



Original Article

Role of preoperative versus postoperative itraconazole in allergic fungal rhinosinusitis

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Abstract

Antifungals used as adjuvant to surgery in AFRS (Allergic Fungal Rhinosinusitis) have shown varying success in delaying recurrences. Itraconazole has been used both as pre-operative and postoperative adjuvant. This study investigates the role of itraconazole in AFRS and compares its role between preoperative and postoperative administration of the drug. Patients were randomly divided into groups as: Group 1 (n = 25), received 4 weeks itraconazole in the preoperative period and operated subsequently, Group 2 (n = 25), received 4 weeks itraconazole in the postoperative period, Group 3 (n = 50), matched patients of AFRS, who didn't receive itraconazole. All the groups received oral steroids in tapering doses starting from 1 mg/kg for 6 weeks in the postoperative period. Symptomatic (SNOT 20), radiologic (Lund Mackay, LM) scores and endoscopic (Kupferberg's NE Grades) were noted. Primary postoperative follow-up was for 24 weeks with routine CT scans and nasal endoscopies, followed by which all the patients were followed with nasal endoscopies only with CT scans when required. Both preoperative and postoperative itraconazole showed significant improvement in the SNOT, LM, and Kupferberg's grades in the follow-up period. Preoperative itraconazole therapy showed significantly better results compared to postoperative itraconazole therapy though the recurrence rates were similar in both groups. Itraconazole is a better preoperative adjunct in AFRS than postoperative.

Key words: Itraconazole, Allergic fungal rhinosinusitis, preoperative Itraconazole, postoperative Itraconazole, adjuvant antifungal therapy in AFRS.

Introduction

Allergic fungal rhino sinusitis (AFRS) is a disease with a noninvasive allergic response to fungal antigens in sinunasal cavities, which was initially described by Katzenstein.¹ Young atopic individuals are the most affected, and presence of nasal polyposis and allergic mucin are characteristic of the disease.¹ Indian subcontinent having warm and humid climate is an endemic region for AFRS.^{2,3} Almost 90% patients of AFRS show evidence of type I hypersensitivity with raised serum immunoglobulin E (IgE) levels and type III hypersensitivity with eosinophilia in sinus mucosa with fungal antigens.^{4,5} Primary treatment in AFRS is surgery. With the goal to decrease the antigen load and improve the aeration of sinuses.⁶ But treatment of AFRS has always remained a challenge and required continuous follow up of patients as recurrence varies from 10 to 79%,⁷ 100%.⁸ Hence adjuvant therapy is an integral part in the management of AFRS.

Various types of adjuvant therapy have been tried in AFRS. Kupferberg⁷ and Marple^{8,9} emphasized the role of steroids as an adjuvant modality and showed to delay recurrences in AFRS. Various antifungals have been tried in AFRS in the search for a promising adjuvant. Topical amphotericin B nasal spray and nasal lavage have shown symptomatic improvement in patients of AFRS but could not produce improvement in endoscopic or radiologic parameters.^{10,11} Rains,¹² Wormald,¹³ Chan,¹⁴ Gupta,¹⁵ Panda¹⁶ have used itraconazole in AFRS as a postoperative adjunct and showed its role in improving the symptomatic, endoscopic, and radiologic parameters and delaying recurrences. Khalil et al.¹⁷ also showed better results by adding topical fluconazole to systemic itraconazole therapy compared to itraconazole alone when given postoperatively in AFRS.

The role of preoperative itraconazole in AFRS has not been well established. One of our previous studies has shown preoperative itraconazole to be effective in AFRS.²⁴ This study was planned to study the role of itraconazole in AFRS and to compare both preoperative and postoperative modes of itraconazole to opine in detail regarding the modes of itraconazole therapy in AFRS to determine our institutional protocol for management of AFRS.

Material and methods

A single center prospective study was done at our tertiary care hospital from January 2010 to December 2014. Institutional ethics and review committee approval was taken for the study and informed consent was obtained from every patient for participation in the study. Information regarding the study and consent was explained to patients

in the language they understand. We included 100 consecutive cases of clinically and histologically diagnosed cases of AFRS. Office-based punch biopsy from the nasal polyps was done under nasal endoscopic guidance for histological conformation for each case before inclusion into the study. Patients with evidence of invasive or granulomatous fungal sinusitis, allergic to itraconazole, extensive intra-orbital or intra-cranial extension, not consenting for participation in the study, those not having histological diagnosis of AFRS in primary office based punch biopsies, patients with definite evidence of immunocompromised status and previously operated cases were excluded from the study. Patients having extensive intracranial and intra orbital involvement were also excluded from the study; however, remodeling and thinning of lamina papyracea and skull base on computerized tomography (CT) scan were included in study population.

