted in adults with CRS. Individuals with nasal polyps and/or history of sinus surgery were excluded. Patients were randomized to receive 8 weeks of either MFNS or mometasone nasal irrigation. The primary outcome measure was change in the 22-item Sino-Nasal Outcome Test (SNOT-22) score between the 2 groups. Secondary outcome measures included patient global response to treatment and Lund-Kennedy endoscopy scores.**

Results: **A total of 43 participants completed the study (n = 22, MFNS; n = 21,mometasone nasal irrigation). Fourteen (64%) participants in the MFNS group and 17 (81%) in the mometasone lavage group had a clinically meaningful improvement in SNOT-22 scores with a proportion difference of 17% (95% confidence interval [CI], −9% to 44%). The least-squares (LS) mean difference between the 2 groups for SNOT-22 was −8.6 (95% CI, −17.7 to 0.58; $p = 0.07$), whereas the LS mean difference between the 2 groups for Lund-Kennedy endoscopy scores was 0.16 (95% CI, −0.84 to 1.15; $p = 0.75$). No adverse events were associated with the study.**

Conclusion: **Both MFNS and mometasone nasal irrigations are beneficial in symptom management of CRS. Our study suggests that patients who perform mometasone lavage do better in a clinically meaningful way, but our results are not definitive and further studies are warranted.** © 2020 ARS-AAOA, LLC.

Key Words:
chronic rhinosinusitis; topical intranasal corticosteroid; nasal lavage

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Persistent sinonasal mucosal inflammation is a hallmark of chronic rhinosinusitis without nasal polyps (CRSsNP). Intranasal corticosteroids (INCS) are the mainstay of treatment in the long-term management of CRSsNP. Corticosteroids exert an anti-inflammatory effect by up-regulating transcription of anti-inflammatory genes; reducing airway inflammatory cell infiltration by eosinophils, mast cells, and T lymphocytes; and suppressing production of adhesion molecules and pro-inflammatory genes and

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mediators, such as nuclear factor-kappaB (NF-κB).[1,2] However, studies have shown that there is limited penetration of nasal sprays beyond the nasal vestibule and into the paranasal sinuses.[3]

Thus, there has been significant interest in the application of large-volume, low-pressure nasal saline irrigation to enhance intrasinus corticosteroid deposition.

Randomized clinical trials (RCTs) have reported on both the efficacy and safety of INCS delivered by nasal irrigations.[4-7] However, the effect sizes in these studies have been varied,[7,8] reflective of the heterogeneous patient population. Although CRSsNP is more prevalent than chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP), many of the studies have examined the effect of distribution of topical medications in surgically opened sinonasal cavities for CRSwNP, limiting the generalizability of the study findings to CRSwNP patients who have undergone surgery.[3] Furthermore, treatment outcomes in those studies have primarily focused on objective outcome measures, such as endoscopic scores, computed tomography (CT) findings, or complication/recurrence rates. To date, only 3% of CRS studies have focused on patient-reported outcome measures (PROMs).[9] However, with the increased focus on patient-centered care, there is greater importance being placed on PROMs. The 22-item Sino-Nasal Outcome Test (SNOT-22), which captures sinonasal symptoms and health-related quality-of-life domains, is a validated and highly specific CRS PROM.[10] The primary objective of this study was to compare the effect of nasal saline irrigation plus mometasone nasal steroid spray vs mometasone nasal irrigation plus nasal saline spray on symptom management in CRSsNP, as measured by both PROMs and objective outcome measures.

Patients and methods

Study design

A single-institution, double-blinded, placebo-controlled, RCT of patients with CRS was conducted between November 2018 and February 2020. The trial was registered at http://www.clinicaltrials.gov (NCT03705793) and the study was approved by the Washington University's Human Protection Research Office.

