Treatment of chronic rhinosinusitis refractory to other treatments with topical antibiotic therapy delivered by means of a large-particle nebulizer: Results of a controlled trial

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OBJECTIVE: **To study the efficacy of nebulized topical saline-tobramycin solution in patients with chronic rhinosinusitis refractory to medical and surgical therapy.**

STUDY DESIGN AND SETTING: **Twenty patients in whom endoscopic sinus surgery failed to relieve symptoms entered a randomized, double-blind trial of tobramycin-saline solution or saline-only solution administered thrice daily to the nasal passages by means of a large-particle nebulizer apparatus for 4 weeks, followed by a 4-week observation period. Outcome measures of symptoms, quality of life, and endoscopic aspect of sinus mucosa were assessed.**

RESULTS: **Both treatments were well tolerated and produced equivalent improvement in symptoms, quality of life, and mucosal aspect. Treatment with the tobramycin-saline solution gave more rapid improvement of pain, but led to the development of nasal congestion.**

CONCLUSION: **Therapy with a 4-week course of large-particle nebulized aerosol therapy improves symptomatology and objective parameters of rhinosinusitis in patients refractory to surgical and medical therapies. Addition of tobramycin appears of minimal benefit. The mechanism of this effect is unexplained.**

SIGNIFICANCE: **Large-particle nebulized aerosol therapy may offer a safe and effective management alternative for patients with refractory rhinosinusitis.**
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Current treatment for acute and chronic rhinosinusitis involves antibiotics, decongestants, mucolytics, and topical corticosteroids as indicated.[1] Sinus disease resistant to this traditional medical therapy is usually managed by endoscopic sinus surgery (ESS). ESS is a reasonably successful treatment modality and affords persistent relief in approximately 76.0% of all patients over a 1- to 3-year follow-up period,[2,3] with a success rate dependant on the severity of the pre-existing illness.[4] This figure underlines that there is nevertheless a significant percentage of patients who are not improved after ESS. In spite of adequate investigations and treatments, these patients manifest persistent mucosal edema, nasal secretions with post-nasal drip, or persistent facial discomfort lasting beyond the normal healing period of 6 to 8 weeks. This is intriguing as there appears to be no obstruction to sinus drainage, the maxillary sinus ostia appear patent and the ethmoid cavities are widely open without obstructive synechiae.

Unfortunately, although this disorder is increasingly common, it is still poorly understood and remains to be defined. Although definitions for the clinical entities of acute, subacute, recurrent acute, chronic, and acute on chronic rhinosinusitis have been published,[5] this population has yet to be characterized, and we have had to evolve a new terminology for it. Thus, in our clinical practice, we refer to rhinosinusitis, which is refractory to medical and surgical treatment, as *refractory rhinosinusitis*. Because this group of patients is significantly affected, with little in the way of curative treatments or effective supportive therapy, we have attempted to develop an alternative treatment modality for their management. Because sinus ostia are patent after ESS, communicating freely with the nasal cavity, it would seem plausible to attempt use of an intranasal delivery method of concentrated solutions of topical antibiotic agents. Nasal irrigation is frequently recommended as a means of irrigating the nasal passages[6]; however, the volumes delivered are considerable and any medication administered in this fashion would have to be diluted in an large volume of water, significantly impairing our capacity to deliver a high concentration locally. Thus, a more suitable alternative to the previously used meth-

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Table 1. Bacteriology of the sinus cavities at the initiation of therapy

Organism No. 1	Organism No. 2	Organism No. 3
Saline solution only		
Coagulase-negative staphylococcus *sp*		
Haemophilus influenzae	Streptococcus viridans	
Candida *sp*	Coagulase-negative staphylococcus *sp*	Paecilomyces
Staphylococcus aureus		
Staphylococcus aureus		
Staphylococcus aureus	Pseudomonas aeruginosa	
Enterobacter cloacae	Klebsiella oxytoca	
Staphylococcus aureus		
Staphylococcus aureus	Agrobacterium radiobacter	
Tobramycin-saline solution		
Serratia marcescens	Coagulase-negative staphylococcus *sp*	
Staphylococcus aureus		
Staphylococcus aureus		
Coagulase-negative staphylococcus *sp*	Streptococcus viridans	
Serratia marcescens	Coagulase-negative staphylococcus *sp*	
Coagulase-negative staphylococcus *sp*		
Pseudomonas aeruginosa	Hemolytic streptococcus group B streptococcus	Non-lactose fermented coliforms
Coagulase-negative staphylococcus *sp*	Streptococcus viridans	Enteobacter *sp*
Staphylococcus aureus	Diptheroids	
Staphylococcus aureus		

