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Effect of Budesonide Added to Large-Volume, Low-pressure Saline Sinus Irrigation for Chronic Rhinosinusitis
A Randomized Clinical Trial

Sarah Tait, BA; Dorina Kallogjeri, MD, MPH; Jasmina Suko, ScB, MSc; Sara Kukuljan, RN;
John Schneider, MA, MD; Jay F. Piccirillo, MD

IMPORTANCE Recent studies suggest that budesonide added to saline nasal lavage can be an effective treatment for patients with chronic rhinosinusitis (CRS).

OBJECTIVE To evaluate the incremental effect of adding budesonide to large-volume, low-pressure saline sinus irrigation.

DESIGN, SETTING, AND PARTICIPANTS This double-blind, placebo-controlled, randomized clinical trial was conducted at a quaternary care academic medical center between January 1, 2016, and February 16, 2017. A total of 80 adult patients with CRS were enrolled; 74 completed baseline assessments; and 61 remained in the trial to complete all analyses. Data analysis was conducted from March 2017 to August 2017.

INTERVENTIONS All study participants were provided with a sinus rinse kit including saline and identical-appearing capsules that contained either budesonide (treatment group) or lactose (control group). Patients were instructed to dissolve the capsules in the saline and use the resulting solution to irrigate both nasal cavities, using half the solution for each cavity, once daily for 30 days.

MAIN OUTCOMES AND MEASURES The primary outcome measure was the change in Sino-Nasal Outcome Test (SNOT-22) scores, pretreatment to posttreatment, in the budesonide group compared with the control group. Secondary outcome measures included patient-reported response to treatment, as measured with a modification of the Clinical Global Impressions scale, and endoscopic examination scored by the Lund-Kennedy grading system.

RESULTS Of the 74 participants who completed baseline assessments (37 in each study arm), mean (SD) age, 51 (14.7) years, 50 (68%) were women. Of the 61 who remained in the trial to complete all analyses, 29 were randomized to budesonide treatment, and 32 to saline alone. The average change in SNOT-22 scores was 20.7 points for those in the budesonide group and 13.6 points for those in the control group, for a mean difference of 7 points in favor of the budesonide group (95% CI, −2 to 16). A total of 23 participants (79%) in the budesonide group experienced a clinically meaningful reduction in their SNOT-22 scores compared with 19 (59%) in the control group, for a difference of 20% (95% CI, −2.5% to 42.5%). The average change in endoscopic scores was 3.4 points for the budesonide group and 2.7 points for the control group. There were no related adverse events.

CONCLUSIONS AND RELEVANCE This study shows that budesonide in saline nasal lavage results in clinically meaningful benefits beyond the benefits of saline alone for patients with CRS. Given the imprecision in the treatment effect, further research is warranted to define the true effect of budesonide in saline nasal lavage.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02696850

+ Supplemental content

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Author Affiliations: Clinical Outcomes Research Office, Department of Otolaryngology–Head and Neck Surgery, Washington University School of Medicine in St Louis, St Louis, Missouri.

Corresponding Author: Jay F. Piccirillo, MD, Department of Otolaryngology–Head and Neck Surgery, Washington University School of Medicine in St Louis, 660 S Euclid Ave, Campus Box 8115, St Louis, MO 63110 (piccirij@wustl.edu).

Chronic rhinosinusitis (CRS) is a condition character-ized by inflammation of the paranasal sinuses and lining of the nasal cavity for 12 weeks or more.[1] It is pri-marily an inflammatory disease, with occasional exacerba-tions associated with infection. Though relatively common, the disease burden associated with CRS is substantial. Patients with CRS visit primary care clinicians twice as often as those with-out CRS and have 5 times as many prescriptions filled.[2] A sur-vey performed in 2007 found that approximately $8.3 billion is spent annually on CRS, primarily on prescription drugs and office-based care.[3]

The recommended medical management of CRS includes large-volume, low-pressure saline nasal lavage, systemic antibiotics, and topical nasal steroid sprays.[4,5] While systemic antibiotics are useful to treat episodic exac-erbations of CRS, there is little evidence to recommend them as long-term treatment. Nevertheless, antibiotics are often prescribed for CRS, and national surveys suggest a large degree of overutilization, which is associated with the development of serious adverse effects and resistant organisms.[6-8] In contrast, topical nasal steroid sprays have been shown to be safe and effective in the long-term man-agement of CRS.[9-11] There is evidence, however, that the penetration of steroid beyond the nasal cavity and into the paranasal sinuses is limited, indicating that a novel delivery method is needed to improve intrasinus corticosteroid deposition.[12-14]

