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Original Research Article

Efficacy of Topical Therapy with 200µg/mL Amphotericin B Solution After Functional Endoscopic Sinus Surgery in Patients of Allergic Fungal Rhinosinusitis

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Conflict of interest: Nil

Abstract:

Aim: Most of the previous studies with topical amphotericin B (AmB) have been done in chronic rhinosinusitis (CRS) patients with controversial results and studies targeting the discrete subgroup of allergic fungal rhinosinusitis (AFRS) are lacking. The purpose of the present study has been to evaluate and compare the efficacies of intranasal lavage by 200µg/mL AmB solution versus normal saline in AFRS patients after functional endoscopic sinus surgery (FESS).

Materials and Methods: Sixty adult AFRS patients were divided postoperatively into two groups for intranasal lavage: group A with normal saline (control) and group B with 200µg/mL AmB solution (intervention). Symptom and nasal endoscopy scores were calculated and assessed in both the groups preoperatively, at 2 weeks, 1 month and 3 months follow-up along with recurrence post-surgery.

Results: In group A, there were marked improvement in the mean symptom and nasal endoscopy scores at 2 weeks follow-up from the preoperative scores. Symptom scores deteriorated slightly at 1 and at 3 months follow-up while nasal endoscopy scores improved at 1 month and further at the end of 3 months. Similarly, group B showed significant improvement in the both the symptom and nasal endoscopy scores at 2 weeks. Mean symptom score deteriorated at 1 and 3 months follow-up while mean nasal endoscopy score improved at 1 month but deteriorated at 3 months follow-up. The intergroup differences were not significant. In group A, 46.66% patients had recurrence whereas in Group B, 70.0% had recurrence.

Conclusion: We concluded that although there was a definite improvement in both the groups after 3 months, post-FESS intranasal lavage with 200µg/mL of AmB, a higher dose than conventionally used, did not confer a greater benefit as compared to normal saline irrigation.

Clinical Significance: Efficacy of post operative topical AmB therapy, even in higher concentration, is no better than that with normal saline when studied exclusively in patients of AFRS.

Keywords: Rhinosinusitis, Antifungal Agents, Amphotericin B, Fungi, Sodium Chloride Solution, Nasal Lavage.

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Introduction

A fungus mediated process is one of the primary causes of CRS (chronic rhinosinusitis), with or without polyps, in which fungal colonization is followed by an allergic or immunological reaction by the host. Role of fungi in CRS persists as an important subject of study and active debate. [1,2]

Currently fungal rhinosinusitis (FRS) is classified into the non-invasive and invasive types. Invasive FRS includes acute necrotizing invasive (fulminant) FRS, granulomatous indolent FRS and chronic invasive FRS. Non-Invasive FRS includes localised fungal colonization, sinus fungal ball (mycetoma) and eosinophilic related FRS. Latter include allergic fungal rhinosinusitis (AFRS), eosinophilic fungal rhinosinusitis and eosinophilic mucin rhinosinusitis. [3,4,5]

AFRS is a unique non–invasive fungal process increasingly recognised as a primary Th2 mediated subtype of CRSwNP (CRS with nasal polyposis) representing an allergic or hypersensitivity response to the presence of extra-mucosal fungi within the sinonasal cavity. The overall incidence is estimated to be 6-9% of FRS. [5] It is common in subtropical

and tropical countries like India, that are hot and humid favoring the environmental fungi to thrive. Clinically, patients are typically immunocompetent young adults, males more than females, with a mean age of presentation in the third decade. According to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020, the diagnosis is made by taking into consideration the Bent and Kuhn criteria with presence of polypoidal sinonasal disease, the identification of 'allergic mucin' (thick, mucinous peanut butter or cottage cheese like material containing laminated mucin, eosinophils, Charcot-Leyden crystals and fungal hyphae) and the absence of invasive fungal disease. [5,6,7]

AFRS causes significant physical symptoms, negatively affecting quality of life (QOL) and can substantially impair daily functions. [2] Therefore, effective rhinosinusitis-specific health QOL instruments are needed to help evaluate the effect of various treatments on patient status. The Sino-Nasal Outcome Test-22 (SNOT-22) asks the patients to rate the severity of their symptoms and the social/emotional consequences attributable to rhinosinusitis. A higher SNOT-22 score indicates worse health related QOL and functional status. [8]

