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Nasal Lavage With Mupirocin for the Treatment of Surgically Recalcitrant Chronic Rhinosinusitis

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Objectives/Hypothesis: To examine the efficacy and tolerability of topical mupirocin for the management of surgically recalcitrant chronic rhinosinusitis (CRS) associated with *Staphylococcus aureus* infection.

Study Design: Prospective open-label pilot study.

Methods: Patients with surgically recalcitrant CRS who had positive nasendoscopically guided cultures for *Staphylococcus aureus* were treated with twice daily nasal lavages containing 0.05% Mupirocin and lactated ringers salts. The duration of treatment was 3 weeks. Patients were assessed before and after treatment in terms of nasendoscopic findings, microbiology results, and Sinonasal Outcome Test (SNOT-20) and visual analogue scale questionnaires.

Results: Fifteen of 16 patients had improved nasendoscopic findings after treatment. Twelve of 16 patients noted overall symptom improvement. Fifteen of 16 patients had negative swab results for *Staphylococcus aureus* after treatment. Only minimal adverse effects were experienced.

Conclusions: Nasal Lavage with 0.05% Mupirocin may represent an effective and well tolerated alternative treatment for postsurgical recalcitrant CRS.

Key Words: Nasal douche, recalcitrant chronic sinusitis, *Staphylococcus aureus*, biofilms.

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INTRODUCTION

Chronic rhinosinusitis (CRS) has a population prevalence of approximately 14% and may cause profound reduction in quality of life.[1] A vast majority of patients can be successfully managed by standard medical and surgical therapies, however, a small group of patients have recalcitrant disease. Patients who have persistent symptoms are often found to have sinonasal colonization by *Staphylococcus aureus* (SA).[2] This organism is known to produce toxins, a number of which have the capacity to act as superantigens. Recently, it has been suggested that such toxins acting as superantigens may have a role in the pathogenesis of CRS with polyps.[3] SA is also a known biofilm producing bacterium, and these biofilms have recently been isolated in patients with CRS.[4] A recent study in our department has also demonstrated that biofilms may predispose patients to poorer outcomes after sinus surgery.[5]

Topical antibiotics are used in many sites, including the skin, lungs, bladder, vagina, eye, and external and middle ears. Theoretical advantages of topical use include achieving high local drug concentrations at the target site, while minimizing systemic absorption of the drug, and therefore reducing adverse effects. Mupirocin is an antibiotic produced by *Pseudomonas fluorescens* and acts by inhibiting bacterial protein synthesis. It undergoes rapid degradation to an inactive metabolite in human serum, so can only be used as a topical antibiotic.[6] Mupirocin displays high levels of activity against SA and is stable in human nasal secretions, retaining 100% of its antistaphylococcal activity.[7] This study was designed to determine whether nasal lavage with a mupirocin solution is both tolerable and effective in the management of patients with recalcitrant CRS.

METHODS

Patients for this study were enrolled from our tertiary referral rhinology clinic. All patients had failed standard medical and surgical treatment including oral antibiotics, oral corticosteroids, and nasal saline lavage and had all undergone at least one sinus surgical procedure. Only patients who had endoscopically guided microbiology swabs positive for SA were enrolled. Patients who were pregnant, aged less than 18, or who had known hypersensitivity to mupirocin were excluded.

A solution of 0.05% (500 μg/mL) mupirocin and lactated ringers salts was formulated specifically for intranasal use by dissolving 100 mg of mupirocin and salts into 200 mL of cooled, previously boiled water. This effective concentration of mupirocin is substantially greater than the mean inhibitory (0.12–1.0 μg/mL) and mean bactericidal (4–32 μg/mL) concentrations of mupirocin against SA. Our solution was independently tested in the laboratories of the Institute of Medical and Vetinary Science in

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Adelaide and found to have equivalent in vitro efficacy as the standard mupirocin preparations.