A recent systematic review by Thomas et al[15] analyzed vari-ous ways to distribute topical therapeutics to the sinuses in patients with CRS. The authors found that large-volume, low-pressure irrigation devices resulted in better distribution to the nasal cavity and sinuses, especially after surgery, than low-volume devices. Large-volume, low-pressure saline sinus ir-rigation is a widely recommended treatment for CRS, which is low cost and has a high patient acceptance and benefit-to-risk margin.[16-20]

Three recent prospective cohort studies examined the use of large-volume, low-pressure, saline sinus irrigation to de-liver budesonide, an anti-inflammatory glucocorticoid ste-roid used for the treatment of allergic rhinitis, nasal polyps, and chronic obstructive pulmonary disease.[21-23] All 3 studies demonstrated statistically and clinically significant subjec-tive improvement in sinus disease after treatment. In addi-tion, 2 of the studies documented significant improvement in objective measures of sinus disease.[21,23]

The objective of the present study was to evaluate the effect of the addition of budesonide to large-volume, low-pressure saline sinus irrigation for patients with CRS in a double-blind, placebo-controlled, randomized clinical trial using both subjective and objective outcome measures.

Methods

Study Design and Participants
This study was a single-site, double-blinded, placebo-controlled, randomized clinical trial of patients with CRS. The trial proto-

Key Points

Question What is the effect of adding budesonide to large-volume, low-pressure saline sinus irrigation for patients with chronic rhinosinusitis (CRS)?

Findings In this randomized clinical trial of 80 patients with CRS, the average changes in Sino-Nasal Outcome Test (SNOT-22) scores, pretreatment to posttreatment, were 20.7 points for patients treated with budesonide and 13.6 points for those treated with saline alone.

Meaning The addition of budesonide to saline sinus irrigation results in clinically meaningful benefits for patients with CRS beyond the benefit experienced with saline alone.

col can be found in the Supplement, and the trial is registered at ClinicalTrials.gov (NCT02696850). The flow diagram of study enrollment and participation is shown in **Figure 1**. Men and women 18 years or older with a diagnosis of CRS were recruited from the Otolaryngology Clinic of the Wash-ington University in St Louis School of Medicine from Janu-ary 1, 2016, to February 16, 2017. The study was approved by Washington University's Human Protection Research Office. All participants provided written informed consent.

Study participants were required to have inflammation of the sinuses, as documented by the recruiting physicians (J.S. and J.F.P.), for 12 weeks or longer and 2 or more of the follow-ing symptoms consistent with CRS: mucopurulent drainage (anterior, posterior, or both), nasal obstruction, facial pain-pressure-fullness, and decreased sense of smell.
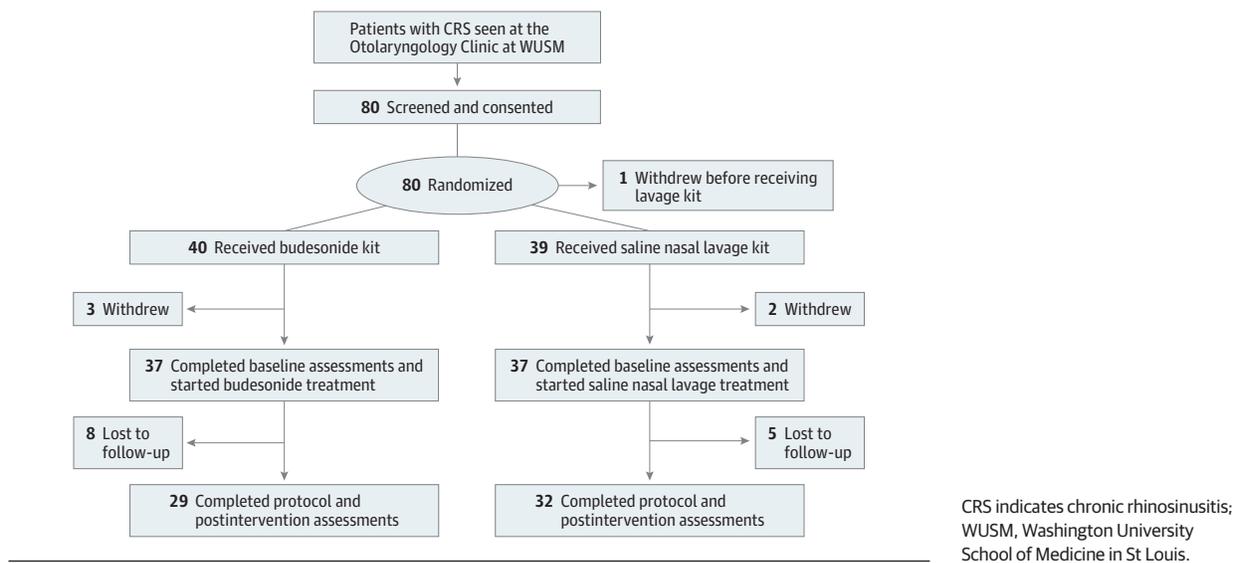
Patients with a history of comorbid mucociliary condi-tions; antibiotic use in the 2 weeks prior to enrollment; sinus surgery in the 6 weeks prior to enrollment; cerebrospinal fluid leak; allergy to topical steroids; tuberculosis lung infection; and/or herpes eye infection were excluded. In addition, pa-tients were excluded if they were pregnant, breastfeeding, or dependent on prolonged corticosteroid therapy for a comor-bid condition.