Study population

Participants consisted of both men and women, ≥18 years of age, with at least 12 weeks of having 2 or more of the following signs and symptoms consistent with CRS[11,12]: mucopurulent drainage (anterior, posterior, or both), nasal obstruction (congestion), facial pain-pressure-fullness, and decreased sense of smell *and* inflammation, as documented by 1 or more of the following findings: purulent mucus or edema in the middle meatus or ethmoid region and/or radiographic imaging showing inflammation of the paranasal sinuses. Patients were excluded if they had nasal polyps, previous sinus surgery, comorbid mucociliary conditions, sinus disease associated with autoimmune or vasculitic diseases, chronic diseases requiring long-term corticosteroid use, history of oral or systemic antibiotic use in the 2 weeks before enrollment, or history of allergy to topical nasal steroids. Participants were also excluded if they were pregnant or breastfeeding. In addition, participants with a baseline SNOT-22 score of ≤9 were excluded due to inability to achieve a pre- and postintervention minimally clinically improved difference (MCID).

In addition to collection of baseline demographic information, overall severity of comorbidity was assessed using the Adult Comorbidity Evaluation-27 (ACE-27) instrument.[13]

Intervention

Participants were randomly assigned to receive 8 weeks of either: (1) nasal saline irrigation and mometasone furoate nasal spray (MFNS; 50 μg in each spray, 2 sprays/nostril); or (2) mometasone nasal irrigation (1.2 mg per capsule, 2 capsules/irrigation) and saline nasal spray. Based on the literature regarding retention of nasal sprays and irrigations in the nasal cavity and consultation with pharmacy colleagues, a daily dose of 2.4 mg mometasone delivered by nasal irrigation was considered to be equivalent to the daily dose of mometasone nasal spray.[14-16] All participants were provided with an 8-oz. sinus rinse bottle (NeilMed® Sinus Rinse™) and a 2-month supply of USP grade sodium chloride and sodium bicarbonate mixture (pH balanced, isotonic and preservative- and iodine-free) in commercially prepared packets. Participants were first instructed to perform nasal irrigation, followed by administration of nasal spray. Mometasone and placebo were provided in identical treatment kits prepared by Jason Jerusik, PharmD (AdvancedRx, Plymouth Meeting, PA), and all study patients and study team members were blinded to study treatment.

Patients who were on concomitant nasal steroid sprays or nasal irrigations before enrollment were asked to discontinue use 2 weeks before starting the study and for the study duration.

Compliance was self-reported and defined as performing the intervention for at least 5 days a week. In addition, study team members were in contact with study participants on a biweekly basis.

Patient-reported outcome measures

The primary outcome measure was the within-subject pre-to posttreatment change in SNOT-22 scores in the MFNS group compared with mometasone nasal irrigation. Participants completed the SNOT-22 at baseline, and then at 2, 4, 6, and 8 weeks after initiation of treatment. A MCID was defined as a change in SNOT-22 score of ≥9 points.[17]

Secondary outcome measures included patient global response to treatment, as measured by the modified Clinical Global Impressions (CGI) scale.[18] For the modified CGI scale, participants were asked to rate their overall response to treatment using a 7-point Likert scale with anchors of

1 = very much improved, 4 = no change, and 7 = very much worse.

Objective outcome measures

Participants had nasal endoscopic examinations performed pre- and postintervention (by J.S.S., C.N.K.C., A.J.D., J.F.P.), and findings recorded using the Lund-Kennedy grading system,[19] which evaluates the pathologic state of each sinonasal cavity using a 0 to 2 scale (0 = absent, 2 = severe) with a maximum score of 20. If participants received sinus CT scans as part of their clinical work-up, radiologic images were reviewed, and findings were recorded using the Lund-Mackay grading system,[19] which evaluates sinus patency using a 0 to 2 scale (0 = normal, 2 = total opacification), with a maximum score of 24.

Cosyntropin test

Although MFNS has been shown to have no discernible effect on the function of the hypothalamus-pituitary-adrenal (HPA) axis in clinical studies in both children and adults,[20] the safety of nasally administered MF saline irrigation has not been demonstrated. Therefore, a random subgroup of 20 enrolled participants (10 from each intervention arm) was offered participation in the cosyntropin stimulation study.