Patients were treated for 3 weeks, using 100 mL of solution per nostril twice a day. The mupirocin containing solution was delivered via a commercially available 200 mL plastic nasal irrigation squeeze bottle. Patients underwent pretreatment and posttreatment nasendoscopy (graded for mucosal edema or polyps, crusting, discharge, and erythema) and endoscopically guided microbiology swabs. Patients were asked to complete Sinonasal Outcome Test (SNOT-20) and visual analogue scale (VAS) symptom questionnaires before, and after treatment, and record adverse effects in a treatment diary. The pretreatment symptom scores and endoscopy scores were performed after completion of a trial of extensive nasal douching for more than 3 weeks and represent the base-line scores against which the posttreatment scores should be compared.

This study was approved by Central Northern Adelaide Health Service Ethics of Human Research Committee.

RESULTS

Demographics and Clinical Data

Between the July 1, 2006 and June 30, 2007, a total of 16 patients with SA related CRS recalcitrant to treatment were enrolled in this study with a male to female distribution of 10:6 and a mean age of 60.2 years (STD ± 16.9 years, range = 27–85 years). The average number of sinus operations per patient was 4.25 (STD ± 3.32, range = 1–14) with 14 of the 16 patients having had at least two or more previous endoscopic surgical procedures.

Bacteriological Findings

Thirteen patients had sinonasal colonization by sensitive SA, whereas three had methicillin resistant species grown on initial culturing. Swabs taken after 3 weeks of mupirocin treatment yielded positive results in three patients, with the organisms cultured being, SA, *Haemophilus influenzae*, and *Aspergillus flavus*.

Posttreatment Outcomes

Table I summarizes the overall median score and interquartile range of each variable measured in all 16 patients pre- and postmupirocin treatment. Figures 1–3 are graphical representations of the changes in nasal endoscopy scores, visual analogue scores and SNOT 20 symptom scores respectively in all 16 patients pre and postmupirocin treatment.

Nasal endoscopy scores. Of the 16 patients, 15 demonstrated endoscopically graded improvement in their sinuses whereas one demonstrated visibly worse sinus mucosal inflammation on endoscopy. Overall statistical analysis showed a significant improvement in the endoscopic sinus scores after treatment with mupirocin (P = .001 Wilcoxon signed rank test, two tailed P value). [Pretreatment median score 8.0 points with interquartile range (7.5–12.5) and posttreatment median score 3.0 with interquartile range (1.5–5.0), see Figure 1].

TABLE I.
Summary of Symptom and Endoscopy Score Pre- and Postmupirocin Treatment in 16 Treatment Resistant CRS Patients.

	Pretreatment Median Score (Interquartile Range)	Posttreatment Median Score (Interquartile Range)
Visual analogue score	32.5 (23.5–38.5)	19 (11.5–27)
SNOT 20 score	45.50 (21.5–65.5)	30.50 (17.0–43.5)
Endoscopy score	8.0 (7.5–12.5)	3.0 (1.5–5.0)

CRS = chronic rhinosinusitis; SNOT = Sinonasal Outcome Test.

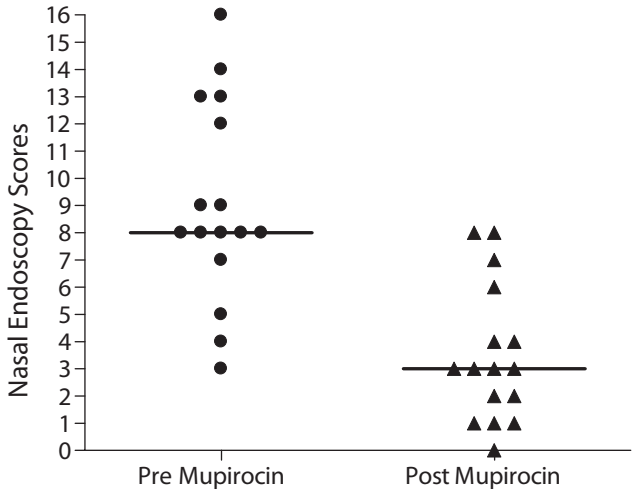

Fig. 1. Nasal endoscopy scores pre- and post-mupirocin treatment for 16 treatment resistant CRS patients. Data represented as scatter dot plot with line at median.