Severity of overall comorbidity was assessed with the Adult Comorbidity Evaluation-27 (ACE-27) instrument.[24] The ACE-27 is a valid comorbidity instrument that rates the degree of organ decompensation for a variety of different comorbid ailments and then generates an overall score (none, mild, moderate, or severe) based on the rating for individual ailments.

Interventions
All study participants were provided with an 8-ounce Sinus Rinse Regular Bottle Kit (NeilMed Pharmaceuticals Inc) and a 1-month supply of United States Pharmacopeia (USP) grade sodium chloride and sodium bicarbonate mixture. Participants were asked to either purchase distilled water or to boil tap water for 5 minutes to use with the saline irriga-tion. A randomized block design was generated by the study statistician (D.K.), and the study coordinator (S.K.) consec-utively assigned participants to the treatment or control groups after enrollment. Participants randomized to the treatment group received 60 capsules of budesonide (0.5

Figure 1. Flowchart of Study Enrollment and Participation

CRS indicates chronic rhinosinusitis; WUSM, Washington University School of Medicine in St Louis.

mg/capsule), while participants randomized to the control group received 60 identical-appearing capsules of lactose. Each study bottle was assigned a number from 1 to 80 corresponding to the randomization schedule. The participants and all members of the study team except the study statistician were blinded to the randomization assignment. Participants were instructed to dissolve 2 capsules of the study drug into the sinus rinse bottle along with the saline, and to irrigate the left and right nasal cavity with one-half of the contents of the nasal rinse once daily for 30 days. All participants received verbal and written instructions on how to conduct the irrigation properly.

Patient-Reported Outcome Measures

The primary outcome measure was the intraparticipant change, pretreatment to posttreatment, in Sino-Nasal Outcome Test (SNOT-22) scores in the budesonide group compared with the control group. The SNOT-22 is a validated, patient-reported outcome measure that captures the physical, functional, and emotional consequences of rhinosinusitis.[25] The SNOT-22 score is calculated as the sum of scores provided for each question and ranges from 0 to 110. All participants were asked to complete the SNOT-22 at baseline, 2 weeks, and after intervention (approximately 4 weeks after baseline). A minimal clinically important difference (MCID) in SNOT-22 scores was considered an improvement of at least 8.9 points, as described previously.[25,26] Patients with a baseline SNOT-22 score below 9 were excluded because these patients would be unable to achieve MCID.

The secondary outcome measure was the patient-reported response to treatment, as measured with a modification of the Clinical Global Impressions (CGI) scale.[27] The CGI questionnaire was given to all participants after intervention, and they were asked to rate their overall response to treatment using a 7-point Likert scale.

Objective Outcome Measure

Objective change in sinus disease was assessed with endoscopic examination by the recruiting otolaryngologist (J.S. and J.F.P.) at baseline and postintervention. Findings were recorded using the Lund-Kennedy grading system.[28]

Statistical Analysis

The sample size was estimated using preliminary data reported by Snidvongs et al.[21] Using a 2-sided α of .05, with 80% power, it was estimated that a sample size of 32 participant per group (total n = 64) would be needed to detect an MCID of 9 points or greater in SNOT-22 scores from before to after treatment between the 2 treatment groups. Anticipating a 20% dropout rate, we set the sample size at 80 qualifying enrollees.