Baseline levels of serum cortisol were measured at the participant's first study visit. Participants received an intramuscular injection of 0.25 mg of cosyntropin to stimulate the adrenal cortex. Serum was then drawn 30 minutes later and cortisol level measured. This test was then repeated upon completion of the study. A poststimulation cortisol level of <18 μg/dL was indicative of adrenal insufficiency. Results are presented as the difference and 95% confidence interval (CI) around the difference in mean cortisol level before and after treatment. Cohen's d was used to define the effect size, with $d = 0.2$ considered a "small" effect, 0.5 a "medium" effect, and 0.8 a "large" effect.[21]

Statistical analysis

The sample size of this study was estimated based on a study of budesonide nasal irrigation in CRS patients by Tait et al.[7] To detect with 80% power at a 2-sided $\alpha = 0.05$ an MCID of ≥9 points on the SNOT-22, the estimated sample size needed was 44 participants (22 participants per arm). With an anticipated 15% dropout/noncompliance rate, the total sample size for this study was set at 51 participants.

Standard descriptive statistics were used to describe the demographics, clinical characteristics, and assessment of the study population. An intention-to-treat approach was used for all data analyses, which included all patients who were enrolled and randomized. The primary outcome measure was analyzed using a mixed-effects model, with repeated-measures approach. The 95% CI around the difference was calculated and used to assess for clinically meaningful differences between the 2 treatment groups. An interim analysis was performed after participant 22 had completed 8 weeks of treatment to assess compliance and treatment response. Statistical analyses were conducted using SPSS version 14 (SPSS, Inc, Cary, NC [SPSS IBM, Armonk, NY, for later versions]).

Results

Between November 2018 and February 2020, a total of 53 patients were enrolled and randomized to either nasal saline irrigation plus MFNS (n = 27) or mometasone nasal irrigation plus nasal saline spray (n = 26). The median age was 48 (range, 19-67) years and the majority of participants were women (n = 33; 62%) and of white race (n = 38; 72%). Twenty-six (49%) of the participants had no significant comorbidities.

Of the 53 patients randomized, 27 received nasal saline irrigation plus MNFS and 26 received mometasone nasal irrigation plus nasal saline spray. A total of 43 participants completed the pre- and postintervention assessments (Fig. 1). Of these participants, there were no meaningful differences in baseline demographic and clinical characteristics between the 2 groups, except all 4 participants with severe comorbidity were assigned to the mometasone nasal irrigation group and the median baseline SNOT-22 score was 40 for the group with nasal saline irrigation and MFNS and 50 for the group with mometasone nasal irrigation and nasal saline spray (Table 1).

Primary outcome measure

The least-squares (LSs) mean change in SNOT-22 scores between baseline and week 8 was 17.7 (95% CI, 10.3-25.04; $p < 0.001$) in the nasal saline irrigation plus MFNS group and 23.18 (95% CI, 15.7-30.7; $p < 0.001$) in the mometasone nasal irrigation plus nasal saline spray group. The LS mean difference between the 2 intervention groups was −8.6 (95% CI, −17.7 to 0.58; $p = 0.07$) in favor of the mometasone nasal irrigation group. The change in SNOT-22 scores within each group throughout the study is shown Figure 2. As can be seen, both groups had improved symptoms, as reflected in the reduction in SNOT-22 scores. Patients who received mometasone nasal irrigation, however, had a greater improvement in their SNOT-22 scores compared with those who received mometasone nasal spray, as shown in the box-and-whisker plot in Figure 3. A total of 14 (64%) participants in the nasal saline irrigation plus MFNS group had an MCID in SNOT-22 scores, whereas 17 (81%) participants in the mometasone nasal irrigation plus nasal saline spray group had an MCID, a proportion difference of 17% (95% CI, −9% to 44%).

Mixed model analysis showed that there was no confounding effect of age, race, gender, or comorbidity for change in SNOT-22 scores.