There are no differences between the two groups for any of the measured parameters.

ods would appear to be the use of a small volume of an aerosolized solution delivered by means of nebulizer. The RinoFlow Nasal and Sinus Wash System, (Respironics Healthscan Inc, Cedar Grove, NJ) is a device specifically designed for delivering large-particle size aerosol therapy to the nasal mucosa.[7]

We hypothesized that this apparatus would be useful in delivering topical antibiotic therapy directly to the surface of the affected sinuses. We have thus performed a pilot study consisting of a trial of topical antibiotic therapy delivered directly to the surface of the sinonasal mucosa by means of a large-particle size atomizer in a group of patients considered ESS failures, for whom no further medical or surgical therapeutic alternatives currently exist, in order to determine whether topical antibiotic therapy delivered in this manner improves the symptoms and signs of chronic rhinosinusitis and their impact on quality of life (QOL).

METHODS AND EXPERIMENTAL DESIGN

We performed a prospective, double-blinded, placebo-controlled pilot study of large-particle aerosolized antibiotic therapy delivered by means of nebulization to patients with refractory rhinosinusitis who failed maximal surgical and medical therapies. This study was reviewed and approved by the McGill University Health Center Institutional Review Board (IRB).

Over a 6-month period (January 1998–May 1998), 20 subjects with rhinosinusitis refractory to medical and surgical treatment were recruited from a tertiary, academic-based, specialized ear, nose, and throat-based nose and sinus care center and enrolled on a voluntary basis. Informed consent was obtained from all participants before inclusion in the study. Refractory rhinosinusitis was diagnosed in patients without immune deficiencies who had undergone previous technically successful ESS, but who were presenting with symptoms of rhinosinusitis that persisted beyond the normal 8- to 12-week healing period after surgery, and who failed further medical management. The use of this nonstandard terminology was required because of the absence of accepted definitions. Symptoms of persistent rhinosinusitis were adapted from the consensus group recommendations for chronic rhinosinusitis.[5] Technical adequacy of previous surgery was defined as absence of anatomic obstruction to drainage of the sinus cavities assessed endoscopically and by CT scan. An additional 21-day course of antibiotic therapy was administered to all patients before their entry into this study. When possible, selection of antibiotic was guided by endoscopically-guided cultures of sinus secretions. Again, because no formal guidelines exist for the treatment of these patients, these had to be adapted from existing recommendations for chronic rhinosinusitis.[1] Duration of treatment, 3 weeks, was selected as a conservative period that is less apt to lead to development of side effects from prolonged use of antibiotics. Only those failing to respond to this additional medical therapy were included in the trial. Existing documented allergies to aeroallergens were treated by avoidance and use of a topical corticosteroid spray. Patients who were unable to give consent or were unable to follow instructions, those with severe renal insufficiency, those allergic to tobramycin or quinine, or those

using loop diuretics such as furosemide, as well as those with pre-existing hearing loss or with isolated frontal rhinosinusitis, were excluded.

Eligible patients were recruited and were randomized into two groups. One group received 3-times daily applications of 4 mL of a 20 mg/mL solution of tobramycin for a 4-week period and the other a placebo solution of 0.9% sodium chloride. In order to ensure blinding as to the solution received, the placebo solution contained quinine (1 mg/mL), duplicating the bitter taste of the tobramycin treatment solution.[8] Aerosols were introduced into the sinus cavities with the RinoFlow Nasal and Sinus Wash System. A 4-mL vial of either 20 mg/mL tobramycin solution or 1 mg/mL control quinine solution was vaporized into the nasal passages by using the high-flow setting (Phase 2). After a 4-week treatment period, therapy was stopped (week 4), and the patients were subsequently re-evaluated after a further 4-week interval (week 8). Compliance with therapy was ensured by weekly follow-up calls from the clinical coordinator and by counting the number of empty vials of medication remaining on the return visits.

Measurement Instruments

QOL was evaluated with the Juniper Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)[9] symptoms by using a visual analog scale and sinonasal endoscopy for assessment of the sino-nasal mucosa. Safety measures were incorporated to ensure against development of drug-resistant bacteria or modifications of renal or auditory function.

Analysis of Data

Baseline scores were recorded on initiation of therapy (Week 0). The two groups were compared at time of enrollment to ensure similarity with the Student *t* test and Fisher exact test. Response to treatment was measured by subtracting the values obtained at the onset of treatment (baseline) from those recorded at the 2-, 4- (end of active treatment), and 8-week (4 weeks after cessation of active treatment) visits. Differences in responses at each timepoint for each treatment group and for differences in between the two treatments were compared with a *t* test. Results are expressed as 95% confidence intervals (CI 95%).