The treatment for AFRS, whether medical or surgical, is still controversial in literature and aimed at decreasing the inflammation and obstruction in the sinonasal pathway. Technological advances and poor response to conservative management have made functional endoscopic sinus surgery (FESS) as the primary therapy for AFRS. Meticulous and complete FESS is the treatment of choice in extensive disease. It aims to re-establish ventilation and mucociliary clearance of sinuses by limited resection of inflammatory or anatomical defects responsible for local persistent inflammation. [7,9]

Medical therapy is used for limited disease and as an adjunct to surgery in extensive disease. Topical corticosteroids are used as standard treatment for AFRS patients especially postoperatively, with oral steroids useful perioperatively and oral antifungals being an option in recalcitrant AFRS.There is high propensity for recurrence in AFRS, ranging from 10-100% and hence, the need for further research avenues to control the disease. [6,9]

The fungus in AFRS is extramucosal in location. Decreasing the fungal load is one of the treatment options available. Systemic therapy with antifungal agents such as AmB is fraught with difficulties in view of systemic side effects requiring stringent monitoring of the patients. Also, its efficacy in AFRS is controversial due to the extramucosal non-invasive nature of the fungus. It is hypothesized that the use topical AmB applied intranasally in patients with AFRS has multiple mechanisms of action and may prove to be an adjunct to standard therapy. It is a broad-spectrum polyene antifungal obtained from the culture medium of streptomyces and binds to ergosterol and increases the fungal cell membrane permeability leading to fungal cell death. Also, it has a direct effect on the integrity of the cell membrane of the polyp's epithelium due to its ability to bind with the cell membrane cholesterol. Thus, the disappearance of polyps could be due to reduction in antigenic load and/or a direct effect resulting in reduced inflammatory response. The theory behind the eosinophilic and fungal etiology of AFRS advocates the use of an antifungal compound like AmB for intranasal lavage. [10,11,12,13]

However, limited information with controversial results is available on the role of topical antifungals like AmB in treatment of CRS and studies proving the role of topical antifungals in its specific and discrete subgroup of AFRS are lacking. [6,14]

The purpose of the present study has been to evaluate the efficacy of post-FESS intranasal lavage by AmB solution in a concentration higher than conventionally used versus normal saline in patients of AFRS.

Our aim was to study pre and postoperative correlation in symptom and endoscopy scores of the patients of both the groups along with effect on their QOL and rates of recurrence of the disease.

Materials and Methods

We conducted a randomized prospective study in our centre over a period of two years from 2024 to 2025. Sixty adult patients (18-60 years age group) of clinically, radiologically and histopathologically diagnosed AFRS were included in the study. Patients who were less than 18 years of age, noncompliant, pregnant/ lactating females, immunocompromised, suffering with acute infective illnesses/ comorbidities/ invasive FRS / orbital or CNS complications of FRS or taking oral antibiotics /antifungals / steroids in last one week before enrolment, were excluded from the study.

Each patient completed the SNOT-22 questionnaire at the preoperative visit. The patients were asked to score a list of 22 symptoms along with social and emotional consequences. Severity of symptoms was graded according to visual analogue scale (VAS). Besides full otorhinolaryngological examination, all patients underwent diagnostic nasal endoscopy (DNE). Findings of DNE were scored according to Lanza and Kennedy. [3] Parameters graded were as follows:

Nasal polyps: 0- absence of polyps, 1- polyps within the middle meatus, 2- polyps beyond middle meatus.

Oedema, scarring and crusting: 0- absent, 1- mild, 2- severe.

Discharge: 0- present, 2- thick, purulent discharge

Scores from each side were added to determine the overall endoscopy score.

Routine blood investigations including absolute eosinophil count (AEC) and serum total IgE levels were done and comorbidities ruled out.

Non-contrast computed tomographic (NCCT) scan of nose and paranasal sinuses with orbital cuts was done for each patient after 6 weeks of preoperative medical treatment with intranasal topical steroid. Preoperative endoscopic biopsies from all patients were sent for histopathology. After completing two weeks of low dose oral prednisolone course and remaining steroid free for next one week, all patients were subjected to FESS under general anesthesia. Intraoperatively, specimens were collected for laboratory detection of allergic mucin, identification of fungal hyphae and histopathological examination of nasal polyps.