All the cases were evaluated with a detailed clinical history general physical examination and complete head and neck examination including anterior rhinoscopy. The symptomatology scores were evaluated as per SNOT 20 (Sino-nasal outcome test) scores. Computerized tomography in axial and coronal planes of Nose and PNS was done in all patients and were evaluated as per Lund Mackay scores. Diagnostic nasal endoscopy along with an office based punch biopsy was done in all patients. Nasal endoscopy findings were graded based on Kupferberg grades. Additionally, total serum IgE, absolute eosinophil counts (AEC), and *Aspergillus* skin hypersensitivity test was done in all patients. Out of the commonly associated fungi with AFRS, *Aspergillus* skin test was done using antigen extract of *Aspergillus flavus* as it was the most common fungi associated with AFRS in majority of the cases in this part of the world. Skin test was performed against aspergillin antigen (culture filtrate antigen of *Aspergillus flavus*, collected from National culture collection center of pathogenic fungi (NCCPF), Chandigarh, India, which were isolated from AFRS patients). At NCCPF, antigen is prepared by the routine method using steps of fungal growth preparation, grinding, defatting, extraction, clarification, dialysis, sterilization, sterility testing, and standardization. In sum, 0.02 ml of aspergillin antigen (protein content 1 mg/ml) was injected intra-dermally. The reading was taken every 15 minutes for the first hour to look for wheal and erythema. Same volume of sterile phosphate buffered saline (pH 7.2) was injected on the other arm, which served as control. In case of AFRS, type I mediated hypersensitivity to fungi (*A. flavus*) is considered the major cause of the disease; hence, only immediate hypersensitivity (Type-I) was recorded when erythema and wheal appeared within 1 hour of injecting the antigen. Skin test showing a wheal of diameter > 8 mm and AEC > 400 were taken as significant. Final

diagnosis was done using Saravanan's¹⁸ criteria before inclusion of the cases into the study.

All patients included in the study were randomly divided using computerized randomization table into two groups, the study group (those who received itraconazole, $n = 50$, group 1 and 2) and the control group (those who did not receive itraconazole, group 3). The study group was again divided into two groups randomly by using computerized randomization table to decide whether they receive itraconazole in the preoperative period (Group 1, $n = 25$) or in the postoperative period (Group 2, $n = 25$). Both patients of group 1 and 2 received itraconazole for 4 weeks in the preoperative and the postoperative period respectively. Group 1 patients were given itraconazole for 4 weeks after the diagnosis and confirmation with the office based punch biopsies. Group 2 patients received 4 weeks of therapy with itraconazole in the immediate postop period. Dose of itraconazole in adult patients was 200 mg (5 mg/kg in children)¹⁹ twice daily for 2 days followed by 100 mg (3 mg/kg in children)¹⁹ twice daily for rest of the time during the 4 weeks therapy period. All patients of group 1 and 2 were followed up with biweekly assay of liver function tests during the course of itraconazole therapy. Patients in the control group (Group 3, $n = 50$) patients were taken directly for surgery after diagnosis and preliminary investigation. Postoperatively all patients of all the three study groups were given 6 weeks of oral steroids in tapering doses starting from 1 mg/kg body weight. Schedule of tapering was 1 mg/kg for 7 days, 0.8 mg/kg for 7 days, 0.6 mg/kg for 7 days, 0.4 mg for 7 days followed by 0.2 mg/kg for 15 days. Hence, a total of 100 patients were recruited during the study period. In sum, 25 patients in Group 1 received 4 weeks of preoperative itraconazole, 25 patients in group 2 who received postoperative itraconazole and 50 control patients in group 3, who were directly taken for surgery were considered for final analysis.

All patients were followed up with regular nasal douching and nasal endoscopy. SNOT 20 scores and Nasal endoscopic grades were determined at 1st, 6th, 12th, and 24th week follow-up. Total IgE levels were done at 6 weeks postoperatively. Computerized tomographic scans of nose and paranasal sinuses were done at 12 weeks and 24 weeks follow-up. Patients who received itraconazole were compared to those who did not receive in terms of the above parameters to see for the effect of itraconazole. Among those who received itraconazole, comparison was done in between those who received it preoperatively to those who received it postoperatively. Patients in all the three groups are under our continuous follow-up until the present date.