Secondary outcome measures

Based on the CGI, 20 participants (95%) in the nasal saline irrigation plus MFNS group and 22 participants

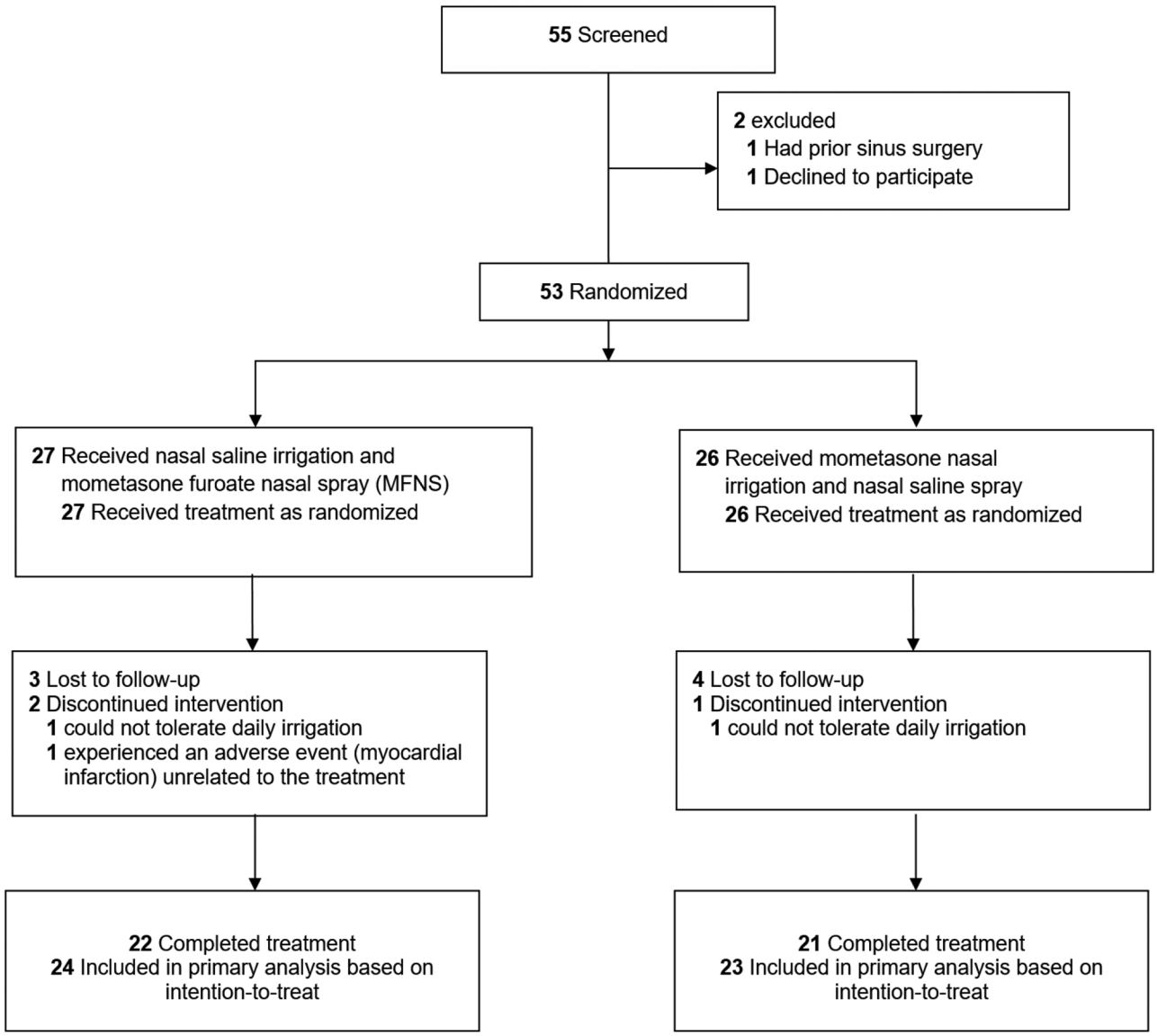

FIGURE 1. Flowchart of patients enrolled and included in analysis.

(96%) in the mometasone nasal irrigation plus saline nasal spray group self-reported some degree of improvement from "slightly better" to "very much better" after study completion.

