The effect of topical vancomycin on the recurrent postoperative sinonasal polyposis: a triple-blinded randomized controlled trial

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Objective
To assess the effect of topical vancomycin on the prevention of recurrent sinonasal polyposis after functional endoscopic sinus surgical procedure.
Design, setting, and participants
A triple-blind, randomized clinical trial of patients aged 18–70 years with sinonasal polyposis whose nasal swab results were positive for *Staphylococcus aureus* and were candidates for functional endoscopic sinus surgical procedure at Besat Hospital, Hamadan University of Medical Sciences, from September 2014 to September 2015.
Interventions
Patients were randomly assigned to receive a solution of normal saline including 1 g/l vancomycin or a solution of normal saline alone (placebo). Patients were asked to irrigate their nose with 20 ml of the prepared solution three times a day for 8 weeks.
Main outcomes and measure
The recurrent polyposis and reinfection with *S. aureus* at 2, 4, and 6 months after sinus surgery.

Results
Of 118 patients identified, 35 patients whose nasal swab results were positive for *S. aureus* remained for analysis, and of those, 18 patients were allocated to the placebo group and 17 to the vancomycin group. There was no statistically significant but clinically important difference in the severity of recurrent postoperative polyposis between the two groups. The recurrence rate of postoperative sinonasal polyposis was clinically different between the two groups, although the difference was not statistically significant. The proportion of reinfection with *S. aureus* in the second month after surgery was 11/18 (61.1%) in the control group versus 3/17 (17.6%) in the vancomycin group (P=0.015). No significant drug adverse effect was reported by the patients.
Conclusion and relevance
This trial indicated that topical vancomycin is a safe drug with no important adverse effects that may reduce the recurrent postoperative polyposis. However, more evidence based on large clinical trials is required to justify the efficacy of topical vancomycin for preventing postoperative polyposis.

Keywords:
clinical trial, endoscopic surgery, nasal polyps, vancomycin

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Introduction

Chronic sinonasal polyposis is a serious health problem. It is estimated that ~10% of patients, who underwent specific features on screening sinus computed tomography, were identified to have sinonasal polyposis [1]. This problem is associated with a number of complications such as chronic nasal inflammation, obstruction, and polyposis [2]. Several possible mechanisms have been proposed for pathogenesis of nasal polyps. One well-known mechanism is that *Staphylococcus aureus* secretes exotoxins in the nose that may act as superantigens. The local nasal immunoglobulin E, which is stimulated against these exotoxins, may create a local allergic inflammation in the nose. These immunologic mechanisms may result in the inflammatory process and polyposis [3,4].

S. aureus is one of the most common bacteria isolated from nasal mucosa. It has been isolated in more than 75% of patients with sinonasal polyposis compared with 25% in the general population [4]. *S. aureus* is suspected to play a key role in the pathogenesis of polyposis [5].

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Previous studies indicated that intraoperative antibiotic irrigations can significantly reduce the amount of *S. aureus* detected postoperatively [6]. Because of the possible adverse effects of long-term use of systemic antibiotics and restrictions on the effective dose in the target organ, systemic antibiotics have no prominent role in the management of chronic sinonasal infections. On the contrary, among many different treatment options for chronic sinonasal infections, topical antimicrobial agents are preferable because of the localized delivery of antibiotics to the sinonasal mucosa and the minimized systemic adverse effects [7]. This approach is particularly important in the treatment of biofilms, where higher concentrations of antibiotics are usually required. However, there is insufficient evidence to ensure that topical antibiotics have a clear benefit in patients with chronic sinonasal [8]. Furthermore, evidence based on different setting is required to support the beneficial effect of using antibiotic in the management of chronic sinonasal. This randomized controlled trial was conducted to assess the effect of topical vancomycin on recurrent rhinosinusal polyposis after functional endoscopic sinus surgical procedure.