Statistics was done by using IBM SPSS Statistics v 20.²⁰ A P value of $<.05$ was taken as the level of significance in each test. Kolmogorov and Smirnov test was used for test-

ing the normality of the distribution of various parameters. Parametric data were compared using t test, and nonparametric data were compared using χ^2 test.

Results

Whole population of 100 patients included 42 females from 11 years to 65 years and 58 males from 7 to 63 years in age. Mean age was 30.60 ± 17.61 years in group 1, 27.20 ± 11.25 in group 2, and 31.30 ± 14.42 in group 3, respectively. In sum, 35% of patients (35/100) were from the younger age group and were in their first and second decade of life.

Nasal discharge, postnasal drip, and nasal obstruction along with allergic symptoms were the most common symptoms. Nasal polyposis was the most common sign (100%). Unilateral involvement (Fig. 1a) of paranasal sinuses was seen in 32% (32/100) of patients and bilateral involvement (Fig. 1b) was more common, which was noted in 68% of patients. Anterior ethmoids were the most common sinus involved on radiology. Bony thinning and destruction of by expansion and remodeling of cell septa and walls of sinuses were seen in anterior ethmoids (92%), posterior ethmoids (84%), maxilla (76%), sphenoid (67%), and frontal sinus (65%). And 93% of patients showed multiple sinus involvement. Lamina papyracea and skull base was eroded in 27 and 8% of patients, respectively (Fig. 1a). On correlating the relationship between LM score and age, it was found that younger individuals had a propensity to have severe disease. Kolmogorov and Smirnov's test showed that study parameters in all three groups were normally distributed except nasal endoscopic grade, which had a skewed distribution in all three groups. This might be due to the nature of the data in case of NE (Kupferberg nasal endoscopic) grades, which is an ordinal data.

At the beginning of the study mean SNOT scores were 31.28 ± 13.79 in group 1, 48.28 ± 10.94 in group 2, and 38.72 ± 12.20 in group 3. Mean NE grades in were 2.92 ± 0.277 in group 1, 2.16 ± 0.688 in group 2, and 2.46 ± 0.676 in group 3. Mean LM scores were 18.04 ± 6.04 in group 1, 17.20 ± 4.22 in group 2, and 16.38 ± 3.79 in group 3. Mean AEC values were 519 ± 252.52 in group 1, 584.86 ± 150.81 in group 2, and 599.90 ± 226.96 in group 3. Similarly, serum IgE levels were 4742.50 ± 3305.30 , 2709.72 ± 595.01 , and 3889.29 ± 2058.80 in group 1, 2, and 3, respectively (Table 1).

In both group 1 and 2, none of the patients developed any severe side effects with itraconazole therapy. Mild elevations of liver enzymes were noted in two patients of group 1 and three patients of group 2. These elevations were less than 3 times the normal values of the liver enzymes and

CORONAL CT PICTURES OF TWO PATIENTS OF GROUP 1(a) AND GROUP 2(b)

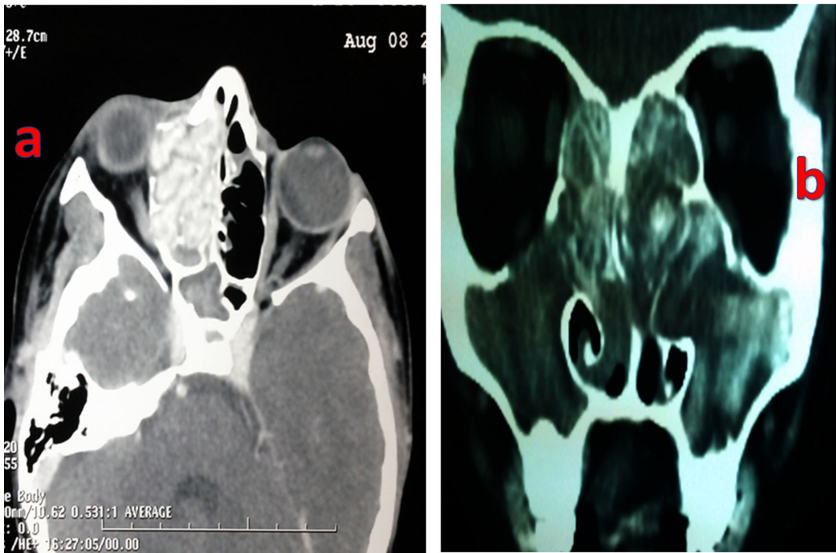


Figure 1. Photograph showing coronal CT pictures of two patients in preoperative and postoperative itraconazole therapy groups. a: Preoperative CT scan of a patient in preoperative itraconazole group. b: Preoperative CT scan of a patient in postoperative itraconazole group.