The LS mean change in Lund-Kennedy endoscopy scores between baseline and week 8 was 2.1 (95% CI, 1.0-3.1; $p = 0.003$) in the nasal saline irrigation plus MFNS group and 2.2 (95% CI, 1.1-3.3; $p = 0.003$) in the mometasone nasal irrigation plus nasal saline spray group. The LS mean difference between the 2 intervention groups was 0.16 (95% CI, −0.84 to 1.15; $p = 0.75$).

Cosyntropin testing and safety

In our subgroup of patients who underwent cosyntropin stimulation, there was no detectable effect of mometasone furoate nasal irrigation on the HPA axis after 8 weeks of intervention. Likewise, consistent with earlier studies, there was no detectable effect of mometasone nasal spray on the HPA axis (Table 2).

One patient in the nasal saline irrigation plus MFNS group had a serious adverse event (myocardial infarction) during study enrollment. However, this serious adverse event was not considered to be related to the drug. A total of 2 patients (1 in each group) could not tolerate daily nasal irrigations, which led to their withdrawal from the study.

Twenty patients (91%) in the nasal saline irrigation plus MFNS group and 19 patients (90%) in the mometasone nasal irrigation plus nasal saline spray group reported compliance at the end of the study.

Participant blinding

Patients were asked to perform a best guess at the end of the study regarding which arm they were randomized to

TABLE 1. Comparison of baseline characteristics between the 2 treatment groups

Baseline characteristic	Total (n = 53)	Nasal saline irrigation + mometasone nasal spray (n = 27)	Mometasone nasal irrigation + nasal saline spray (n = 26)	Difference (95% CI)
Age (years), median (min-max)	48 (19-67)	50 (19-66)	48 (19-67)	−1 (−10 to 7)
Sex, n (%)				
Male	20 (37.7)	9 (33.3)	11 (42.3)	
Female	33 (62.3)	18 (66.7)	15 (57.7)	9 (−17 to 35)
Race, n (%)				
White	38 (71.7)	21 (77.8)	17 (65.4)	12.4 (−11.7 to 36.5)
African American	11 (20.8)	4 (14.8)	7 (26.9)	−12.1 (−33.8 to 9.6)
Other	4 (7.5)	2 (7.4)	2 (7.7)	−0.3 (−14.5 to 13.9)
Overall comorbidity, n (%)				
None	26 (49.1)	12 (44.4)	14 (53.8)	−9.4 (−36.2 to 17.4)
Mild	18 (34)	12 (44.4)	6 (23.1)	21.4 (−3.4 to 46.1)
Moderate	5 (9.4)	3 (11.1)	2 (7.7)	3.4 (−12.2 to 19.0)
Severe	4 (7.5)	0 (0)	4 (15.4)	−15.4 (−29.2 to −1.5)
Baseline endoscopic score, median (min-max)	4 (0-8)	4 (0-8)	4 (1-8)	0 (−1 to 1)
Baseline SNOT-22 total, median (min-max)	42 (11-99)	40 (11-71)	50 (12-99)	−11 (−21 to 0)

CI = confidence interval; SNOT-22 = 22-item Sino-Nasal Outcome Test.

in order to assess the effectiveness of participant blinding. Participants guessed no better than chance alone, suggesting they were effectively blinded throughout the course of the trial.

Discussion

In this double-blind, placebo-controlled RCT, we found that delivery of mometasone, either via nasal spray (and performing nasal saline lavage) or nasal irrigation, resulted in clinically meaningful improvement in both clinical and endoscopic endpoints for CRSsNP patients who have not undergone sinus surgery. Furthermore, the addition of mometasone to the nasal irrigation was associated with a greater improvement in SNOT-22 score when compared with mometasone nasal spray. These results suggest that sinus surgery may not be required for the CRSsNP patient to receive benefit from topical nasal steroid administration and sinus lavage.