Descriptive statistics were used to summarize the demographic and clinical characteristics and assessments of the study population. The effect size was measured as the pretreatment to posttreatment change in SNOT-22 scores. The 95% confidence interval (CI) around the difference was calculated and used to assess for clinically meaningful differences between the 2 treatment groups. Recognizing the variability in individual responses and the distortion this variability can cause in summarizing treatment effects as a difference in means, the observed difference in the percentage of participants who achieved an MCID between the 2 treatment groups and the 95% CI around this percentage difference was calculated.[29]

A mixed general linear model approach was used to explore whether the magnitude and pattern of change in SNOT-22 scores between baseline and postintervention was different in the 2 treatment groups, and to estimate mean scores in the 2 groups after controlling for confounders.

All analyses were repeated within subgroups of nasal polyp and previous surgery participants. An interim analy-

Table. Comparison of Baseline Characteristics Between the 2 Treatment Groups[a]

Baseline Characteristic	Total (N = 74)	Budesonide (n = 37)	Saline Nasal Lavage (n = 37)	SNOT-22 Score Difference (95% CI)
Age, mean (SD), y	51 (14.7)	53 (14.1)	48 (15.2)	5 (−1.6 to 11.9)
Sex				
Male	24 (32)	12 (32)	12 (32)	0 (−21 to 21)
Female	50 (68)	25 (68)	25 (68)	
Race				
White	67 (90)	33 (89)	34 (92)	−3 (−16 to 10)
African American	5 (7)	3 (8)	2 (5)	3 (−8 to 14)
Other	2 (3)	1 (3)	1 (3)	0 (−8 to 8)
Overall comorbidity				
None	41 (53)	17 (46)	22 (60)	−14 (−37 to 9)
Mild	30 (38)	18 (49)	10 (27)	22 (0 to 44)
Moderate	5 (6)	2 (5)	3 (8)	−3 (−14 to 8)
Severe	2 (3)	0 (0)	2 (5)	−5 (−12 to 2)
Polyps				
Yes	18 (25)	12 (34)	6 (16)	18 (−1 to 37)
No	54 (75)	23 (66)	31 (84)	
History of sinus surgery				
Yes	21 (28)	9 (24)	12 (32)	−8 (−28 to 12)
No	53 (72)	28 (76)	25 (68)	
Baseline endoscopic score, mean (SD)	5.3 (2.2)	5.8 (2.5)	4.9 (1.9)	0.9 (−0.2 to 2.0)
Baseline SNOT-22 total, mean (SD)	44.1 (18.5)	43.4 (17.5)	44.8 (19.7)	−1.4 (−10 to 7.2)

Abbreviation: SNOT-22, Sino-Nasal Outcome Test.[25,26]

[a] Unless otherwise indicated, data are reported as number (percentage) of study participants.
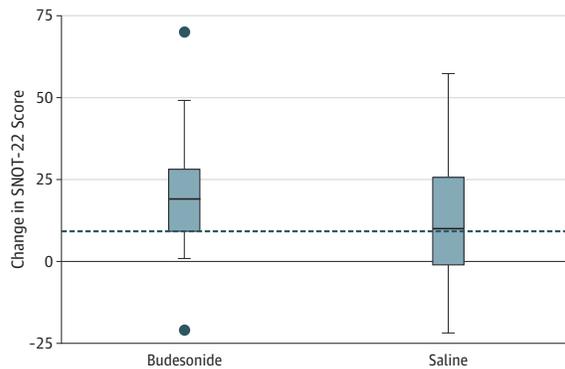
Results

A total of 80 patients were enrolled in the study between January 1, 2016, and February 16, 2017, and were randomized to either budesonide (n = 40) or placebo (n = 40) saline nasal lavage. Six participants withdrew after randomization, and 74 completed baseline assessments and started their assigned interventions. Thirteen participants were lost to follow-up, and 61 completed the intervention and postintervention assessments (Figure 1).

The baseline characteristics of all participants are summarized in the **Table**. The mean (SD) age was 51 (14.7) years, and most participants were women (n = 50; 68%) and of white race (n = 67; 90%). Approximately half of the participants had no other comorbidities (n = 41; 53%), and 7 (9%) reported moderate or severe comorbidities.