Table 1. Mean $\pm$ SD of various parameters at the beginning of the study in groups 1, 2, and 3.

			Age	SNOT score	NE grades	LM scores	AEC	IgE levels
GROUP	1	Mean	30.60	31.28 $\pm$ 13.79	2.92 $\pm$ 0.277	18.04 $\pm$ 6.04	519 $\pm$ 252.52	4742.50 $\pm$ 3305.30
	2	Mean	27.20	48.28 $\pm$ 10.94	2.16 $\pm$ 0.688	17.20 $\pm$ 4.22	584.86 $\pm$ 150.81	2709.72 $\pm$ 595.01
	3	Mean	31.30	38.72 $\pm$ 12.20	2.46 $\pm$ 0.676	16.38 $\pm$ 3.79	599.90 $\pm$ 226.96	3889.29 $\pm$ 2058.80

SNOT: Sino nasal outcome test.
NE: Kupferberg’s nasal endoscopic grades.
LM: Lund Mackay scores.
AEC: Absolute eosinophil counts.

returned to normal in subsequent biweekly liver function test estimations. As these elevations were mild, we did not consider stopping the therapy in between and continued with the therapy with close observation and routine liver function tests.

Postoperative nasal endoscopic grades, SNOT scores, and the LM scores were compared between those who received itraconazole (group 1 and 2) and those in the control group (group 3). Significant difference could be seen between the groups in terms of NE grades at 12th week (1.20 ± 0.756 in itraconazole users and 1.86 ± 1.34 among controls, mean difference = 0.66, $t = 3.03$, $P = .003$) and LM scores at 12th week (1.60 ± 1.927 in itraconazole users and 2.68 ± 1.789 among controls, mean difference = 1.08, $t = 2.90$, $P = .005$) and 24th week (1.66 ± 1.465 in itraconazole users and 2.34 ± 1.533 among controls, Mean difference = 0.68, $t = 2.26$, $P = .026$). However, there was no difference in terms of the SNOT scores obtained at 12th week (Mean difference = 2.38, $t = 1.11$, $P = .27$) and 24th

week (Mean difference = 0.26, $t = 0.143$, $P = .88$) postoperatively between those who received itraconazole (group1 and 2) and those in the control group (group 3).

Postoperative values obtained at 6th, 12th, and 24th week postop were compared between group 1 (preoperative itraconazole) and 2 (postoperative itraconazole). NE grades at 6th, 12th, and 24th week postop visit were 0.22 ± 0.422 , 0.84 ± 0.80 , 0.64 ± 0.81 in group 1 and 1.80 ± 0.64 , 1.56 ± 0.50 , and 0.72 ± 0.73 in group 2, respectively. These were significantly better in group 1 compared to group 2 ($P = .00$, 0.00 and 0.71 at 6th, 12th, and 24th week postop; Table 2). Figure 2a and 2b shows the nasal endoscopic images of two patients of group 3 and 2, respectively, at 12th week postop. Figure 2c and 2d shows nasal endoscopic picture of two patients of group 1 at 12th week postop. Similarly, mean SNOT scores in group 1 were 5.26 ± 3.18 , 5.00 ± 3.24 , and 4.24 ± 2.94 and in group 2 were 26.76 ± 10.03 , 21.76 ± 10.69 , and 15.28 ± 10.12 at 6th, 12th, and 24th week postop visit, respectively. These

Table 2. Comparison of postop parameters between those who received itraconazole preoperatively (group 1) and those who received postoperatively (group 2). Also shows corresponding values in group 3.