Post-FESS, each patient was prescribed analgesics and antibiotics for 7 days. The nasal pack was removed on the either third or fifth postoperative day. There was equal and random division of patients into two groups for intranasal lavage to be done twice daily for 12 weeks.

Group A (n=30): Each intranasal lavage with 20ml of normal saline (control).

Group B (n=30): Each intranasal lavage with 20ml of 200µg/mL AmB solution (intervention).

AmB solution was prepared by adding 100 mg in 500ml of distilled water to achieve a concentration of 200 µg/mL and storing in light rejection bottles. Fresh solutions were prepared every 2 weeks. During the study period, no concomitant therapy was given.

None of the patients had any significant local or systemic side effects to the lavage except two, who complained mild burning sensation post amphotericin lavage.

Serial postoperative nasal endoscopies were carried out in all patients to remove any granulations, crusts, synechae and debris. The patency of the ostium was confirmed, and the sinus mucosa was examined for remnant or recurrent disease on each follow-up visit.

Postoperative SNOT-22 scores and nasal endoscopy scores were calculated in both the groups after 2 weeks (almost at the start of lavage), 1 month and 3 months (at the completion of lavage) of surgery.

The study was carried out in accordance with the ethical standards of institutional research committee and with the 1964 'Declaration of Helsinki' and its later amendments.

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 23.0. Descriptive statistics was calculated to find range, percentage, mean, median, standard deviation, and percentage improvement. Paired Student's t-test was used to compare pre- and post- operative values of SNOT-22 and nasal endoscopy for both the groups separately. Unpaired Student's t-test was used to compare pre- and 3 months post-operative values of SNOT-22 and nasal endoscopy between the groups. Pearson's correlation was used to find the strength of association between SNOT-22 and nasal endoscopy at 3 months for each group separately.

Results

The average age at the time of presentation was 31.45 years with range of 15-60 years.

The study included 23 males and 37 females, the male to female ratio being 1:1.5. None of the cases had history of previous surgical intervention.

Nasal obstruction, thick nasal discharge, postnasal discharge, need to blow nose and sneezing were present in all the 60 patients (100% cases).

The SNOT-22 symptom scores of all these 60 patients were added together and averages obtained.

Mean Preoperative SNOT-22 score of all these patients was 26.57±8.080 with a range of 11-43 (Table-1).

Anterior rhinoscopy had revealed in all cases presence of pinkish or greyish white polypoidal mass in either of the nasal cavities, which was insensitive to probing, did not bleed and was free from septum. It also revealed presence of edematous mucosa or thick purulent nasal discharge. Posterior rhinoscopic examination showed in some cases, pale fleshy polypoidal mass obstructing the choana either unilaterally or bilaterally along with presence of postnasal discharge.

Routine blood investigations were normal. Raised AEC was present in 46 (76.66%) cases.

S. Total IgE values were elevated in 49 (81.66%) cases, values ranging from 835 U/mL to 1590 U/mL. NCCT scans showed characteristic heterogeneity of signals in the involved sinuses (the 'starry-sky', 'ground-glass', 'serpiginous' patterns or 'double-density' sign) best appreciated in the soft tissue cut sections. All the 60 patients (100% cases) showed partial or complete opacification of anterior ethmoids, maxillary sinus and osteomeatal complex blockage. Posterior ethmoids were involved in 52 (86.66%) patients. Sphenoid sinus was involved in 23 (38.33%) cases and frontal sinus in 36 (60%) cases.

Anatomical variants were present in 17 patients; deviated nasal septum in 9, concha bullosa in 6, Haller cell in 1 and Onodi cell in another patient.

Preoperative mean diagnostic endoscopy score for all 60 patients was 7.98 ± 1.609 with a range of 5-10.

Microbiological examination of polyps and fungal debris revealed septate hyphae on potassium hydroxide mount, aspergillus flavus species on cultures and allergic mucin in all 60 patients. Histopathological examination showed fungal elements with inflammatory polyps.

Results After Fess and Intranasal Lavage

Postoperative Snot-22 Symptom Scores: Mean postoperative SNOT -22 scores at 2 weeks, 1 month and 3 month follow-up for both groups with range and the percentage improvement from preoperative value are shown in table-2.