Materials and methods

We conducted this triple-blind randomized controlled trial in Besat Hospital, affiliated with Hamadan University of Medical Sciences, in the west of Iran, from September 2014 to September 2015. We received written informed consent from all patients. The ethics committee of the university approved the protocol. The protocol was registered with the Iranian Registry of Clinical Trials on August 16, 2014 (IRCT201312299014N20).

Based on a clinical trial conducted by Wynn *et al.* [9], the probability of recurrent polyposis after endoscopic sinus surgery was estimated at ~60%. Assuming that using vancomycin reduces the recurrent polyposis to ~20%, we arrived at a sample size of 18 for each group and a total sample size of 36, with 95% significance level and 90% statistical power.

The study population included patients aged 18–70 years with sinonasal polyposis whose nasal swab results were positive for *S. aureus* and were candidates for functional endoscopic sinus surgery. Patients with any of the following characteristics were excluded from the study: (a) known systemic diseases such as diabetes, chronic renal failure, malignancy, cystic fibrosis, or granulomatosis disease; (b) immunodeficiency; or (c) pregnancy.

We randomly assigned the eligible patients into two groups using the balance block randomization method. For this purpose, we prepared four sheets of paper, writing on two sheets 'V' for 'vancomycin' and on two 'P' for 'placebo'. We pooled the paper sheets and placed them in a container and drew randomly one at a time for each patient without replacement until all four sheets were drawn. Then, we placed back the four paper sheets into the container, and we repeated this action until the sample size was reached.

We remained the allocations blinded during the study. For this purpose, one of our colleagues, who was the coordinator of the trial group (J.Y.), conducted the random allocation, so that neither the patients nor the surgeon, who evaluated the effect of treatment, were aware of the administered drugs. In addition, the statistical analyst was unaware of the trial groups until the data were analyzed and the labels were decoded.

Before surgery, we performed axial and coronal computed tomography scans of the paranasal sinuses as well as nasal endoscopy for all patients. We measured the size of the polyp by endoscopic evaluation using the Lund Kennedy criteria on a scale of 0–2 for each side of the nose, and a total score of 4 for both sides. Zero denoted no polyp was seen on endoscopy; 1, denoted the polyp was limited to the middle meatus; and 2, denoted the polyp spread into the nasal cavity.

During the surgical procedure, we obtained a sterile nasal swab from the opening of the maxillary sinus for all patients. Samples were submitted to the laboratory by transport medium and were cultured on blood agar. The coagulase-positive and catalase-positive colonies more than 5000 were considered positive. The two groups received loratadine 10 mg daily for 14 days and fluticasone spray two puffs a day for 14 days. Starting 48 h after the surgical procedure (when the results of *S. aureus* cultures were evident), the patients whose nasal swab results were positive for *S. aureus* were randomly assigned to the intervention and control groups. The intervention group received a solution of normal saline included 1 g/l vancomycin, and the placebo group received a solution of normal saline alone (placebo). The patients were asked to irrigate their nose with 20 ml of the prepared solutions three times a day for 8 weeks. The coordinator of the trial group prepared and labeled solutions in similar containers.

The primary outcome of interest was recurrent polyposis based on nasal endoscopy at the baseline and in the second, fourth, and sixth month after

surgery. The score of polyp equal to or greater than one was considered a case of recurrent polyposis. The secondary outcome of interest was reinfection with *S. aureus* which was examined by nasal swabs in the second month after surgery. Another secondary outcome of interest was possible drug adverse effects such as nasal dryness or sensitivity, which were evaluated with history taking at each visit.

The independent *t*-test was used for analysis of continuous variables and the Fisher exact test for nominal variables. All statistical analyses were performed at a significance level of 0.05 using Stata software, version 11 (StataCorp., College Station, Texas, USA).