	Group Statistics				Comparison between group 1 and 2	
	Group	N	Mean	SD	t	Sig. (2-tailed)
NE_6wk	group 1	25	.22	.422	-9.960	.00
	group 2	25	1.80	.645		
	group 3	50	.98	.915		
NE_12wk	group 1	25	.84	.800	-3.802	.00
	group 2	25	1.56	.507		
	group 3	50	1.86	1.340		
NE_24wk	group 1	25	.64	.810	-.365	.71
	group 2	25	.72	.737		
	group 3	50	.62	.725		
SNOT_6wk	group 1	25	5.26	3.180	-10.176	.00
	group 2	25	26.76	10.030		
	group 3	50	15.76	11.972		
SNOT_12wk	group 1	25	5.00	3.240	-7.500	.00
	group 2	25	21.76	10.694		
	group 3	50	11	9.846		
SNOT_24wk	group 1	25	4.24	2.948	-5.236	.00
	group 2	25	15.28	10.122		
	group 3	50	9.50	8.904		
LM_12wk	group 1	25	2.20	1.848	-1.950	.05
	group 2	25	3.16	1.625		
	group 3	50	1.60	1.927		
LM_24wk	group 1	25	1.40	1.414	-1.262	.21
	group 2	25	1.92	1.498		
	group 3	50	2.34	1.533		
IgE_6wk	group 1	25	1530.75	1133.149	-.192	.84
	group 2	25	1483.68	414.201		
	group 3	50	857.72	737.509		

SNOT: Sino nasal outcome test.

NE: Kupferberg's nasal endoscopic grades.

LM: Lund Mackay scores.

Group 1: Preoperative itraconazole therapy group.

Group 2: Postoperative itraconazole therapy group.

Group 3: Control group.

SD: Standard deviation.

mean SNOT scores in the postoperative period were significantly better in group 1 compared to group 2 ($P = .000$ at 6th, 12th, and 24th week). Mean LM scores at 12th and 24th week postop were 2.20 ± 1.84 and 1.40 ± 1.41 in group 1 and 3.16 ± 1.62 and 1.92 ± 1.49 in group 2, respectively. The LM scores were significantly better in group 1 compared to group 2 at 12th week ($P = .05$). However, at 24th week postop, though the mean LM score in group 1 was less compared to group 2 but was not statistically significant ($P = .21$) (Table 2).

Difference between the preoperative and postoperative values in each parameter were obtained to look for the amount of decrease in the values as a result of treatment

given and mean of these differences were analyzed. It was seen that the decrease in the mean NE grades in postoperative period from those at the beginning of the study were significantly higher in group 1 compared to group 2 ($P = .00$ at 6th, 12th, and 24th weeks) (Table 3). Similar calculations in terms of SNOT scores and LUND MACKAY scores did not reveal statistically significant differences between group 1 and 2. However decrease in the IgE values in group 1 were significantly higher than that of group 2 ($P = .003$). Similar calculations were done between group 1 and 3 and group 2 and 3 taking the means of the differences between pre- and postop values into consideration. Decreases in the parameters from beginning of the study to those in

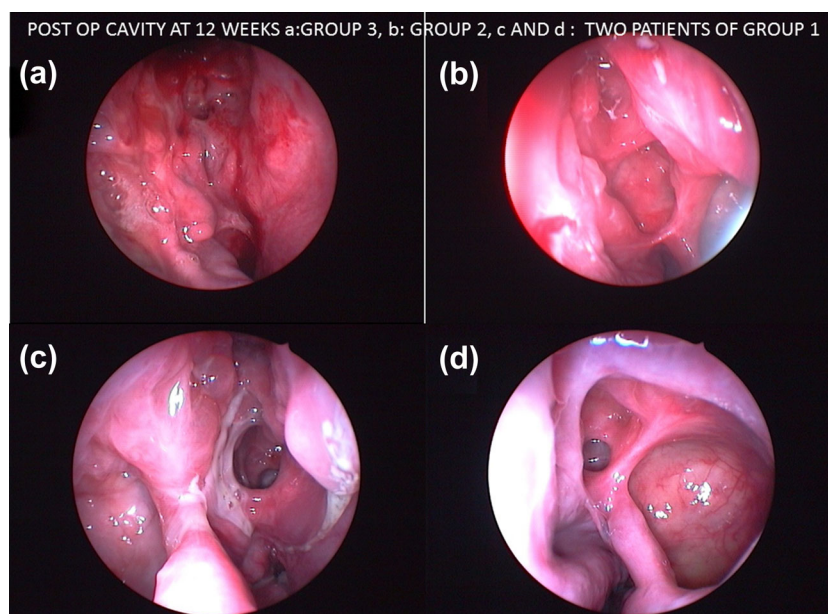


Figure 2. Photograph showing pictures of nasal cavities taken during nasal endoscopic examinations performed at 12 weeks of follow-up. a: Postoperative cavity status of a patient in control group at 12 weeks. b: Postoperative cavity status of a patient in postoperative itraconazole group at 12 weeks. c and d: Postoperative cavity status of two patients in preoperative itraconazole group at 12 weeks.