Nasal Endoscopy Results: Pre and postoperative nasal endoscopy scores have been compared and depicted in table-3

In group A, there was marked improvement in the mean symptom and nasal endoscopy score at 2 weeks follow-up from the preoperative scores. Symptom scores deteriorated slightly at 1 and at 3 months follow-up while nasal endoscopy scores improved at 1 month and further at the end of 3 months. Similarly, group B showed significant improvement in the both the symptom and nasal endoscopy scores at 2 weeks. Mean symptom score deteriorated at 1 and 3 months follow-up while mean nasal endoscopy score improved at 1 month but deteriorated at 3 months follow-up. The intergroup differences were not significant.

Patients with recurrence presented back mostly after 3-6 months of surgery. A total of 35 out of 60 cases (58.33%) showed recurrence or persistence of disease, i.e., AFRS symptoms and/or presence of allergic mucin and polypoidal mucosa. Patients showing recurrence had individual total SNOT-22 score above 10 except for two patients who had a score of 8. Most patients also showed increased scoring on nasal endoscopy.

In group A, 14 out of 30 patients (46.66%) had recurrence whereas in Group B, 21 out of 30 (70.0%) had recurrence.

After 3 months of initial postoperative follow up, these patients having recurrence were put on medical treatment (low dose oral steroid and steroid nasal sprays) for a minimum period of 2 weeks or till symptom free.

Kupferberg's endoscopic staging system was used for assessment of recurrence.[3] Revision surgery was required for 6 out of 14 patients in group A and 10 out of 21 in group B who were found to be in stage III of Kupferberg's endoscopic assessment after 6 months of initial surgery. Patients in earlier stages improved on medical management.

Table 1: Preoperative SNOT-22 symptoms and scores

Symptoms	No. of patients	VAS mean score ± SD
Thick nasal discharge	60	3.54±1.005
Nasal Obstruction	60	3.15±0.845
Postnasal discharge	60	2.79±0.784
Need to blow	60	2.29±0.755
Sneezing	60	1.78±0.669
Running nose	60	2.39±0.670
Cough	12	0.21±0.405
Ear fullness	14	0.22±0.427
Ear pain	12	0.21±0.405
Dizziness	0	0.00
Facial pain	60	2.15±0.935
Difficulty in falling asleep	56	1.66±0.957
Waking up at night	38	0.89±0.810
Lack of good night sleep	34	0.81±0.804
Waking up tired	26	0.42±0.503
Fatigue	30	0.49±0.510
Reduced productivity	36	0.79±0.760
Reduced concentration	36	0.82±0.790
Frustrated	60	2.32±0.755
Sad	60	1.72±0.637
Embarrassed	50	1.02±0.613
Loss of smell/taste	28	0.46±0.503

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Table 2: Improvement of mean SNOT-22 symptom score of both groups compared pre and post-operatively

		Preop	Postop		
			2 weeks	1 month	3 months
Group A	Average score (Range)	26.32±9.044	0.72 ± 1.943 (0-6)	3.28 ± 3.533 (0-11)	13.19 ±7.281 (2-29)
	% improvement		97.23%	87.57%	49.85%
Group B	Average score (Range)	26.80±7.301	0.73 ± 1.943 (0-6)	4.93 ± 3.389 (0-11)	9.81 ± 6.427 (0-23)
	% improvement		97.27%	81.61%	63.42%

Table 3: Improvement of mean nasal endoscopy scores of both groups compared pre and post-operatively

		Preop	Postop		
			2 weeks	1 month	3 months
Group A	Average score (Range)	8.00±1.812	3.53±0.6342 (2-4)	2.27±0.798 (1-4)	1.87±1.597 (0-6)
	% improvement		55.86%	71.63%	76.61%
Group B	Average score (Range)	7.93±1.437	3.47±0.515 (3-4)	1.93±1.224 (0-4)	2.53±2.948 (0-8)
	% improvement		56.23%	75.67%	68.08%