There were 18 (25%) participants identified as having nasal polyps during medical examination and 21(28%) participants who reported having prior sinus surgery. The mean (SD) endoscopic score at initial visit was 5.3 (2.2) points, and the mean (SD) SNOT-22 score was 44.1 (18.5).

No significant differences were found between treatment groups in the distribution of baseline demographic characteristics, comorbidity, endoscopic scores, SNOT-22 scores, or history of sinus surgery. The percentage of participants with polyps was higher in the budesonide group (n = 12; 34%) than in the saline nasal lavage group (n = 6; 16%), for a difference of 18% (95% CI, −2 to 37).

There were 29 participants randomized to budesonide treatment and 32 to saline nasal lavage who completed post-intervention study assessments. The mean (SD) change in SNOT-22 scores for participants in the budesonide group was 20.7 (17.9) points, and for those in the saline nasal lavage group, it was 13.6 (18.8) points, for a mean difference of 7 points in favor of the budesonide group (95% CI, −2 to 16) and a Cohen d of 0.39 (medium effect size) (**Figure 2**). A mixed within-between participants model was used to explore the change in SNOT-22 score from before to after intervention and to test whether this change was significantly different between the 2 study groups. The interaction effect between time of assessment and treatment group was not statistically significant. There was 1 patient who completed the study assessment but was not compliant with treatment in the budesonide group. When the noncompliant participant was excluded, a mean (SD) decrease in SNOT-22 scores of 22.1 (16.3) was observed in the budesonide group, corresponding to a mean difference in the change in SNOT-22 scores between treatment groups of 8.5 (95% CI, −0.6 to 18.0). The mean (SD) change in endoscopic scores from before to after intervention was 3.4 (2.3) points for participants in budesonide group and 2.7 (1.9) points for those

sis was performed after participant 32 was enrolled in the study to assess compliance with treatment and response to treatment. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc). Statistical significance was evaluated at the 2-sided α level of .05. Effect size and 95% CIs around the effect size are reported.

Figure 2. Comparison of Change in SNOT-22 Score Between the 2 Treatment Groups

The horizontal lines within the boxes represent mean change in Sino-Nasal Outcome Test (SNOT-22) score; the bottom and top lines of the boxes, 25th and 75th percentiles; the whiskers extending below and above the boxes, the minimum to the 25th percentile and 75th percentile to the maximum, respectively; and the circles above and below the budesonide graph, 2 outlier cases. The dotted line at 0 represents no difference in SNOT-22 score, posttreatment compared with pretreatment. The dashed line above it represents the amount of SNOT-22 score change (9 points), posttreatment compared with pretreatment, that is deemed clinically meaningful.[25,26]

Figure 3. Distribution of Participants by SNOT-22 Score Change in Each Treatment Group

SNOT-22 indicates Sino-Nasal Outcome Test, for which a 9-point change is deemed clinically meaningful.[25,26]

in the placebo group. The average difference of the change between participants in the 2 groups was 0.7 points (95% CI, −0.6 to 2.0 points) in favor of the budesonide group.

A reduction of 9 or more points in SNOT-22 score was considered clinically meaningful. A total of 23 participants (79%) in the budesonide group experienced a reduction of 9 or more points in their SNOT-22 scores compared with 19 (59%) of those in the saline nasal lavage group, for an observed difference of 20% (95% CI, −2.5% to 42.5%) (Figure 3) and an odds ratio of 2.6 (95% CI, 0.84-8.2). When the noncompliant budesonide participant was excluded, 82% in the budesonide group achieved the MCID, for an observed difference of 23% (95% CI, 1%-45%) and an odds ratio of 3.15 (95% CI, 0.95-10.42) in favor of budesonide.

We investigated the role of polyps, history of sinus surgery, and comorbidity as potential confounders of the effect of budesonide treatment. Based on SNOT-22 scores, none of the variables were found to be confounders.

We explored the effect of budesonide treatment among the participants with nasal polyps. Among participants with no polyps, there was an average difference of 10.2 points (95% CI, −1.6 to 22.1) in the change in SNOT-22 scores between the budesonide (n = 18) and saline nasal lavage treatment (n = 26) groups. Among participants with polyps, there was an average difference of −4.1 points (95% CI, −20.4 to 12.2) in the change in SNOT-22 scores in the budesonide group (n = 10) compared with the saline nasal lavage group (n = 6) (Figure 4A).