RESULTS

Patient Population

Twenty patients were enrolled, and 18 subjects successfully completed the trial (12 women, 8 men; mean age 49 years, range 23-89; history of atopy, 12). The two treatment groups were similar. Organisms recovered are detailed in Table 1. There was no difference between the placebo and treated groups in distribution of demographic parameters or in organisms cultured.

Response to treatment for the two groups is summarized in Figs 1, 2, and 3. Both saline and tobramycin solutions led to clinically significant improvements in QOL, symptoms, and parameters of sinonasal endoscopy, with the effects first becoming evident only at 4 weeks. Interestingly, the effect of treatment persisted beyond the 4-week treatment period, with improvements at 8 weeks greater than at the end of the 4-week treatment period.

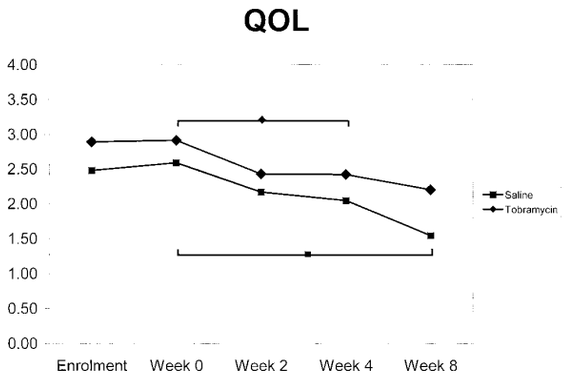

Fig 1. Quality of life over the course of the trial as assessed by the Juniper RQLQ scale. *Solid bars* indicate significant change ($P < 0.05$) compared with baseline (week 0) for each of the different treatment arms.

Comparison of the saline-only solution and saline-tobramycin solution groups showed only minor differences. For symptoms of pain, treatment with tobramycin solution was superior at week 2 (but not at weeks 4 and 8). However, because topical treatment with tobramycin appeared to actually increase nasal congestion, saline solution was clearly superior in improving the sensation of nasal obstruction at weeks 2, 4, and 8.

Adverse Events

Treatment was well tolerated locally. There was no statistically significant difference in adverse events between the saline and tobramycin solution-treated groups. No tobramycin-resistant organisms developed. Pneumonia developed in one patient during an exacerbation of bronchitis, and that patient was dropped from the study. This was successfully treated with oral antibiotics on an outpatient basis and did not require hospitalization. This occurred in the saline-only solution group.

DISCUSSION

Treatment with both aerosolized saline solution and tobramycin-saline solution was well-tolerated and led to improvements in QOL, symptomatology, and endoscopic aspect of the nasal mucosa. These beneficial responses were initially noted by the fourth week of treatment and continued to improve even after treatment