Results

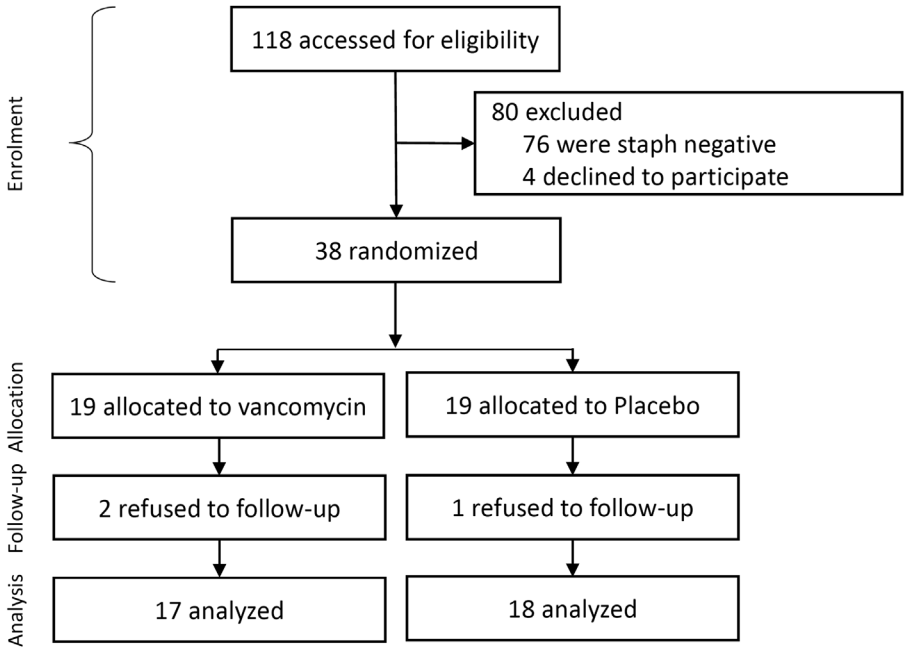
Of 118 patients identified, 76 were ineligible because their nasal swab specimen results for *S. aureus* were negative and four declined to participate. The randomization was based on the remaining 38 patients, of whom 19 patients were allocated to the placebo group and 19 to the vancomycin group. Moreover, three patients declined follow-up, including one patients in the placebo group and two patients in the vancomycin group. The analysis was based on data from the remaining 35 (29 men and six women) patients including 18 in the placebo group and 17 in the vancomycin group (Fig. 1). The mean (SD) age of the patients was 42.20 (10.92) years in the control group and 40.82 (11.97) years in the vancomycin group (P=0.690). The male : female ratio was 15 : 3 in the control group and 14 : 3 in the vancomycin group (P=0.939).

The effect of topical vancomycin versus placebo on the size of recurrent postoperative polyposis, based on the endoscopic evaluation, is shown in Table 1. There are no statistically significant, but clinically important, differences between the two group at baseline and during the follow-up after surgery. The distribution of the grade of polyps at baseline was relatively

Table 1 The effect of topical vancomycin versus placebo on the size of recurrent postoperative polyposis based on endoscopic evaluation

Grade of polyp	Placebo (n=18)	Vancomycin (n=17)	P value
At baseline			0.908
II	4	4	
III	7	8	
IV	7	5	
Second month			0.229
I	15	17	
II	3	0	
Fourth month			0.123
I	13	15	
II	1	2	
III	4	0	
Sixth month			0.051
I	11	15	
II	1	2	
III	4	0	
IV	2	0	

Figure 1



Flowchart of progress through the trial.

homogenous between the two groups. However, 2 months after surgery, three patients in the placebo group, but no patient in the vancomycin group, had polyps of score 2. After 4 months, four patients in the placebo group, but no patients in the vancomycin group, had polyps of score 3. After 6 months, four patients in the placebo group had polyps of score 3 and two had polyps of score 4, whereas, no patients in the vancomycin group had any polyps of score 3 or 4.

The recurrence rate of postoperative sinonasal polyposis in the vancomycin and placebo groups is given in Table 2. There is clinically important difference in the recurrence rate of polyposis between the two groups, although the difference is not statistically significant. The recurrence rate of polyposis in the placebo group was 3/18 in the second month, 5/18 in the fourth month, and 7/18 in the sixth month after surgery, whereas the recurrence rate of polyposis in the vancomycin group was zero in the second month and 2/17 in the fourth and 6 months after surgery.