Table 4: Studies Showing Effects of Topical AMB IN CRS +/- AFRS

Author	Study	Test drug and dosage	Control	Concomitant Therapy	Results	Conclusion
Jiang et al (2017) [18]	Nasal irrigation post-FESS in 73 CRS cases (q.d. for 8 weeks)	200µg/ml AMB (TDD-20mg) (n=37) using pulsatile irrigator	NS with yellowish dye (n=36)	None	Test group: significant drop in SS but not in ES, UPSIT-TC score and saccharine transit time. Control group: No change in SS No intergroup significant differences	Intranasal AMB irrigation with 200µg/ml improved symptoms in post-FESS patients with no additional benefit compared to NS.
Jiang et al (2015) [19]	Nasal irrigation post-FESS in 77 CRS cases. (q.d. for 8 weeks)	100µg/ml AMB solution. (TDD- 20ml) (n=38)	NS with yellowish dye (n=39)	None	Test group: significant improvement in UPSIT-TC score Control group: improvement in SS	Irrigation with 100µg/ml AMB solution proved no better than NS irrigation.
Hashemi et al (2011) [20]	Nasal irrigation post-FESS in 50 cases of CRSwNP (b.i.d for 24 weeks)	50mg of AMB in 500cc sterile water. (100µg/ml) (n=25)	NS (n=25)	Post-FESS ciprofloxacin tablets and beclomethason nasal spray	Improvement in CT scores in 84% of test and 88% of control group Deterioration in none No intergroup difference	Topical AMB solution was effective in reducing CT scores in combination with FESS but showed no benefit over NS.

Gerlinger et al (2008) [21]	Nasal spray post-FESS in 30 CRSwNP (AFRS excluded) patients. (2 puffs b.i.d for 12 months)	AMB spray (TDD-4mg) (100µg/puff) (n=14)	Placebo (acriflavin chloride) (n=16)	Nasal steroid sprays No recent systemic steroid, antibiotic, antifungal or antihistaminic	Both groups: improvement in SS and QOL. Test group: ES improved Placebo group: CT scores improved No significant intergroup differences	AMB nasal spray given for 12 months post-FESS in CRSwNP patients is not beneficial over placebo.
Liang et al (2008) [22]	Nasal irrigation in 64 CRSsNP cases (q.d. for 4 weeks)	40µg/ml 250ml/nostril using pulsatile irrigator) (TDD-20mg) (n=32)	Yellowish dye in 60ml sterile water (4ml in 500ml of saline) (n=32)	None	Both group: significant decrease in SS (more in AMB group) No significant intergroup differences AMB group: significant decrease in ES No intergroup significant differences in bacterial and fungal culture rates	Nasal irrigation with AMB decreased SS and ES but had no additional benefit over NS
Helbling et al (2006) [23]	Open trial; Nasal sprays in 21 patients of CRSwNP (t.i.d. for 12 weeks)	1 puff (0.1ml)/nostril of 1% AMB spray (n=21) (TDD-3mg)	No control group.	None	ES: improved in 3 (14%), unchanged in 16 (76%), deteriorated in 2 (10%) SS: improved in 7 patients	1% AMB nasal spray was found not effective for treatment of nasal polyps.
Ebbens et al (2006) [24]	Multicentric; Nasal lavage in 116 CRS (AFRS excluded) patients post-ESS (b.i.d. for 13 weeks)	25ml AMB solution (100µg/ml)/ nostril through nasal douching device (n=59)	Cemevit multivitamin dissolved in sterile water with 2.5% glucose. (n=57)	Intranasal steroids (70% in AMB group and 67% in placebo group) Antibiotics in few	Mean VAS scores, QOL scores, peak nasal inspiratory flow values and polyp scores: no significant differences before and after treatment in both groups. Total, postnasal drip and rhinorrhoea VAS score: significant difference	Topical intranasal AMB application is not additionally beneficial to intranasal steroids and irrigation in CRS post-FESS.

					only in placebo group ES: significant difference in both groups No intergroup differences observed	
Weschta et al (2004) [25]	Nasal spray in 78 CRS patients (clinically suspicious AFRS excluded) (2 puffs/nostril q.i.d. for 8 weeks)	3mg/ml AMB with buffering in 5% glucose solution. (1 puff-100µL) (TDD-4.8mg) (n=28)	Tartrazine, chinin sulphate, naphthol sulfo acid and choline in 5% glucose solution (n=32)	Long term medications continued. No recent drugs started.	CT score: 50% reduction post lavage. Control group: no positive response. AMB group: 2 out of 28 responded, median SS worsened Both groups: no significant changes in median CT scores. ES similar with no significant change after treatment	Intranasal AMB application does not benefit patients with CRS.
Ponikau et al (2005) [26]	Nasal irrigation in 30 patients with CRS. (b.i.d./ nostril for 6 months)	Irrigation with 20ml of AMB in sterile water solution by bulb syringe (250µg/ml) (TDD-20mg) (n=15)	Sterile water with yellow dye (n=15)	Intranasal steroids (47% in placebo group, 53% in test group). Antihistaminic, decongestants in few	AMB group: reduced inflammatory mucosal thickening on CT scans and the disease stage on nasal endoscopy Reduced levels of intranasal markers for eosinophilic inflammation in CRS (compared to placebo) Improved SS in 90% Placebo group: improved SS in 64% SS: No overall improvement with treatment	Objective signs of CRS could be positively altered after 6 months of treatment with intranasal AMB. No benefit observed by placebo instillation.
Ricchetti et al	Intranasal topical AMB in 115	20ml of 1% AMB suspension	Two application modes of	Nasal lavages with saline and	Both groups: Total disappearance	Nasal lavage versus nasal spray of