In participants with a history of sinus surgery, a mean difference of −0.1 points (95% CI, −19.6 to 19.4) was observed in the change in SNOT-22 scores between the budesonide (n = 9) and saline nasal lavage groups (n = 9). In participants with no prior sinus surgery, a mean difference of 10.1 points (95% CI,
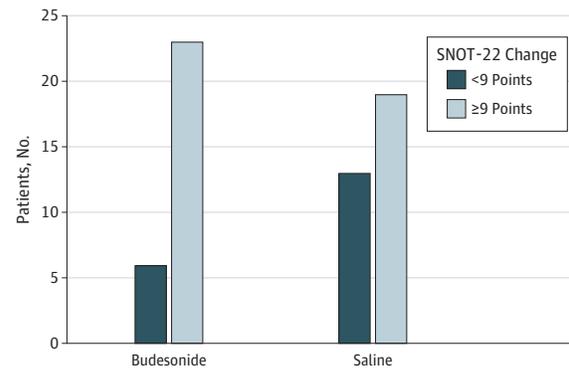
−1.1 to 21.3) was observed in SNOT-22 scores between the budesonide (n = 20) and saline nasal lavage groups (n = 23) (Figure 4B).

Based on CGI, 24 participants (83%) in the budesonide group and 20 (67%) in the saline nasal lavage group self-reported that they were "minimally improved," "much improved," or "very much improved." The observed difference in the percentage of participants who self-reported some degree of improvement between the 2 arms was 16% (95% CI, −6% to 38%) in favor of the budesonide group. There were no related adverse events in either intervention group.

Discussion

In this double-blind, placebo-controlled, randomized clinical trial, we found that the addition of 1 mg of budesonide to daily large-volume, low-pressure saline sinus irrigation for 1 month resulted in a clinically meaningful improvement in self-reported functional status and quality of life measures as well as objective measurements of CRS. The estimates of benefit were imprecise, and while the confidence interval does not exclude the possibility of no effect in the population, the upper bound of the confidence interval suggests that this effect can also be very strong. A greater benefit of budesonide was seen among patients with no history of surgery than in those who had undergone surgery, contrary to current understanding that surgical opening of the sinuses is required for medicated saline lavage to be effective. The presence of polyps was greater in the budesonide arm and was associated with a smaller improvement in symptoms with budesonide than when polyps were not present. Budesonide was well tolerated, and there were no reported adverse events associated with its use.

Currently, CRS is primarily treated as an infectious disease process with frequent administration of antibiotics. Research suggests that as much as 50% of the antibiotics prescribed for sinusitis may be inappropriate and associated with

Figure 4. Comparison of Change in SNOT-22 Scores, Pretreatment to Posttreatment, Between Different Clinical Groups
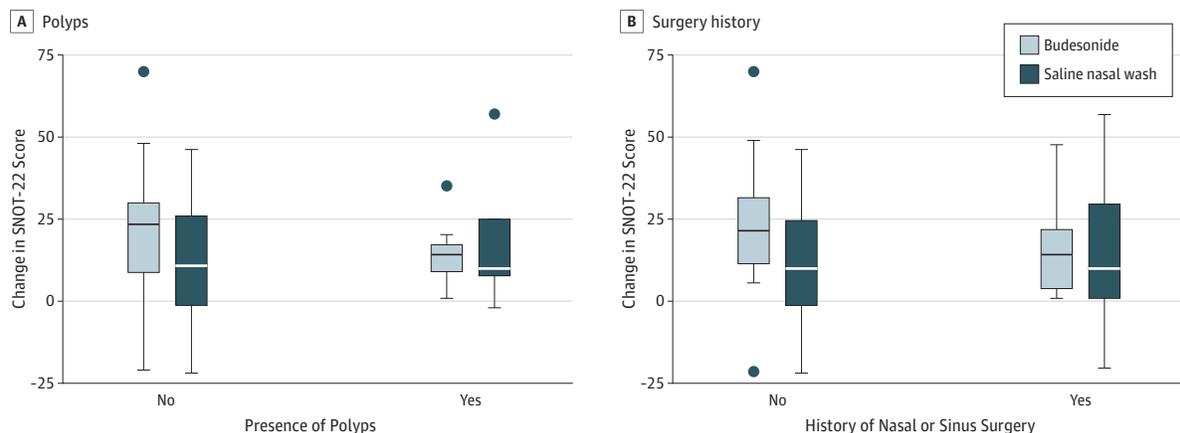
The horizontal lines within the boxes represent mean change in Sino-Nasal Outcome Test (SNOT-22) score; the bottom and top lines of the boxes, 25th and 75th percentiles; the whiskers extending below and above the boxes, the minimum to the 25th percentile and 75th percentile to the maximum, respectively; and the circles above and below some of the graphs, outlier cases. A SNOT-22 score change of 9 points is deemed clinically meaningful.[25,26]