the follow-up period were compared between preoperative itraconazole group (group 1) and control group (group 3). Preoperative itraconazole group (group 1) showed higher reductions in NE grades as compared to controls ($P = 0.00, 0.00, 0.06$ for 6th, 12th, and 24th weeks) (table 3). Mean decrease in LUND MACKAY scores from beginning of the study to 24th week postop between group 1 and 3 had P value of .04 ($t = 2.050$, mean difference = 2.60). Comparisons of decrease in SNOT scores were statistically similar between groups 1 and 3. However reductions in parameters in postop itraconazole group (group 2) and control group (group 3) were comparable.

All the patients in our study had histological diagnosis of AFRS both in the preoperative office based punch biopsies and in the postop HPE results (Fig. 3). Presence of fungal hyphae, eosinophils, allergic mucin, granulomas, and any evidence of mucosal or vascular invasion by the fungal elements were looked for. None of our patients had any evidence of invasive fungal sinusitis in histopathology such as granulomas and mucosal and vascular invasion in postoperative surgical specimens which might be explained by the exclusion of non AFRS cases by office based punch biopsies before inclusion into the study. All positive fungal cultures (64/100) showed *Aspergillus flavus*.

Recurrence was defined as LM score > 10 and NE grade ≥ 2 . These objective criteria for recurrence were considered in order to decide the need of surgery as > 10 LM score and polypoidal mucosa and polyps as present with NE grades ≥ 2 indicates almost all sinus involvement which

requires re surgery rather than short courses of oral and topical steroids. For symptomatic recurrences which did not have such extensive pan sinus involvement as defined above, short courses of topical steroids were used. None of the patients in all three groups showed any evidence of recurrence in 6 months of follow-up. However, after the initial 24-week postop, all patients were followed up in every 3-month intervals until date. The recurrences where repeat surgery was needed occurred between 8 and 14 months in three patients of Group 1, one patient in group 2 at 13th month after surgery and between 7 and 11 months in seven patients of Group 3. Mean time to recurrence was 11.4 months in group 1, 13 months in group 2, and 9.6 months in group 3. Difference in the time to first recurrence between these groups were not statistically significant, though the recurrence rates were lesser in those who received itraconazole (group 1 and 2) compared to the control group who did not receive itraconazole therapy (group 3).

Discussion

Antifungal therapy has been used as adjuvant therapy to prevent recurrences in allergic fungal rhino sinusitis with varying success rates. Studies have showed the efficacy of itraconazole in preoperative period and postoperative period as adjunct to surgery for the treatment of allergic fungal rhino sinusitis.^{12,14,20} However, comparisons between both modes of adjuvant therapy with itraconazole in similar groups of patients in the same study has never been

Table 3. Comparison of groups in terms of difference in scores between follow up values from those at the beginning of the study in order to look for the objective reduction in parameters with the different modes of therapy administered across the three groups.

Change in parameters from the initial initial scores to those at follow up.	Group Statistics					
	Group	N	Mean	SD	<i>t</i>	Sig. (2-tailed)
D_NE_NE6wk	Group 1	25	2.72	.458	5.762	.00
	Group 3	50	1.60	1.212		
D_NE_NE12wk	Group 1	25	2.08	.812	4.948	.00
	Group 3	50	1.04	.880		
D_NE_NE24wk	Group 1	25	2.28	.792	1.882	.06
	Group 3	50	1.88	1.003		
D_LM_LM12wk	Group 1	25	15.84	6.060	.794	.432
	Group 3	50	14.78	3.945		
D_LM_LM24wk	Group 1	25	16.64	5.758	2.050	.048
	Group 3	50	14.04	3.758		
D_IgE_IgE6wk	Group 1	25	3085.68	2692.428	.464	.644
	Group 3	50	2823.62	2090.614		
D_NE_NE6wk	Group 1	25	2.72	.458	14.14	.00
	Group 2	25	.68	.557		
D_NE_NE12wk	Group 1	25	2.08	.812	6.33	.00
	Group 2	25	.68	.748		
D_NE_NE24wk	Group 1	25	2.28	.792	3.22	0.002
	Group 2	25	1.52	.872		

D: Difference between

NE: Kupferberg's nasal endoscopic grades at the beginning of the study.