(2002) [27]	patients of persistent NP (70% post-FESS) (b.i.d. for 4 weeks)	(nasal lavage in group I and nasal spray in group II) in each nostril (TDD-800µl/d)	AMB suspension compared. No placebo. (n I=75) (nII=40)	topical corticosteroids	of NP in 39% and 43% of total and 48 % and 64% of post-FESS patients, respectively.	fungicidal suspension had similar beneficial effects. Effect of topical corticosteroid can't be ruled out.
Ponikau et al (2002) [28]	Pilot open-label trial; Nasal irrigation in 51 (45 post-FESS) refractory CRS (b.i.d. for 6 months)	80 ml/d of 100µg/ml AMB irrigation by bulb syringe (20ml/nostril) (TDD-8 mg) (n=51)	No placebo	37% used topical and systemic steroids 29% only topical steroids	SS: improved in 38 (75%) patients ES: highly significant improvements by atleast one stage in 38 (75%) patients with 18 (35%) becoming disease free. CT scores: Significant improvement	Intranasal AMB is effective and safe in almost all CRS patients

ABBREVIATIONS: AmB (Amphoteicin-B), TDD (Total Daily Dose), SS (Symptom Score), ES (Endoscopic Score), NS (Normal Saline), NP (Nasal Polyposis), q.d. (once daily), b.i.d. (twice daily), t.i.d. (thrice daily), q.i.d. (four times daily), AFRS (Allergic fungal rhinosinusitis), FESS (Functional endoscopic sinus surgery), CRS(chronic rhinosinusitis), CRSwNP (CRS with nasal polyposis), CRSsNP(CRS without nasal polyposis), QOL (Quality of life), VAS (visual analog scale)

Discussion

AFRS is a distinct entity affecting 110 individuals per 100000 inhabitants in northern India. It is also common in Southern Asia, Middle east, Sudan, Southern North America.[5] The most common causative fungi are demateaceous, including Curvularia, Bipolaris, Pseudallescheria and the hyaline molds such as Aspergillus and Fusarium. More than 90% cases have Aspergillus flavus as the isolated fungi in rural northern India. [2] Interactions with social determinants of health and altered gene expression leads to exaggerated inflammatory response to fungi. [2,6,15] Ethmoid sinuses are the most affected followed by maxillary, sphenoid and frontal. [5]

Management of AFRS has been ever evolving with still considerable uncertainty with effects of topical antifungals unclear. [5,6]

The use of antifungals like AmB, itraconazole, voriconazole and ketoconazole has been advocated as an adjunct to standard treatment. To avoid the systemic side effects of oral administration, different concentration and dosages of various topical antifungals given by different delivery systems like douching, nebulisation, atomization, inhalations, irrigation, spray, drops or powder insufflations, have been studied over the past two decades. [16,17]

According to the literature, there have been many studies, either denying or supporting the role of topical intranasal AmB. However, they mostly studied patients of CRS and infact, three major RCTs excluded AFRS patients particularly. These studies with their heterogeneity and controversial and contrasting results have been summarized in table-4 [18-28.]

We studied the role of postoperative lavage by 200µg/mL of AmB in comparison to normal saline in 60 patients of AFRS at our centre.

