

Original Article

Does amphotericin B nasal douching help prevent polyp recurrence following functional endoscopic sinus surgery?

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Abstract

BACKGROUND: Recurrence of nasal polyposis following surgical intervention is very common. Antifungal therapy has been an appealing alternative to reduce its recurrence and severity. Early studies showed definite positive response, but recent studies have raised doubts about its efficacy in treatment of polyposis.

METHODS: This prospective case-control clinical trial was conducted on 50 patients suffering from nasal polyposis in Isfahan university of medical sciences. All patients underwent functional endoscopic sinus surgery. CT scanning of paranasal sinuses was done preoperatively and 6 months postoperatively to stage the disease. Patients were assigned to two groups: amphotericin B group were instructed to irrigate the nasal cavity with a solution of amphotericin B, while the normal saline group used the physiologic normal saline for 6 months.

RESULTS: 68% of patients in Normal saline and 84% of cases in amphotericin B group reported history of allergies. In amphotericin B group, stage of the disease improved in 84% of patients and remained unchanged in the rest. In normal saline group, imaging stage improved in 22 patients and remained unchanged in 3. The two cohorts were compared for reduction in imaging stage and no significant difference was found between them.

CONCLUSIONS: This study showed no benefits for topical amphotericin B solution over normal saline. It might be better to retreat to the traditional normal saline nasal douching following functional endoscopic sinus surgery in the treatment of polyposis.

KEYWORDS: Nasal Polyp, Amphotericin B, Functional Endoscopic, Sinus Surgery.

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Nasal polyposis is an inflammatory disease of nasal cavity and paranasal sinuses affecting 1%- 4% of population.¹ Etiology of polyposis has not been widely understood, but chronic inflammation, allergy, asthma, cystic fibrosis, aspirin sensitivity and anatomical anomalies have all been studied.¹⁻⁵ Furthermore, positive family history and certain HLA types (DR7-DQA1, DR7-DQB1) have been proposed as predisposing factors leading to polyp formation.⁶ Its pathologic features consist of epithelial rupture and prolapsus of lamina propria accompanied by interstitial

edema and infiltration of inflammatory cells.² Rhinorrhea in these patients shows abundant numbers of eosinophils and neutrophils.^{2,3,5}

Among the possible etiologies, fungi have gained wide attention in recent years.^{1,2,4,5,7,8} It was believed that the only role of fungi in sinusitis was limited to fungal rhinosinusitis, but now it is known that almost every human being carries fungi in his/her sinonasal mucosa. Fungal particles act as antigens in mucosa of sensitized individuals, resulting in recruitment of inflammatory cells- namely eosinophils- and release of MBP (Major Basic Protein), which

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finally causes mucosal damage and superinfection by shifting other inflammatory cells into the location. It should be mentioned that the process is not an allergic reaction and is not mediated by IgE.²

Fungal elements have been identified in 82% of specimens of CRS patients undergoing FESS.^{1,2,8} In one study in Europe, this rate was as high as 96% of specimens.¹

Different modalities of treatment have been proposed and practiced for nasal polyposis, including prolonged antibiotics, systemic or topical steroids, intranasal steroid injection, outpatient polypectomy, topical capsaicin, topical furosmide, amphotericin B nasal irrigation, UV phototherapy, etc.² In cases unresponsive to medical therapy, surgical interventions are indicated, with the goal being removal of polyps and pathologic mucosa and opening of osteomeatal complex. Usually a combination of medical and surgical treatment is required to reduce recurrence rate. Recurrence following surgical intervention is very common, reaching 60% in some studies.⁹

With the discovery of the possible role of fungi in nasal polyposis, antifungal medical therapy has been an appealing and promising alternative in maintaining treatment following FESS to reduce recurrence and its severity in polyposis patients. Early studies showed definite positive response after administration of amphotericin B solution following FESS,^{5,7,8} some even suggesting a reduction in expression of genes which code cytokines and a lower level of IL5.¹⁰ Nevertheless, recent studies have raised doubts about the efficacy of topical antifungal regimen in treatment of polyposis.^{3,11} Looking back at the controversial results following intranasal administration of amphotericin B, the current study was designed and conducted to compare topical antifungal medical therapy with routine normal saline nasal douching in their effects against relapse of polyposis following FESS.