harm.[7] As a result, multiple national organizations, including the Centers for Disease Control and Prevention (CDC), have begun antibiotic stewardship programs to measure and improve how antibiotics are prescribed by clinicians and used by patients.

Among specialists, there is a growing recognition that CRS may reflect a dysfunctional immune interplay between different host susceptibilities and environmental modifiers that are responsible for the chronic inflammatory response.[30,31] This dysfunctional interplay creates targets for nonantibiotic therapy in chronic sinusitis. As there are a variety of different "phenotypes" of CRS, including patients with and without polyps, it is likely that there are a variety of different abnormalities within the innate and adaptive immune system or "endotypes" that can serve as targets for therapy.[31] This new area of potential treatment is referred to as "biologic therapy," and potential targets for therapy include epithelial cell–derived cytokines and IgE.

Saline nasal lavage has been shown to be an effective form of treatment for sinusitis and can be an effective delivery system for various therapeutics, including corticosteroids. Large-volume, low-pressure nasal lavage results in better distribution of therapeutics to the nasal cavity and sinuses than low-volume devices.[15] Furthermore, these large-volume, low-pressure devices can mediate adverse effects of head position or nasal cavity anatomy on distribution.[14,18] Saline nasal lavage is low cost and has both high patient acceptance and a high benefit-to-risk margin.[17,19] Though the evidence regarding large-volume saline irrigation is promising, more high-quality evidence is needed to definitively establish its benefit compared with other forms of treatment such as nasal spray.[16,27]

The impact of budesonide added to saline nasal lavage for the treatment of CRS has been investigated with several prospective cohort studies. Sachanandani et al[22] found clinically significant improvement in SNOT-20 scores and no change in adrenal function in 9 patients with CRS treated with saline na-

sal lavage with budesonide for 30 days. Steinke et al[23] performed a similar study evaluating budesonide saline nasal irrigation treatment in 8 patients with CRS and demonstrated similar significant improvements in several objective and subjective sinus outcome measures. The conclusions from these studies, while promising, were largely speculative given the small sample sizes. Most recently, Snidvongs et al[21] demonstrated significant and sustained objective and subjective clinical improvement in a large cohort of patients with CRS treated after endoscopic sinus surgery with topical steroid nasal irrigations. All 3 of these studies have been limited, however, by lack of a control group.

In the present trial, we observed a clinically significant benefit of budesonide among patients who had not had previous sinus surgery. These results are surprising and suggest that a large number of patients with CRS would benefit from budesonide without sinus surgery. The mechanism for this benefit is unclear as, previous research[15] has suggested that the distribution of topical agents is significantly reduced without prior sinus surgery. The benefit found in the present study of budesonide among participants without a history of sinus surgery may be explained by many factors, including the ability of the budesonide molecule to stick to nasal mucosa and, through reduction of inflammation, allow penetration of the sinus cavities. We also observed that patients with nasal polyps had only a minor benefit of budesonide. Patients with nasal polyps may have reduced topical application and penetration of budesonide and thus less beneficial effects. Furthermore, patients with nasal polyps may have endotypes that are less responsive to the anti-inflammatory effects of the glucocorticosteroids.

Limitations

There are several limitations to this study. First, the duration of the trial was only 4 weeks and, given the long duration of symptoms and chronic nature of the condition for many participants, this may have been an insufficient amount of

time to see the complete effect of the budesonide therapy. Compliance was assessed by patient self-report, as we did not have formal compliance assessments. Thus, we cannot be certain that participants completed the full 4 weeks of treatment. Despite these limitations, the observed magnitude of the benefit of budesonide was clinically significant, as evidenced by the effect size, and the true effect could be even greater, as evidenced by the upper bound of the 95% CIs. However, the low precision of the estimates of the effect, as demonstrated by the width of the 95% CIs, and the inclusion of the null for many of the comparisons, undermines our ability to make definitive conclusions from this trial. Furthermore, the size of certain subgroups, such as those with nasal polyps, was so small

and unequally divided between the 2 treatment groups as to further prohibit definitive conclusions.