In our study the mean preoperative scores of SNOT-22 were 26.32±9.044 in group A (control) and 26.80±7.301 in the Group B (intervention), the intergroup difference not being statistically significant (p=0.878). Post-FESS, at 2 weeks follow-up, group A showed an improvement of 97.23% and group B of 97.27% over the preoperative scores. This was almost at the commencement of postoperative lavage. At 1 month this worsened to 87.57% and 81.61%, respectively. At 3 months, that is, the end of lavage, group A score worsened to only 49.85% improvement over preoperative score and group B only 63.42% improvement, the intergroup difference not being significant (p=0.186).

Most of the nasal symptoms in patients of both groups showed improvement in the postoperative period.

There was a definite improvement in both the groups after 3 months in comparison to the preoperative baseline scores, but this fact cannot be ignored that the patients in both the groups were best relieved at 2 weeks after surgery. Here, the beneficial effect of surgery itself can't be ruled out as maximum improvement was at the start of nasal lavage making role of latter alone questionable in alleviating symptoms.

The rates of improvement between the two groups did not differ significantly, further implying that the effects of 200µg/mL AmB and physiological normal saline were the same indicating beneficial role of mechanical clearance by lavage, as in previous studies.

The placebo-controlled pilot study by Ponikau et al, at 3 months, showed improvement of 57% in the placebo group and 56% in the amphotericin group along with reduction of inflammatory markers of CRS (eosinophil derived neurotoxin, IL-5 in mucosa) advocating the beneficial role of the antifungal. [26]

In our study, the mean preoperative endoscopy score was 8.00±1.812 in group A and 7.93±1.437 in group B. At 2 weeks follow up postoperatively, group A showed 55.86% improvement over preoperative score and group B of 56.23%. At 1 month this further improved to 71.63% and 75.67% over the preoperative scores, respectively.

At 3 months, there was marked improvement by 76.61% in group A over the preoperative scores. Group B, however, showed a slight deterioration in the score as compared to that at 1 month follow-up although still 68.08% improved over the baseline score. The inter-group difference was not significant (p=0.450).

The study by Ponikau et al in 2005 showed improvement of 29% in the placebo group and 70% in the AmB group at 3 months recommending latter as beneficial in treatment of CRS post-FESS. [25] Their study in 2002 demonstrated 75% improvement in symptoms and endoscopy by intranasal AmB. [28]

SNOT-22 and the Nasal Endoscopy scoring at 3 months in both the cases and control groups demonstrated significant correlation (p=0.029).

Shirazi et al showed that the in vitro antifungal concentration of 100µg/mL was ineffective in eradicating the fungi during the 6 weeks period. [29]

We used solution of 80ml/day of 200µg/mL forming a daily dose of 16 mg whereas Ponikau et al [26] used 80ml/day of 250µg/mL.

Our results are similar to Jiang et al, who did two placebo-controlled studies in 2015 and 2017 with 100 and 200 µg/mL of AmB, respectively. Their studies also compared post-FESS preirrigation and postirrigation scores along with effects on olfaction and mucociliary clearance. [18,19] Our scores at 2 weeks follow-up, around which the lavages had just commenced, may be considered equivalent to their post-surgery pre-irrigation scores.

We can infer from our study that intranasal AmB lavage at a higher concentration of 200µg/mL proved advantageous as an adjunct postoperatively, but it showed no additional benefit over normal saline lavage.

This is in accordance with the recommendation given by Wei CC, Adappa ND and Cohen NA in their contemporary review for use of topical nasal therapies in the management of CRS. [30]

All the previous studies make reaching a single conclusion difficult as they differ in total daily dosage, concentration, duration and mode of application of intranasal antifungal drugs. Also sample size, status of previous surgery, concomitant therapies and the disease entity taken for studies also varied.

It is also important to check if the AmB solution was stored properly and therefore, was stable at the time of treatment. [31]

The mode of drug delivery is also important for better effects of this therapy. All our patients performed irrigation with 20ml syringe for AmB nasal lavage. This method may not be very effective in delivering solution to the nasal and sinus cavities and some of it may be lost without coming in contact with the mucosa.

Also, the contact period of the drug with the mucosa may not have been adequate to produce the desired effect. Intranasal sprays, which turn to gel form on contact with the mucosal surface, can be used and may be better in delivering drug to the target sites. Thus, better mode of delivery using inhalation or sprays or placing AmB pellets in the sinus cavities may help in more uniform and consistent distribution of drugs and their better contact with mucosal surface resulting in improved benefit.