Topical corticosteroids are a mainstay treatment for CRS patients. Several prospective trials have evaluated the effect of INCS delivered by nasal irrigation. However, the effect sizes in those studies has been variable due to heterogeneous study cohorts and study designs and are not generalizable to patients who are managed medically only, as most of these studies evaluated medication effectiveness after sinus surgery.[8]

Although the use of budesonide nasal irrigation has become widespread in the management of CRS, especially after endoscopic sinus surgery, mometasone is a promising alternative. Mometasone furoate (MF) has several structural modifications that confer more favorable pharmacologic properties when compared with budesonide. All corticosteroid molecules are derived from cortisol, the parent molecule, and share the same carbon framework backbone of three 6-carbon rings and one 5-carbon ring. For MF, the addition of a 21-chloro 17 (2′ furoate) group increases the compound's topical anti-inflammatory activity.[22] Furthermore, the addition of the halogen, chloride, at positions 9 and 21, increases the compound's affinity for the corticosteroid receptor and decreases its susceptibility to esterase degradation, respectively.[22] These structural changes not only increase the lipophilicity of mometasone, but also promote its rapid and extensive hepatic metabolism. Thus, compared with budesonide, mometasone has negligible systemic absorption (<0.1% vs 34%, respectively).[16]

Although several randomized, controlled, parallel-group or placebo trials have shown no significant effect of MFNS on HPA axis function,[20] to date no study has examined the effect of mometasone nasal irrigation on HPA axis function. Our study is the first to show that mometasone nasal irrigation can be safely used in the short term for patients with CRS without observed suppression of the HPA axis. Given mometasone's very low systemic absorption and

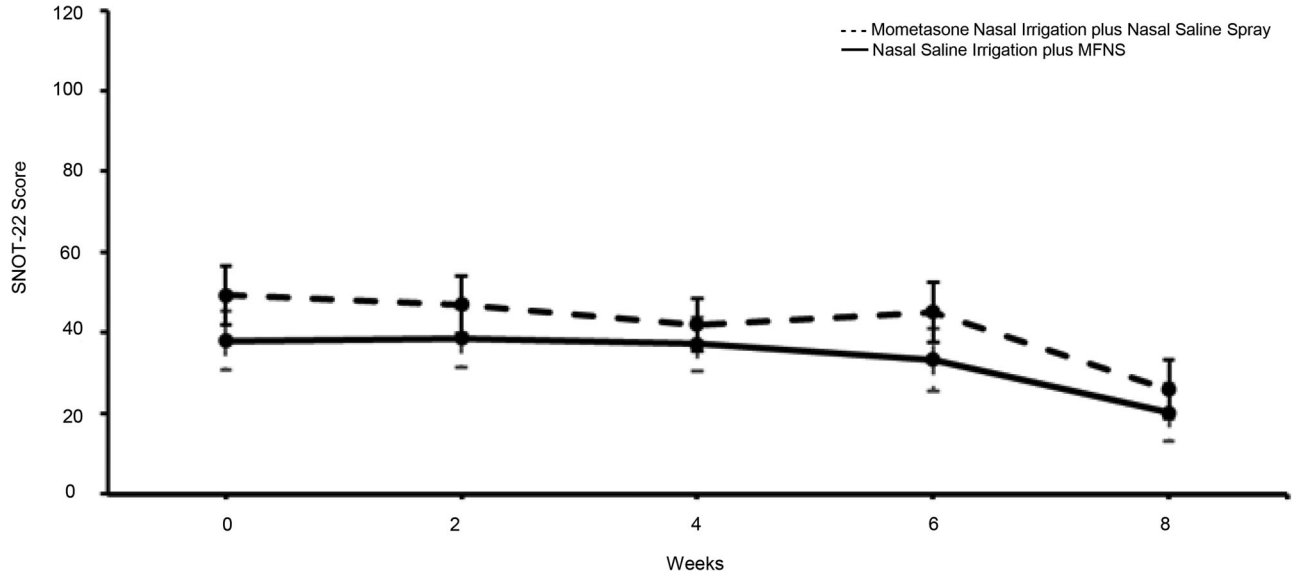

FIGURE 2. SNOT-22 scores by treatment group over time. The dashed line represents the mometasone nasal irrigation group plus nasal saline spray, and the solid line represents the saline nasal irrigation plus MFNS group. The error bars represent the minimum and maximum SNOT-22 values. MFNS = mometasone furoate nasal spray; SNOT-22 = Sino-Nasal Outcome Test.