NE6wk: Kupferberg's nasal endoscopic grades at 6 weeks follow-up.

NE12wk: Kupferberg's nasal endoscopic grades at 12 weeks follow-up.

NE24wk: Kupferberg's nasal endoscopic grades at 24 weeks follow-up.

LM: Lund Mackay scores at the beginning of the study.

LM12wk: Lund Mackay scores at 12 weeks follow-up.

LM24wk: Lund Mackay scores at 24 weeks follow-up.

IgE: IgE values at the beginning of the study.

IgE6wk: IgE values at 6 weeks follow-up.

Group 1: Preoperative itraconazole therapy group.

Group 2: Postoperative itraconazole therapy group.

Group 3: Control group.

SD: Standard deviation.

tried. This study is unique in a way that preoperative and postoperative modes of adjuvant itraconazole therapy have been compared in the same study in similar patients to understand which form of adjuvant therapy is most effective for AFRS.

Postoperative nasal endoscopic grades and Lund Mackay scores in patients who received itraconazole (preop and postop) were significantly different from those who did not receive itraconazole as adjuvant therapy for AFRS (P value < .05). This suggests that itraconazole used as adjuvant therapy (preop or postop) in AFRS delays recurrence and improves postoperative cavity status. This is in accordance with the previous studies by various authors.^{12,13,15,21}

NE grades at 6th week and 12th week, SNOT scores at 6th, 12th, and 24th weeks and LM scores at 12th week were significantly better in group 1 (preoperative itraconazole group) compared to group 2 (postoperative itraconazole). This suggests that preoperative itraconazole was more effective as compared to postoperative itraconazole in AFRS. Preoperative itraconazole was found to achieve better endoscopic, symptomatic, and radiologic cure. Wormald¹³ in their study also reported improvement in symptomatic and endoscopic parameter in 82.6% (19/23) patients with postoperative adjuvant itraconazole therapy. Chan had showed improvement in 9/32 patients in symptomatology scores and 12/32 patients in endoscopic examination in cases of refractory cases of allergic fungal sinusitis who were

HPE PICTURE SHOWING ALLERGIC MUCIN, EOSINOPHILS AND HYPHAE

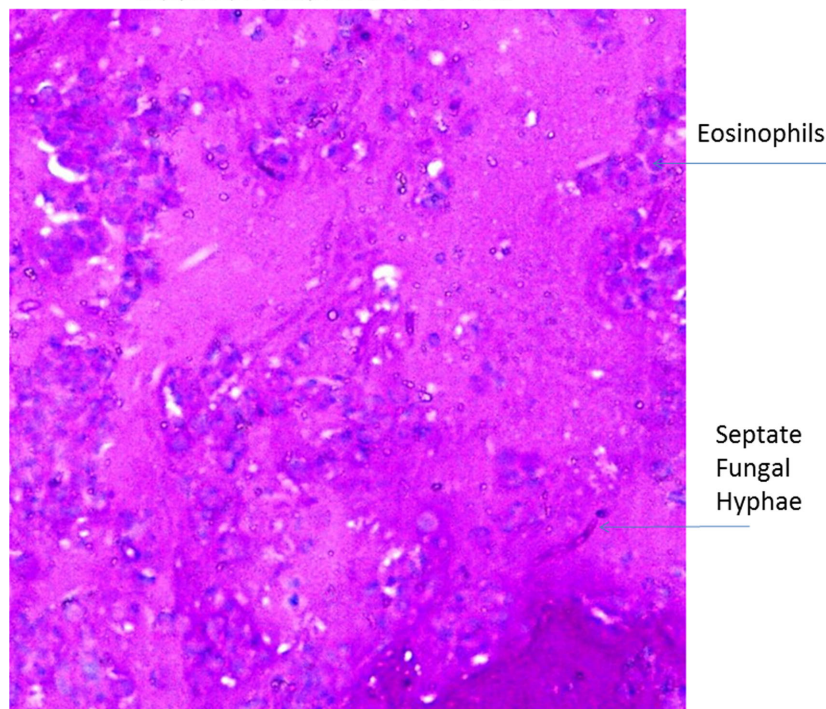


Figure 3. Photomicrograph taken from the histopathologic examination performed on the nasal tissue specimen of a patient showing fungal elements, eosinophils, and allergic mucin. (H and E stain).

previously treated with surgery.¹⁴ Along with the benefits with postoperative (group 2) itraconazole therapy, this study also showed improvement in patients of AFRS with preoperative itraconazole therapy (group 1).

