

Role of Amphotericin B in Nasal Irrigation for Chronic Rhinosinusitis with Nasal Polyps

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ABSTRACT

Objective: To determine the effect of topical antifungal irrigation fluid containing amphotericin B on nasal polyp and their recurrence pattern, and to study the association of serum IgE in predicting the presence of fungus along with the nasal polyps.

Study Design: An interventional study.

Place and Duration of Study: Dow University Hospital, Dow International Medical College, DUHS, Karachi, from June 2015 to June 2017.

Methodology: All adult patients having nasal polyps, who had not undergone any previous nasal surgery, were included in the study. Patients aged under 18 years, history of granulomatous diseases, immunosuppression, invasive fungal sinusitis, and pregnant ladies were excluded from the study. The ratio was kept as 1:2; one receiving irrigation with amphotericin B and the other only saline nasal irrigation without the medicine. After surgery, the patients were divided into two groups; 58 patients were in the placebo group and 29 in the amphotericin group. Serum IgE levels were documented before and one month postoperative treatment. Serum IgE level of more than 250 ng/ml was taken as a high value. All the patients were followed for six months. Recurrence was defined as the recurrence of nasal symptoms and recurrence of mucosal thickening based on repeat CT scan. Frequency tables and cross tabulations using Chi-square test were performed with p-values of 0.05 taken as significant were performed on different variables.

Results: A total of 87 patients were inducted. Overall 22 (25.3%) patients had recurrence of symptoms at six-month follow-up visit. Twelve (13.7%) of these were in the placebo group and 10 (11.5%) were in the amphotericin B nasal irrigation group. Serum IgE level preoperatively ranged between 52 - 9344 ng/dl; postoperatively it ranged from 13-1050 ng/dl. When pre and postoperative serum IgE level were compared with each other and CT scan scores, using Chi-square test, the difference was significant ($p < 0.001$).

Conclusion: Amphotericin B improved the CT scan score of the patients. The nasal irrigation of amphotericin B did not show significant change in the recurrence pattern of chronic sinuses with polyps. Serum IgE can be used as marker for the presence and response to treatment for non-invasive fungal sinusitis.

Key Words: Chronic rhino sinusitis, Nasal irrigation fluid, Amphotericin B, Antifungal treatment, Serum IgE level.

INTRODUCTION

Chronic rhinosinusitis (CRS) is a relatively common problem which can be approximately 15% in some studies.¹ The clinical picture is associated with inflammatory changes with or without polyps. It is associated in 96% of patients with fungus.² Allergic fungal sinusitis (AFS) is a known clinical entity. Here, fungus acts as a nidus for developing an intranasal allergic reaction leading to polyp formation. Since it is not invasive and the vascularity of polyp is also low, oral antifungal treatment is not recommended for intranasal fungus.³⁻⁵ Though it has been used in some studies to lower the need for oral corticosteroid therapy.¹ Saline irrigation has been used

and documented in studies to have better quality of life after treatment and lower rate of recurrence.^{1,6,7} Oral antifungal agents have shown efficacy in reducing the symptoms and recurrence rates,¹ but they are associated with systemic side effects. It is hypothesized that topical intranasal application of amphotericin B (AmB) can decrease the fungal load in the sinonasal region, thereby decreasing the local eosinophilic inflammatory reaction to fungal antigens seen in many CRS patients.^{8,9} Post-surgical recurrence rate is from 15% - 20%.^{10,11} Also considering that these patients will have to undergo Redo functional endoscopic sinus surgery (FESS), which not only adds to the cost of surgery but also the difficulty and greater risk of surgical complication to these patients.¹²

Various treatment strategies have been devised to reduce this recurrence rate further; such as systemic and topical nasal steroids, long term macrolide therapy.⁷ The focus of this study was on a novel noninvasive method of delivery of antifungal treatment to reduce the recurrence rates of nasal polyps. The rationale for using amphotericin B for nasal irrigation was that it is not at all absorbed through the gut mucosa when ingested orally

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Received: August 08, 2018; Revised: December 08, 2018;

Accepted: April 12, 2019

and very minimal absorption from the nasal mucosa, therefore there is no probability of it causing systemic side effects,⁹ and also give a wide range of antifungal local activity.

The objective of the study was to evaluate the response and recurrence pattern of nasal polyps to topical irrigation with amphotericin B, and determine the association of serum IgE in predicting the presence of fungus along with the nasal polyps.

METHODOLOGY

It was an interventional study which was conducted at Dow University Hospital, Dow International Medical College, DUHS, Karachi, from June 2015 to June 2017. Patients with age above 18 years of any gender who had allergic fungal sinusitis, chronic rhinosinusitis with nasal polyps, fungal ball, had not undergone any previous nasal surgery were included in the study. Pregnant ladies, age below 18 years, antrochoanal polyps, invasive fungal polyp, known drug allergy, other immunosuppressive therapy, those having sinonasal malignancies, granulomatous and vascular diseases and those who refused were also excluded from the study.