The proportion of nasal swab results that were positive for *S. aureus* in the second month after surgery was 11/18 (61.1%) in the control group and 3/17 (17.6%) in the intervention group (P=0.015). No significant drug adverse effect was reported by the patients.

Discussion

S. aureus is a common bacteria isolated from nasal mucosa. The exotoxins that are secreted by this bacteria can trigger the inflammatory process and hence polyposis [3,4]. Several treatments have been suggested for management of sinonasal infections including nasal steroids and local and systemic oral antimicrobial therapies [10–15]. Although oral and intravenous antimicrobial therapies are prescribed traditionally to manage sinonasal infections, topical administration of these agents has become more popular in recent years, because topical administration can localize the antibiotic delivery to the sinonasal mucosa and minimize the possibility of the systemic adverse effects. This method of treatment is particularly important in the treatment of biofilms, where higher concentrations of antibacterial agent are usually required [6,7]. Nonetheless, there is no sufficient evidence to support the effectiveness of using topical antibiotics in the prevention of recurrent postoperative polyposis [8]. However, a few clinical trials have addressed the effect of topical antimicrobial agents on chronic sinonasal and polyposis as follows.

Bonfils *et al.* [16] conducted a multicenter double-blind randomized clinical trial to explore the effect of tobramycin aerosol versus isotonic saline aerosol on bacteriological eradication in patients with nasal polyposis. They allocated 32 patients to tobramycin group and 23 to isotonic saline group. They concluded that tobramycin aerosol had eradicated bacterial infection better than isotonic saline. Hatton *et al.* [17] invented a calcium mupirocin nonaqueous nasal spray that may be used to treat recurrent acute bacterial sinusitis. It has been shown that mupirocin is effective in reducing the incidence of recurrent paranasal sinusitis when administered two puffs of spray twice daily over a 7-month period. Seiberling *et al.* [6] investigated the effect of intraoperative mupirocin irrigation on *S. aureus* within the maxillary sinus in 16 patients with symmetric maxillary chronic sinonasal. In each patient, they irrigated the right maxillary sinus with 240 ml of normal saline and the left one with 240 ml of normal saline mixed with 60 mg mupirocin. They found that mupirocin irrigations significantly reduced the amount of *S. aureus* within the maxillary sinus mucosa compared with normal saline alone.To date, no clinical trial has been conducted to address the effect of vancomycin on prevention of recurrent sinonasal polyposis. We found that the proportion of nasal swab results that were positive for *S. aureus* was significantly greater in the control group than in the intervention group (P=0.015). We also indicated that topical vancomycin had a clinical effect on the relative reduction of the recurrence of polyposis after endoscopic sinus surgery, although the results were not statistically significant. However, the main limitation of this study was the small sample size. We enrolled 118 patients who underwent endoscopic sinus surgery, but 76 patients were excluded from the study, because their nasal swab results were negative for *S. aureus*. This issue limited

Table 2 The recurrence rate of postoperative sinonasal polyposis in the vancomycin and placebo groups

Polyp relapse	Placebo (n=18)		Vancomycin (n=17)		P value (Fisher)
	Absent	Present	Absent	Present	
Second month	15	3	17	0	0.220
Fourth month	13	5	15	2	0.402
Sixth month	11	7	15	2	0.121

the number of eligible patients. Another limitation of this study was the short period of follow-up. We avoided giving topical vancomycin for a long time to prevent development of antibiotic resistance. Despite this limitation, we found a clinically important difference in the rate and severity of recurrent sinonasal polyposis in the vancomycin group versus the control group, although the difference was not statistically significant. Conduction of a similar study with a larger sample size is suggested.

Conclusion

This trial indicated that topical vancomycin is a safe drug with no important adverse effects that may reduce the recurrence of postoperative polyposis. However, the results of this trial are limited to a small group of patients and hence insufficient. More evidence based on large clinical trials is required to justify the efficacy of topical vancomycin for preventing recurrent postoperative polyposis.

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Conflicts of interest

There are no conflicts of interest.

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