Conclusions

This study shows that the use of budesonide in large-volume, low-pressure saline nasal lavage results in clinically meaningful benefits for patients with CRS. Additional randomized clinical trials of the effect of budesonide in saline nasal lavage for those with CRS vs saline-alone controls and, furthermore, budesonide vs steroid nasal spray are needed and will help define the true effect of budesonide within unique patient subgroups.

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Invited Commentary

Building the Evidence for Corticosteroid Irrigation Therapy in Chronic Rhinosinusitis

Peter H. Hwang, MD

Owing to our limited understanding of the pathophysiology of chronic rhinosinusitis (CRS), expansion of the armamentarium of medical therapies for CRS has remained notably constrained for decades. Over the last 30 years, advances in medical treatment for CRS have not kept pace with innovations in surgical treatment. And yet, since many physicians believe that CRS remains a medical disease first and foremost, there is often a sense of frustration that we do not have more innovative medical therapies to offer our patients with CRS.

Clinicians have often resorted to off-label use of medications in the treatment of CRS, a reflection of a need and desire to offer a broader range of therapeutic options to our patients. Without rigorous regulatory standards to guide their use, off-label prescribing of medications is often associated with spottily documented efficacy and safety. For example, despite widespread use of oral antibiotics by practitioners in the treatment of CRS,[1] there are still no antibiotics that are approved by the US Food & Drug Administration for CRS, and the evidence to support routine antibiotic use in CRS remains low.[2] Topical antibiotics are another category of medication favored by many otolaryngologists treating patients with CRS, yet the evidence for their efficacy is surprisingly slim.[2]

Topical corticosteroid irrigation is another commonly used off-label medical therapy for CRS. Although highly favored among clinical experts and increasingly prevalent in general otolaryngologic practice, topical corticosteroid irrigation therapies have a relatively small body of literature to support their use in terms of efficacy and safety. As a result, many insurance carriers have chosen not to cover corticosteroid irrigations, leaving patients to self-pay for a therapy that many patients and their physicians find beneficial. Without the backing of pharmaceutical industry funding for large-scale clinical trials, the burden of proof for establishing the safety and efficacy of topical corticosteroid irrigations has fallen on independent investigators.

Tait et al[3] have executed a well-designed randomized clinical trial comparing budesonide irrigation with plain saline irrigation. The study evaluated 80 patients with CRS randomized to once-daily nasal irrigation with either 1.0 mg of budesonide plus saline or placebo plus saline, administered via a high-volume rinse bottle, for 30 days. The authors found that patients receiving budesonide had an average of 7 points greater reduction in the SNOT-22 score (Sino-Nasal Outcome Test) compared with those receiving placebo (medium effect size). However, the 95% confidence interval for the difference between groups in pretreatment vs posttreatment scores did include 0, leading the authors to acknowledge that "the estimates of benefit were imprecise, and…the confidence interval does not exclude the possibility of no effect."[3]

Furthermore, there were interesting and perhaps unexpected findings in the subgroup analysis, suggesting that subgroups of patients with CRS may have differential responses to budesonide irrigations. For example, those patients with CRS without nasal polyps showed a greater reduction in SNOT-22 scores with budesonide irrigation than those with nasal polyps. In addition, patients with a history of prior sinus surgery showed minimal symptomatic benefit from budesonide irrigation vs placebo, whereas patients without prior surgery showed a greater benefit from budesonide irrigation vs placebo. Subgroup analysis was limited by smaller numbers in each of the comparison cohorts, and the 30-day duration of treatment was relatively short.

While this well-structured randomized clinical trial offers level 1 evidence for assessing the value of budesonide irrigations in patients with CRS, there are many questions raised by this report that require further study to understand its clinical applicability. Given our understanding of CRS as a heterogeneous disease process, a much larger study appears necessary to enable statistically sound subgroup analysis; this is necessary to achieve clarity on which subgroups of those with CRS may experience the greatest benefit from budesonide irrigations. In addition, while the choice of a saline placebo group is reasonable from the standpoint of study design, practically