Methods

This is a prospective case-control clinical trial on patients suffering from sinonasal polyposis

disease, admitted to Al-zahra and Kashani hospitals in Isfahan University of Medical Sciences, Isfahan, between spring 2008 and summer 2009. Sampling was carried out by simple consecutive type method and assignment to case or control groups was simple randomly performed. Patients suffering from Aspirin sensitivity were omitted, as were patients with contraindications to corticosteroid or amphotericin B administration. Pregnant and lactating women were also excluded. The number of cases was calculated by the formula $n = (Z_1 + Z_2)^2 \times [P_1(1-p_1) + P_2(1-p_2)] / (P_1 - P_2)^2$. Every patient signed a written informed consent following thorough explanation of the study.

Fifty patients suffering from nasal polyposis entered the study and were assigned to two groups, each consisting of 25 patients: 1) amphotericin B group, 2) normal saline group. All pertinent data (e.g. age, sex, history of allergies, history of previous sinus surgeries) were recorded in a questionnaire designed for this study. CT Scanning of all patients' paranasal sinuses was done preoperatively by appropriate algorithms to stage the disease according to Lund-Mackay staging system (table 1).

Table 1. Lund-Mackay Staging system for sinonasal polyposis in regard to CT scan findings

Stage	Involvement
0	Normal, mucosal thickening less than 2 mm
I	Unilateral disease
II	Bilateral involvement, limited to ethmoid or maxillary sinus
III	Bilateral disease, involvement of frontal or sphenoid sinus
IV	Pansinusitis

The physician responsible for staging of pre- and postoperative CT scans was blinded to the patients' group and patients' pretreatment stage. All patients filled out subjective data in questionnaire and were treated by functional endoscopic sinus surgery by one of the first two authors. Postoperatively, all patients received ciprofloxacin tablets (500 mg daily for 2 weeks, Sobhan Co, Iran) and Beclomethason nasal spray (50 microgram each

puff, Apotex inc. Toronto, Canada) for 1 month. In the amphotericin B group, patients were instructed to irrigate the nasal cavity with a premade solution of 50 mg amphotericin B (Fungizone, Bristol-Myers Squibb, France) in 500 cc sterile water twice daily for 6 months. In the Normal saline group, patients used the physiologic normal saline for intranasal douching every 12 hours for 6 months.

Patients were followed in the first week postoperatively and then every month for 6 months. At the end of the treatment period, another CT Scan of paranasal sinuses was performed and the new stage of the disease was recorded. Also, patients filled out the subjective postoperative data in the data sheet.

Data were analyzed using chi square, Fisher exact, Mann Whitney and Wilcoxon signed ranks tests according to the different values.

Results

The study was carried out on 25 patients in amphotericin B group and 25 patients in normal saline group. Thirty five patients were male and 15 were female.

Mean age of the cohort was 40.2 ± 12.03 years (range: 17-64 years) in amphotericin B group and 40.1 ± 10.8 years (range: 23-64 years) in normal saline group. Independent t test failed to show any significant differences in mean age of the two groups ($p = 0.971$).

Focusing on history of allergies, 17 patients in normal saline group (68%) and 21 cases in amphotericin B group (84%) reported history of some kind of allergies. Chi square test did not show statistically significant discrepancy between the two groups in this regard ($p = 0.160$). Similarly, the two groups were compared for the history of previous sinus surgeries; 4 cases in normal saline group (16%) and 5 patients in amphotericin B group (20%) had history of previous sinonasal surgery which was statistically insignificant according to Fisher exact test ($p = 0.710$).

Preoperative and postoperative CT Scans of paranasal sinuses were staged according to Lund-Mackay staging system and data of each group were compared. Table 2 shows the fre-

quency distribution of different stage scores pre- and postoperatively in amphotericin B group. The same frequency distributions for normal saline group are depicted in table 3.

Table 2. Frequency distribution of each stage in amphotericin B group, pre- and postoperatively

Stage	% Preop (Number of cases)	% Postop (Number of cases)
0	0 (0)	24 (6)
I	8 (2)	44 (11)
II	8 (2)	16 (4)
III	24 (6)	4 (1)
IV	60 (15)	12 (3)

Table 3. Frequency distribution of each stage in Normal saline group, pre- and postoperatively

Stage	% Preop (Number of cases)	% Postop (Number of cases)
0	0 (0)	20 (5)
I	0 (0)	20 (5)
II	16 (4)	32 (8)
III	12 (3)	16 (4)
IV	72 (18)	12 (3)

In amphotericin B group, according to Wilcoxon signed ranks test, stage of the disease improved in 21 patients (84%), remained unchanged in 4 (16%) and a deterioration in CT Scan stage was not seen in any of the patients. This observation shows that disease stage has a statistically significant improvement following FESS and amphotericin B nasal douching ($p < 0.001$).