The duration for which the topical AmB was prescribed can also be increased to see better results. Hashemi et al for this reason particularly prescribed topical antifungal for 24 weeks and Gerlinger et al for 12 months. [20,21]

Another major issue is whether saline irrigation without AmB was sufficient for improvement of patients. Heatley et al has reported the daily nasal hypertonic saline irrigation resulted in symptomatic improvement in 70% patients with CRS but no objective assessment was done in that study.[32]

Even electrolyzed acid water, hydrogen peroxide, povidine -iodine, xylitol, sodium hyluronate and manuka honey have been tried as nasal irrigation solutions. [9,33,34,35,36,37] Ponikau et al countered it 67% of patients who had shown objective improvement with AmB nasal lavage have failed to respond to saline lavage before AmB treatment. He also studied the efficacy of intranasal administration of itraconazole in 10 patients and found that the symptom score improved by 48%. [26] This further suggests that the therapeutic effect is because of antifungal effect and is not limited to AmB but shown by other antifungal agents as well. Ricchetti et al also supported the use of AmB both as lavages and sprays and their study included concomitant steroid therapy. [27] Corridini et al advocated that combined lysine acetylsalicylate and AmB are effective in reducing nasal polyposis of fungal etiology. [38]

Lavage itself has been hypothesized to cause mechanical clearance of debris and reduction of fungal antigenic load along with mucosal edema and inflammatory markers as a result of which Weschta et al [25], Gerlinger et al [21] and Helbling et al [23] used nasal sprays to deliver the drug.

We mainly focused on clinical outcomes of patients and did not study effects of higher concentration of 200µg/mL AmB on mucociliary clearance, olfaction, inflammatory markers or fungal antigenic load in mucus.

Our study in AFRS was similar to all other major RCTs which, although, done in CRS patients (with few excluding AFRS), disapproved of any additional benefit of topical antifungals over placebo. In fact, Helbling et al [23] and Weschta et al [25] denied any beneficial effects of amphotericin altogether.

Khalil et al did a study to determine the role of antifungal therapy in prevention of recurrent AFRS post-FESS in 50 patients. Postoperatively they were divided into 5 groups with each given concomitant steroid therapy. First group received oral itraconazole, second group received fluconazole nasal spray, third were given combined itraconazole and nasal fluconazole, fourth received fluconazole nasal irrigation and fifth group served as control who received concomitant medical therapy only. Recurrence rates in the 5 groups were 66.7, 10.0, 14.3, 28.6, and 75.0%, respectively. They concluded that use of topical fluconazole, either as nasal spray or as irrigant, is effective in reducing recurrence post-surgery. Oral itraconazole, both alone and in combination, was ineffective.[39] Verma et al confirmed itraconazole to be a better preoperative adjunct than postoperative.[40]

According to the available literature, there are many medical modalities for AFRS such as topical steroids, oral steroids, topical antifungals, oral antifungals, immunotherapy, biologics, and leukotriene modulators. Post-FESS, systemic and standard nasal steroids are recommended. Nonstandard topical nasal steroids, oral antifungals, biologics like omalizumab and immunotherapy are options in cases of recalcitrant AFRS. As there is insufficient clinical research reported in the literature regarding the adjunctive postoperative use of topical antifungals in AFRS, additional studies with higher concentrations and prolonged duration of treatment and comparing different delivery methods are required for creating high level of evidence to either recommend or refute their use.

Fungal immunotherapy and biologics are also promising but is not cost effective in developing countries and still better designed research is required to establish its efficacy and safety due to lack of RCT in AFRS patients. [3,5,6,7,9 41]

Conclusion

We conclude that post-FESS nasal lavage with 200 µg/mL of AmB for 3 months by conventional syringe irrigation did not confer a greater benefit than that of normal saline nasal irrigation.

There are still controversies in use of antifungals as post-FESS adjunctive therapy among researchers. Topical antifungal therapy for AFRS is unproven. Larger RCTs will be required to determine if changes in dosages, concentrations, treatment time or route of administration and delivery techniques of different antifungals could improve the results in addition to topical corticosteroids used as the standard treatment in the management of AFRS as an exclusive subset of CRS.

Clinical Significance: Efficacy of post-operative intranasal lavage by AmB therapy, even in higher concentration, is no better than that with normal saline when studied exclusively in patients with AFRS.

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Ethical Consideration (Research involving human participants): This study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study has been approved by ethical committee of the institution.

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