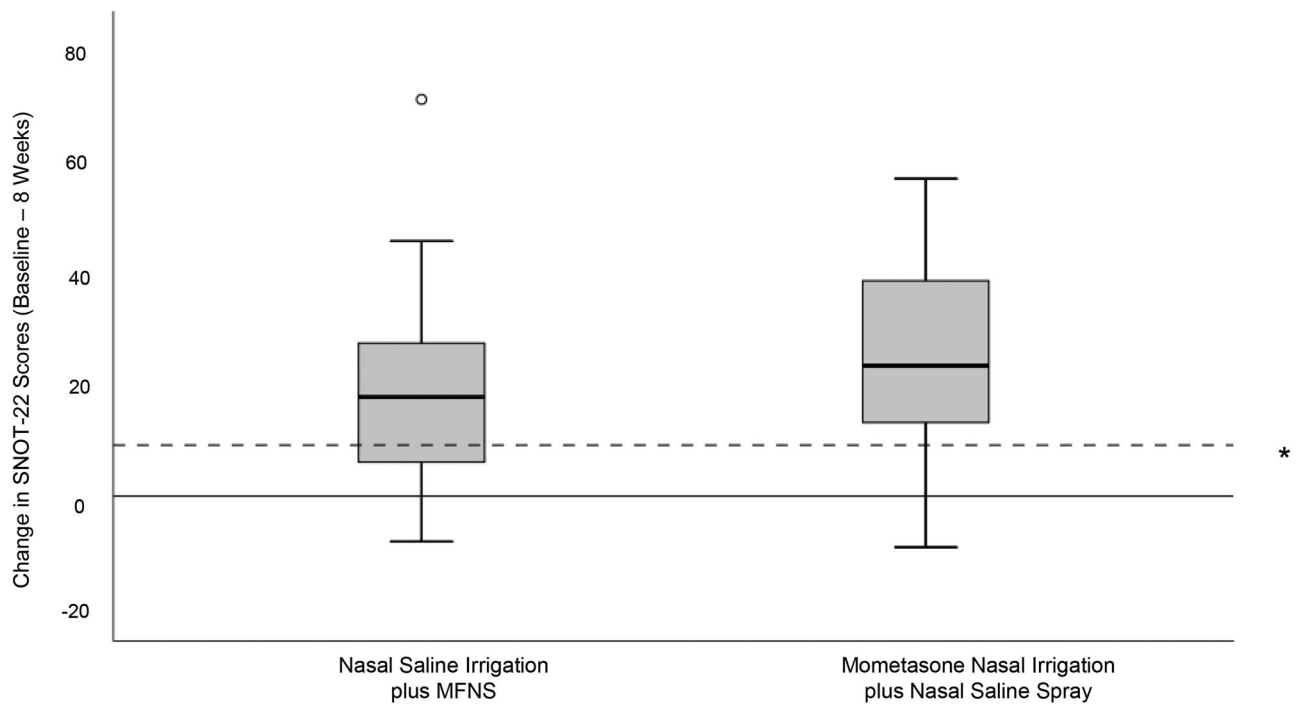

FIGURE 3. Comparison of change in SNOT-22 scores between the 2 treatment groups. The box-and-whisker plots represent change in SNOT-22 within each treatment group. The solid dashed line within the box represents the median value, the upper and lower part of the box represents the 75th and 25th percentile, the "whiskers" represent the upper and lower extreme of values, and the open circle represents outliers. The dashed horizontal line represents the clinically meaningful important difference of SNOT-22 score by 9 points. SNOT-22 = Sino-Nasal Outcome Test.