In normal saline group, according to Wilcoxon signed ranks test, imaging stage improved in 22 patients (88%), remained unchanged in 3 patients (12%) and a deterioration in CT Scan stage was noticed in no one. This means that FESS in combination with postoperative nasal saline douching results in a statistically significant improvement in CT scan staging ($p < 0.001$).

Finally, the two cohorts were compared using Mann-Whitney test for negative ranks (a reduction in imaging stage) and the test could not show a significant difference between the two groups ($p = 0.170$).

Discussion

The main aim of the current study was to compare the effect of amphotericin B solution and

Normal saline in preventing the recurrence of polyps in sinonasal tract following FESS.

Based on the results, amphotericin B solution was effective in reducing the stage score of patients on CT Scan after functional endoscopic removal of polyps. Similar results were achieved in the normal saline group and statistical analysis failed to show any significance in this regard. This means that although FESS and frequent irrigation of nasal cavity helps prevent recurrence of polyposis disease, no significant difference can be observed between Physiologic normal saline and amphotericin B solution in CT scan scores. The present study confirmed some of the previously done experiments in this field.

For example, in a study on 116 patients suffering from chronic rhinosinusitis (CRS) with polyps, patients were treated with amphotericin B solution for 3 months, but no objective improvement was observed compared to placebo group.¹¹ In another experiment, patients suffering from chronic rhinosinusitis (CRS) were treated by nasal irrigation of either amphotericin B or normal saline solutions for 8 weeks postoperatively. The study could not show any meaningful difference in improvement of signs and symptoms in the two subgroups.³

Not all researchers agree on the lack of effect of amphotericin B in polyposis. An early study on this dilemma was conducted by Ricchetti et al in 2002/2003 on 74 CRS with polyp patients, who were treated with amphotericin B and placebo for 4 weeks after FESS. The study concluded that amphotericin was more effective than placebo in reducing disease stage, documenting total resolution of polyps in 62% of mild and 42% of moderate polyposis cases.⁷ Two other studies by Ponikau et al in 2002 and 2005 supported the hypothesis of effectiveness of amphotericin B in reduction of polyposis. Interestingly, these studies documented a significant reduction in inflammation and thickness of sinonasal mucosa and eosinophilic inflammatory markers.^{8,12}

Previous studies, either supporting or denying the use of amphotericin B solution, had a drug administration period of 4 to maximally

12 weeks after endoscopic sinus surgery. This short time span could have masked the effectiveness of the drug. The present study was designed to omit this possible bias factor by expanding the drug administration duration to 24 weeks before a judgment on the drug effects was made.

Nonetheless, although amphotericin B solution was successful in reducing CT score of polyposis patients in combination to FESS, the present study was unable to show any benefits for this treatment regimen over normal saline. It should be remembered that the probable mechanism of effect for normal saline nasal irrigation is washing out the fungal fragments, depriving the mucosal immune system of the stimulus. In this mechanism, normal saline and amphotericin B solution act similarly.

Another possible explanation for conflicting results in different studies is that amphotericin B solution might have been more effective in patients suffering from CRS and polyposis, who had a background specific allergic reaction to fungi. This would mean that a subset of polyposis patients with allergies to fungi and concomitant high fungal load in sinonasal tract would actually benefit from this treatment. We were unable to assess the fungal load in sinonasal mucosa. This would be a challenge to be solved by further studies.

Keeping in mind the side effects of amphotericin B solution such as its high cost, difficult preparation, bothersome maintenance and minor discomfort during administration, it may be a better idea to retreat to the traditional normal saline nasal douching following FESS in the treatment of CRS with polyposis.

Conclusions

Although antifungal therapy is theoretically an interesting adjunct treatment in management of sinonasal polyposis, our study was unable to document an actual benefit to this regiment in comparison to routine normal saline nasal irrigation. Sticking to the time-tested physiologic saline nasal douching following endoscopic removal of polyps seems a logical and prudent choice for the time being.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

SMH and FM designed the study and introduced most of patients to the study. They also supervised the patients' surgeries and preparation of the manuscript. MK and HO assisted in performing the surgeries, supervised imaging studies and imaging reports, and prepared the manuscript. All authors have read and approved the content of the manuscript.

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