The sample size was estimated with Open Epi sample size calculator. It was used for the estimation of sample size taking confidence interval (CI) 95%, power 80%, reported mean airspace occluded by inflammatory mucosal thickening on CT scan. Ratio of sample size (group1/group 2) 1: 2, sample size came out to be 87 (29 amphotericin, 58 placebo). The ratio was kept as 1:2 due to lack of available funding. Institution Review Board (IRB) approval was taken before starting the study (IRB-594/DUHS/Approval/2015/57). Informed consent was taken from all participants. All the procedures were performed by a single surgeon.

The diagnosis of CRS used the criteria published by the American Academy of Otorhinolaryngology.^{13,14} In addition to CRS symptoms for >3 months, the patients demonstrated mucosal thickening on coronal CT scans in two or more sinuses and on nasal endoscopy. After recruitment in the study and all the patients had undergone surgical clearance of nasal polyps with FESS (sample for fungus culture was collected per- operatively), blinding was applied by the department postoperatively. They were randomised into two groups of patients; one receiving the medication and the other only saline nasal irrigation without the drug. The grouping was done with the help of closed envelopes suggesting group A (Placebo group) and group B (AmB group) in the ratio as decided according to sample size calculation, keeping a total of 87 envelopes. The medication was dispensed by the pharmacy department. The patient and surgeon were blinded as to which group patients belonged to. All patients were followed for six months. The data was recorded in a self developed performa. The blinding was

opened after the patient had completed six months of the study duration and results were calculated.

Pre-treatment and post-treatment CT scan of PNS was obtained for documentation and staging. The Lund Mackay CT scan scoring was used.¹⁵ Recurrence was defined as recurrence of nasal symptoms and demonstration of mucosal thickening or obliteration on repeat CT scan of PNS score (modified after Lund and Mackay).¹⁵ Each side was separately evaluated for opacification of maxillary, anterior and posterior ethmoidal, sphenoidal and frontal sinus. Score 0 was given to a sinus when it was not opacified; Score 1 when less than 1/3 sinus opacified; Score 2 when sinus was between 1/3 and 2/3 opacified; Score 3 = More than 2/3 opacified, but still air-containing; Score 4 when sinus was completely opacification (no air).

Serum IgE level was documented before and one month post-treatment. The serum IgE level of more than 250 ng/ml was taken as a high value. All the patients were followed for six months.

Nasal endoscopy was at the time of induction of study, one month after study and at six months after study and documented on a performa by principle investigator. After a week of the surgical clearance of nasal polyps with FESS, all patients with nasal polyps who were assigned to the AmB group, were asked to irrigate their nose with a saline preparation of amphotericin B in concentration of 1ml solution diluted in 1000 ml of distilled water (one per one thousand) twice a day for one month. The participants were instructed to keep the solutions in refrigerator compartment. Dispensed solutions were foiled to protect from light. A pre- and post-treatment CT scan PNS and a nasal endoscopy were done for documentation. They were followed for 6 months for any recurrence. All patients had undergone a surgical clearance of nasal polyps, their intraoperative specimens were sent for fungus culture. The placebo group received irrigation with 1 liter water to which 1 teaspoon table salt and ¼ teaspoon baking powder were added for daily irrigation of nose, the placebo was colored with a permissible yellow dye for the purpose of blinding. No difference in taste or smell was detected between the two preparations.

Data was entered on SPSS 16.0, frequency tables and cross tabulations with Chi-square tests were performed with p-values of 0.05, taken as significant, were performed on different variables. All relevant data were documented on a self-developed questionnaire.

RESULTS

The age of 87 patients ranged from 18 to 65 years, mean 36.53 ±13.21 years. Sixty-one (70%) were males and 26 (29.9%) were females in this study. Eleven (12.6%) had comorbid of diabetes mellitus and 17 (19.5%) had asthma. Other significant comparison is given in Tables I and II.

Table I: Biometric data of study participants n=87.

Comorbidities		
Diabetes	11	12.6%
Asthma	17	19.5%
Allergic to dust and smoke	9	10.3%
Fungus culture		
Positive	26	29.9%
Negative	61	70.1%
Peroperative fungus (as seen during surgery)		
Yes	37	42.5%
No	50	57.5%
Double density sign on CT scan		
Yes	25	28.7%
No	62	71.3%

Table II: Comparison between amphotericin B nasal irrigation and placebo groups n = 87.

Particular	Amphotericin B nasal irrigation group n=29	Placebo group n=58	p-value
Peroperative fungus (During FESS surgery)			
Yes	14 (16%)	25 (28.7%)	0.647
No	15 (17.2%)	33 (37.9%)	
Fungus culture (positive)			
Yes	10 (11.4%)	16 (18.3%)	0.508
No	19 (21.8%)	42 (48.2%)	
Double density sign on CT scan I (positive) preoperative			
Yes	11 (12.6%)	14 (16.9%)	0.180
No	18 (20.6%)	44 (50.5%)	
Double density sign on CT scan II after (6 months)			
Yes	1 (1.3%)	1 (1.3%)	0.613
No	28 (32.1%)	57 (65.5%)	
Recurrence after six months			
Yes	10 (11.4%)	12 (13.7%)	0.163
No	19 (21.8%)	46 (52.8%)	

The mean total preoperative CT score according to Lund Mackay was 29.4 SD \pm 10.25. Twenty-five (28.7%) patients also had thick pus within the sinuses during the surgical exploration. Histopathology of all the patients came out to be allergic nasal polyp. Twenty-six patients (29.9%) had a positive culture for fungus; however, the double density sign was positive for 25 (28.7%) patients and 39 (44.8%) patients had fungus during surgical exploration of sinuses. CT scan scores were compared with the pre- and postoperative (after six months) double density signs. The p-value were 0.009 and 0.552, respectively.