TABLE 2. Post-cosyntropin stimulation cortisol levels

Treatment arm	Cortisol level before treatment[a] (μg/dL)	Cortisol level after treatment[a] (μg/dL)	Difference (μg/dL) (95% CI), Cohen's *d*
Nasal saline irrigation plus mometasone nasal spray (n = 10)	23.19 (3.51)	23.91 (2.56)	−0.72 (−3.41 to 1.97), 0.23
Mometasone nasal irrigation plus nasal saline spray (n = 10)	24.18 (4.76)	24.22 (3.84)	−0.04 (−3.83 to 3.75), 0.01

Cohen's *d* interpretation: *d* = 0.2 considered a "small" effect, *d* = 0.5 a "medium" effect, and *d* = 0.8 a "large" effect.
[a]Data expressed as mean (standard deviation).
CI = confidence interval.

excellent safety profile, we believe that providers may prefer to offer patients either mometasone or budesonide nasal irrigation for medical management of CRS. However, future studies that directly compare budesonide to mometasone are warranted.

To our knowledge, only one other study has performed a direct comparison of INCS vs corticosteroid nasal irrigation for the treatment of CRS. Harvey et al evaluated the efficacy of mometasone nasal spray compared with mometasone nasal irrigation in CRS patients with or without nasal polyps after endoscopic sinus surgery.[15] After 1 year of treatment, participants who received corticosteroid irrigations had significantly greater improvements in subjective nasal symptoms as well as endoscopic and radiologic findings compared with those who received corticosteroid nasal spray.

Overall, among CRSsNP participants who have not undergone sinus surgery, significant improvement in PROMs were observed after treatment with either nasal saline lavage and mometasone nasal spray or mometasone nasal irrigation. For CRS patients who cannot tolerate or afford nasal steroids, nasal saline lavage alone may be an effective therapy in symptom management. These results suggest that a surgically opened sinonasal corridor may not necessarily be needed for patients to have the beneficial effects of topical nasal steroid administration. Compliance in both study arms was high as was participant satisfaction, suggesting that providers can equivalently offer both treatment options to patients.

For patients who are refractory to maximal medical management, surgical intervention is often warranted. In a study by Rudmik et al, CRS patients with a baseline SNOT-22 score >30 had a >80% chance of having an MCID in their SNOT-22 scores after endoscopic sinus surgery.[23] At baseline, the average SNOT-22 score for our patient cohort was 42 and the majority of patients (72%) achieved an MCID with medical therapy alone. In this study, we intentionally did not assess patients who had undergone endoscopic sinus surgery. However, we believe future studies examining incremental improvement in SNOT-22 scores after endoscopic sinus surgery for failed medical therapy with nasal irrigations would be invaluable in managing provider and patient expectations about quality-of-life improvement after surgery in cases where medical management alone cannot meet the desired level of improvement.

A limitation of this study was the treatment duration. As CRS is a chronic disease, patients may need to be on topical steroids for a longer duration than that allotted in our study's 8-week time-frame. However, due to financial costs and resources, it was not feasible for our treatment period to be extended beyond the 8 weeks. Furthermore, compliance was self-reported. In addition, only a minority of our participants received sinus CT imaging pre- and postintervention, and only at the clinical discretion of their primary otolaryngologist. Thus, we were limited in our ability to objectively quantify changes in mucosal disease in the sinonasal cavities beyond what was seen on endoscopy exam. However, according to the American Academy of Otolaryngology–Head and Neck Surgery Practice Guidelines for Adult Sinusitis, the use of CT imaging should be reserved for patients with refractory or prolonged symptoms.[24]

Despite these limitations, we believe our study has provided clinically meaningful information regarding the comparative effectiveness of nasal saline lavage plus mometasone nasal spray to mometasone nasal irrigation in symptom control for CRSsNP patients who have not undergone sinus surgery.

Conclusion

For patients with CRSsNP who have not undergone surgery, treatment with either nasal saline lavage and topical mometasone nasal spray or mometasone nasal steroid irrigation is beneficial in symptom management. Mometasone nasal steroid irrigation was associated with a greater clinically meaningful improvement in PROMs as compared with nasal saline lavage plus mometasone nasal spray. However, these findings are not definitive and further studies are needed with larger sample sizes, longer treatment duration, and direct comparison to surgery to add to the body of knowledge regarding the efficacy of mometasone nasal steroid irrigation.

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