Symptom scores. Using the VAS, 12 of the 16 patients reported an overall improvement in their symptoms after mupirocin treatment. Overall analysis of all 16 patients demonstrated a statistically significant reduction in the VAS scores recorded by patients after treatment (P = .02 Wilcoxon signed rank test, two tailed *P* value). [Pretreatment VAS scores median 32.5 points with interquartile range (23.5–38.5) and posttreatment VAS scores median 19.0 points (11.5–27.0), see Figure 2]. Symptom scores using the SNOT-20 system yielded similar results

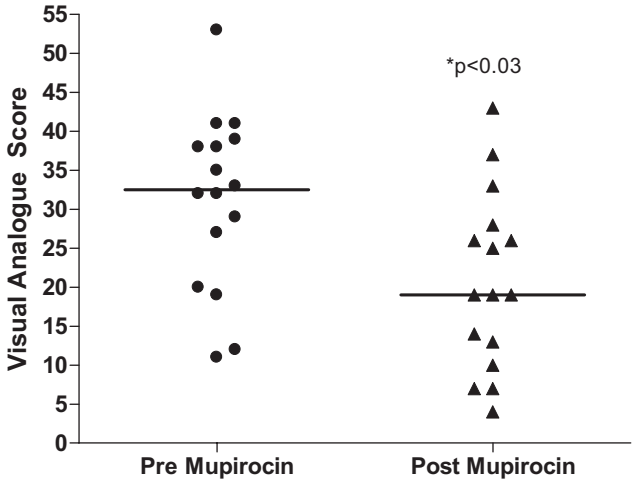

Fig. 2. Visual Analogue Symptom scores pre- and post-mupirocin treatment for 16 treatment resistant CRS patients. Data represented as scatter dot plot with line at median.

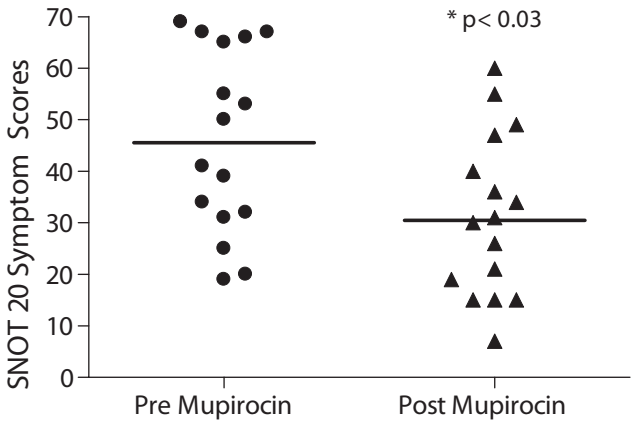

Fig. 3. SNOT-20 symptom scores pre- and post-mupirocin treatment for 16 treatment resistant CRS patients. Data represented as scatter dot plot with line at median.

to the VAS with 13 of the 16 patients reporting an improvement in symptoms. Again a statistically significant reduction was seen when analyzing the SNOT-20 Scores in all 16 patients. (P = .0255 Wilcoxon signed rank test, two tailed P value). Pretreatment SNOT-20 scores median 45.5 interquartile range (31.5–65.5) and posttreatment SNOT-20 scores median 30.5 (17.0–43.5), see Figure 3.

Adverse Effects

The mupirocin douches were well tolerated with minimal adverse effects. Two patients reported a mild burning sensation immediately after their initial use of the mupirocin douche. This was short lived, however, and did not prevent the patients completing their full course of treatment.

DISCUSSION

Over the last decade, interest surrounding the use of topical antibiotics to treat CRS has grown.[8] A number of mostly retrospective studies have described the administration of various antibiotics using different delivery devices.[9–15] In our department, SA is the most common pathogen cultured in patients with CRS who have been previously treated surgically. Our experience with treating SA related disease using appropriate oral antibiotics has been disappointing and all patients included in this study had failed multiple previous courses of culture directed antibiotics. This may be due to inadequate drug penetration of sinonasal mucoperiosteum and bone, or because SA is able to exist as a biofilm, and thus remain relatively resistant to antibiotic treatment. We have therefore been interested in developing alternative strategies to manage these patients. Topical antiseptics were initially trialed but we found that povidine-iodine was poorly tolerated because of severe intranasal discomfort experienced immediately as the solution contacted the nasal mucosa.