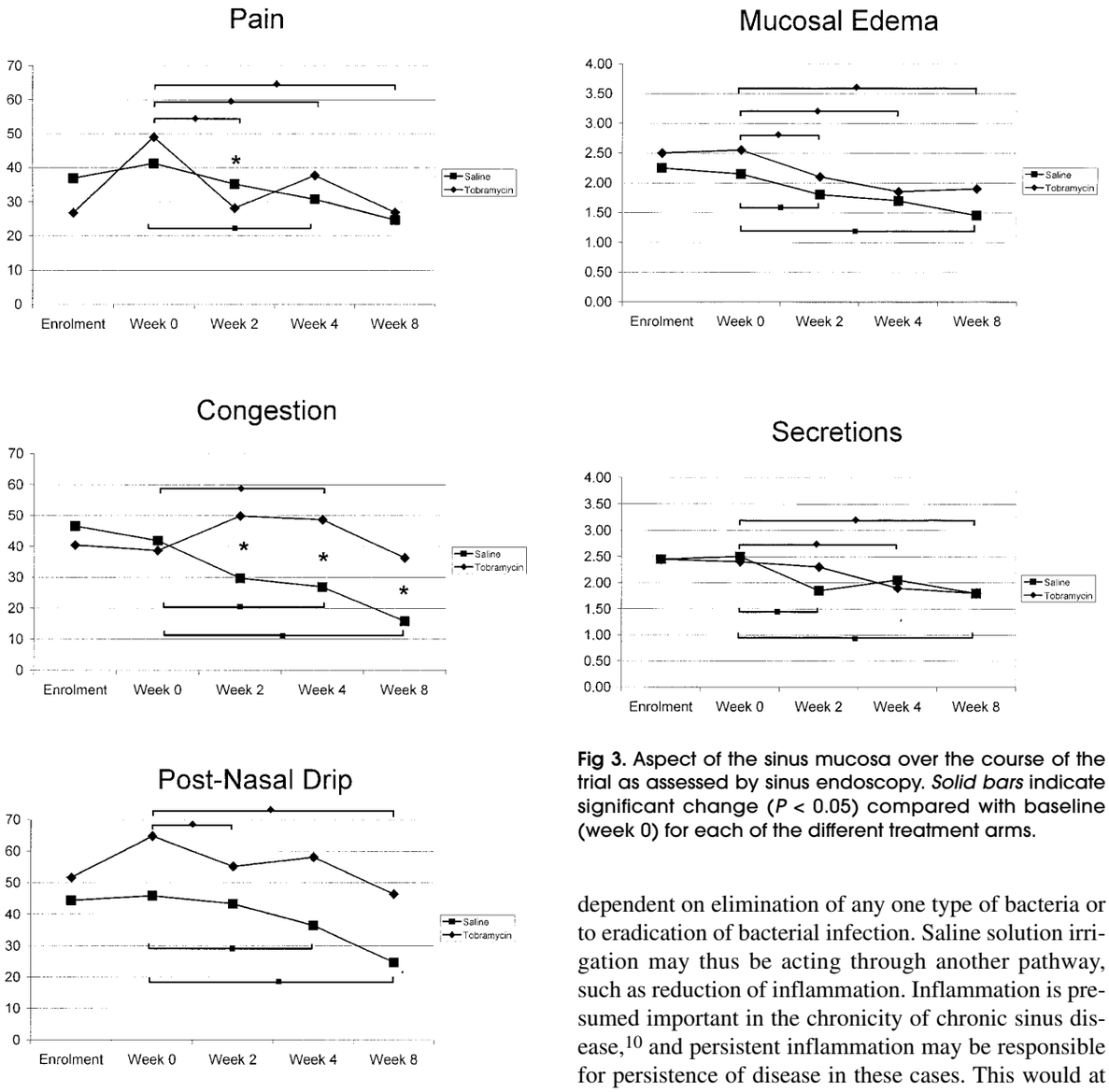

Fig 2. Symptoms over the course of the trial as assessed by visual analog scale. *Solid bars* indicate significant change ($P < 0.05$) compared with baseline (week 0) for each of the different treatment arms. *Asterisks* indicate significant difference ($P < 0.05$) in response between the two treatments.

Fig 3. Aspect of the sinus mucosa over the course of the trial as assessed by sinus endoscopy. *Solid bars* indicate significant change ($P < 0.05$) compared with baseline (week 0) for each of the different treatment arms.

cessation, with maximal results attained after 8 weeks. The principal differences between the two treatments were an increase in nasal congestion with tobramycin-saline solution.

This article reaffirms the conventional wisdom of the practice of sinus irrigation with saline solution alone. The mechanism by which this treatment exerts its beneficial effect is unknown, but does not appear to be dependent on elimination of any one type of bacteria or to eradication of bacterial infection. Saline solution irrigation may thus be acting through another pathway, such as reduction of inflammation. Inflammation is presumed important in the chronicity of chronic sinus disease,[10] and persistent inflammation may be responsible for persistence of disease in these cases. This would at least partially explain the lack of effectiveness of antibiotics as monotherapy for the treatment of these patients and underline the importance of developing adjunct treatment modalities. In these instances, the actions of saline solution lavage may be effected through a mechanical cleansing effect of the sinus surface, altering the composition of the mucus, or reducing local concentrations of bacteria or fungal organisms, their toxins, or proinflammatory substances released during inflammatory responses to these.

CONCLUSION

This preliminary study demonstrates that thrice-daily treatments of 4 mL of aerosolized saline solution delivered by means of a large-particle nebulizer for a 4-

week period is well-tolerated and improves parameters of QOL, symptomatology, and aspect of the sinonasal mucosa in patients with rhinosinusitis refractory to surgical and medical therapies. Addition of tobramycin 20/mg mL to the solution appears of minimal benefit and actually seems to increase nasal obstruction. The mechanism of this beneficial effect remains unexplained, but does not appear to depend on complete eradication of infectious agents. It may thus be due to a reduction of underlying inflammation.

Given the safety and effectiveness of this treatment, it may offer an interesting alternative for the management of patients with this increasingly important disorder. Further large-scale studies will be required to explore this.

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