After the surgery, the patients were divided into two groups; Group A: 29 in the AmB group and Group B: 58 patients were in the placebo group. All patients were operated by a single surgeon. The second visit was recorded at one month postoperatively. All patients were symptom-free in the second visit one month after surgery. Twenty-two (25.3%) patients had recurrence of symptoms at six-month follow-up visit. The repeat nasal endoscopy

and CT scan were done. The postoperative CT scan score range was 8-36; the average score of CT scan was 16.5. There was one patient who had a hypersensitivity reaction to AmB irrigation resulting in acute exacerbation of asthma and irrigation had to be stopped for this patient.

Out of 87 patients, 22 patients (25.3%) had a recurrence of disease. Twelve (13.7%) of these were in the placebo group and 10 (11.5%) were in the AmB nasal irrigation group. The variables were compared and the results are shown in Table II.

Out of the total 87, thirty patients did not get a serum IgE level. The serum IgE level preoperatively ranged between 52 - 9344 ng/dl, the p-value was 0.163; postoperatively, the range was from 13-1050 ng/dl, the p-value was 0.092. The serum IgE level were compared with CT scan scores using Chi-square test, the p-value was <0.001, which is significant. The serum IgE score gives us a screening tool for the presence of fungus in the sinuses and response to treatment as well when compared with the pre- and postoperative levels. The CT scan score also was found high in patients having high serum IgE level.

DISCUSSION

The age of the patient group was similar to the international literature.⁷ According to Ahmedine, males were 60.3% more affected with polyps in their study population of 297.⁷ In this study, there were 70% males affected by nasal polyps, which is a little higher as compared to literature.^{16,17}

The comorbidity of asthma was higher in this population (19%); which is similar to the study conducted by Ahmedin 10.4%,⁷ and was lower than 43% as lower from reported by Hashemain *et al.*⁸ Another study from France reported the association of asthma as 45%, which is higher as compared to this study.⁹

Serum IgE is an important biological marker for presence of atopy. All 26 patients, having a positive fungal culture, were also the ones having a high serum IgE more than 250 ng/ml. The postoperative serum IgE was much lower from the preoperative serum with a p-value of <0.001. Kim *et al.* reported that patients with nasal polyps had higher IgE level.¹⁸ Some authors propose that the nasal polyp may be forming IgE on their own as well.¹⁹ Serum IgE can, therefore, be used as a serological marker for presence of fungus in the sinus and for the recurrence of fungus as well.^{17,18}

Forty-two percent of sample of 50 were positive for fungus, a study conducted by Razampa.²⁰ In this study, 29% samples were positive for fungus though 39 (44.8%) patients had gross fungal balls removed from sinuses; of these, 25 (28.7%) belonged to the placebo group and 14 (16%) to amphotericin B nasal irrigation group. The lower capture of surgery culture results may be a result of the culturing techniques used by the Hospital

laboratory. PoniKare were able to culture fungus in 96% of a sample of 210 CRS patients with their sampling techniques.² It has been reported that 64% healthy subject and 34% of allergic rhinitis patients may have colonisation from *aspergillus* species.²¹

The recurrence rate of chronic rhinosinusitis after FESS surgery has been quoted as 13.4% in a study conducted in 179 patients and followed for at least six months.²² It can be as high as 40%.²³ Most studies reported a 15-20% recurrence rate.¹⁸ The present recurrence rate was 25.3%; patients in the placebo group had a higher recurrence rate 12 (13.7%) as compared to amphotericin B nasal irrigation group 10 (11.5%).

Therefore, it can be inferred that the patients in the AmB group had a slightly lower recurrence rate. All those who had the recurrence had positive fungus cultures. There was only one related side effect in which the patient had developed acute exacerbation of asthma, which means that amphotericin B nasal irrigation is overall well tolerated for the purpose of nasal irrigation.

The total CT scan scores mean 29.4 \pm 10.25 reduced after 6 months to 4.86 \pm 9.6, which was a marked change; however, it did not reach statistical significance.

A larger and multi-centre trial can further improve the result. A special applicator needs to be developed for patient comfort while applying amphotericin B nasal irrigation. Increasing the strength of the Am B irrigation may decrease the recurrence rate of the polyps.

CONCLUSION

Amphotericin B improved the CT scan score of the patients. The nasal irrigation of amphotericin B does not seem to have any significant impact on reducing the chances of recurrence of nasal polyps. Serum IgE and CT scan scoring can be used as markers for the presence and response to treatment of fungal infection in para nasal sinuses.

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