Mupirocin is an antibiotic that is stable in human nasal secretions, retaining 100% of its antistaphylococcal activity.[6] It has minimal systemic absorption when used topically and its unique mechanism of action of selectively inhibiting bacterial isoleucyl tRNA synthetase, makes the development of cross resistance with other antibiotics unlikely. Mupirocin has been used widely to eradicate SA colonization of the nasal vestibule in an attempt to reduce nosocomial infections related to SA.[16] Furthermore, recent in vitro studies in our department have shown that mupirocin is capable of effectively treating SA growing as a biofilm.[17] We therefore selected mupirocin as our topical antibiotic of choice for further investigation.

The results of this study demonstrate that nasal lavage using a solution containing 0.05% mupirocin and lactated ringers salts for 3 weeks is effective in treating recalcitrant CRS associated with SA colonization. A large majority of patients had improved symptom scores, and all but one patient was better based on nasendoscopic grading of disease. Fifteen out of 16 patients had negative swabs for SA after treatment. Importantly, this treatment seems well tolerated, with only two patients complaining of very minor local irritation. No systemic side effects were encountered, and all patients were able to complete the entire course of treatment.

The patients enrolled in this study had remained symptomatic despite multiple operations and intensive medical therapies. As a group they represent some of the most difficult patients that our tertiary referral rhinology clinic is asked to manage. We are encouraged by some quite dramatic responses to this treatment, especially given the relative ease of drug administration and lack of treatment related morbidity. In particular, patients who presented with severe crusting, purulent discharge, and polypoid mucosal disease responded impressively.

One patient clearly failed treatment and had worsening symptoms and signs at follow-up. In this case, we were treating isolated left-sided frontal sinusitis that had failed both maximal medical therapy and an adequate frontal recess clearance. It is likely that the nasal lavage was not adequately penetrating the frontal sinus because of severe inflammatory disease around the ostium. This patient has subsequently undergone revision surgery to enlarge the frontal ostium in an attempt to obtain penetration of the douche and this was administered in the postoperative period with excellent outcome and he is now asymptomatic.

Our study was a prospective open label pilot project that did not contain a formal control arm, although one could argue that each patient served as there own control. As such, it is impossible for us to conclusively state that a mupirocin solution is more efficacious than lactated ringers salts alone although all patients included in the trial had been using saline and lactated ringers solution to douche the nose prior to be included in the study. The high percentage of patients with negative microbiology swabs posttreatment suggests that this mupirocin solution achieved eradication of the plantonic SA from the sinuses.

Our follow-up period was short and patients were assessed only once immediately after the cessation of their treatment. We therefore are unable to comment on the longevity of clinical improvement. It is known that patients can quickly recolonize their nasal vestibule after application of mupirocin ointment. This is probably because they are carrying an identical strain of SA in other

extranasal carriage sites such as the groin or pharynx, and rapidly contaminate their nose with their fingers after eradication. In the only other study involving the use of mupirocin in the sinonasal cavities, Solares et al. retrospectively reviewed their use of topical mupirocin to treat CRS exacerbations caused by methicillin resistant species.[13] Although two thirds of episodes treated initially had symptomatic improvement after a 4-week course of mupirocin irrigations (and various oral antibiotics), half of their patients had a recurrence of symptoms during their mean follow-up period of 11.8 months.

We had one patient who had a positive culture for SA after treatment. The isolate was sensitive to mupirocin when tested in vitro. This patient had significant narrowing of both the frontal and maxillary ostia and it is likely that the mupirocin douche did not penetrate the sinuses adequately. Another explanation may be that the SA had formed a biofilm and that the duration of contact with the mupirocin was insufficient to eradicate the SA existing in this form. Further research is required to understand how long antibiotics need to remain at the target site to be effective and what conditions may alter their bioavailability. It is possible that in the future, mucoadhesive substances such as chitosan and carbopol could be used to deliver drugs in a more efficient manner.

CONCLUSION

Nasal lavage with a mupirocin solution may represent an effective alternative to manage patients with recalcitrant CRS due to SA infection. It is well tolerated and involves reduced treatment related morbidity when compared with standard oral or systemic drug delivery. Further research is needed to better understand the pharmacodynamics of topical drug use in the sinonasal cavities.

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