Mean reductions in nasal endoscopic grades at 6th, 12th, and 24th weeks and reductions in Lund Mackay scores at 24th weeks from those at the beginning of the study were compared among all groups. Mean reductions in nasal endoscopic grades and reductions in Lund Mackay scores were found to be statistically significant between group 1 (preoperative itraconazole) and control group (group 3). While mean reductions in the nasal endoscopic grades and reductions in Lund Mackay scores were found to be statistically nonsignificant between group 2 (postoperative itraconazole) and group 3 (control group). The mean reductions in nasal endoscopic grades in group 1 (preop itraconazole) were found to be significantly higher than those of those who received postoperative itraconazole (group 2). Previously, Rupa et al.²² have shown significantly better cavity conditions when steroids and itraconazole were given to patients in their placebo controlled blinded study. This suggests that itraconazole aides in achieving better cavity conditions in AFRS along with surgery and steroid therapy. The postoperative cavities were found to be better when the drug was administered in the preopera-

tive period as compared to the postop administration. This suggests that itraconazole is a better adjunct when given preoperatively as compared to postoperative therapy.

SNOT scores at 12th and 24th weeks postop was not statistically different in those who received itraconazole (group 1 and 2) compared to those did not receive (group 3). SNOT scores are symptomatic scores describing the severity of symptoms and quality of life parameters which troubles a patient of chronic sinusitis and as all the patients of AFRS are classically atopic and have chronic allergic symptoms even when the polyps are cleared from the paranasal sinuses and adequate aeration is achieved. Some amount of dysfunction of mucociliary clearance does persist in the postoperative in all postfunctional endoscopic sinus surgery patients, and it is never equal to those in the normal population. Hence we postulate that the persistence of pathophysiological atopic phenomenon in these patients of AFRS is responsible for nonsignificant difference between the groups 1 and 2 and 3. However, the significant reductions in the LM scores and NE grades does definitely signify the effectiveness of itraconazole in delaying the pathophysiological processes that leads to recurrence in these cases.

Reductions in the mean IgE values were also found to be significantly higher in group 1 (preop itraconazole) than compared to group 2 (postoperative itraconazole). This

suggests that immune response of type 1 hypersensitivity, which leads to the manifestations of AFRS, is also reduced in a significantly better way when itraconazole is given preoperatively than compared to postoperative administration.

All of our patients showed *Aspergillus flavus*, which is contrary to the world literature where *Aspergillus fumigatus*²³ is the most common species associated with AFRS however this is similar previous reports from our part of the world.^{3,24}

When recurrence was taken into account, it was found that patients who received itraconazole (group 1 and 2) had lesser recurrence rate compared to those who didn't receive (group 3). This suggests lesser recurrence rates with itraconazole therapy. However there was no difference between group 1 and 2 in terms of recurrence. Mean time to recurrence was also statistically similar between groups 1 and 2. This suggests that though itraconazole delays recurrence, modes of adjuvant therapy do not affect the recurrence rates in AFRS. This is similar to earlier published literature by Wormald¹³ and Chan¹⁴ and contrary to higher recurrence rates of 66.7% as documented by Khalil et al.¹⁷ Rains et al.¹² showed in their study that 17/83(20.5%) patients developed recurrence requiring revision surgery after itraconazole therapy with mean time to recurrence being 10.8 months. The present study shows a similar time to recurrence of 11.4 months in group 1 and 13 months in group 2. However, our study showed a lower reoperation rate as only 8% (4/50) patients among those who received itraconazole (group 1 and 2) required revision surgery. This lesser rate of recurrence might be due to the effects of itraconazole which has already been proven to delay recurrences in AFRS^{13–15,21} and is similar to its steroid sparing effect in ABPA,^{25–27} a condition with similar pathophysiology as AFRS.

Studies in literature have shown effective results with use of itraconazole along with steroids as adjuvant therapy in AFRS. This study has also shown similar results with itraconazole therapy. It has also proven the advantages of giving itraconazole in the preoperative period than in the postoperative period as this produced better cavity conditions in nasal endoscopic and radiologic observations in the follow-up period. This was along with the added advantage of achieving decreased disease load and extent of disease prior to the surgery which in turn leads to an easier surgery.

This study was done in patients from the same geographic location i.e. from north India, all surgical procedures were done by the single lead surgeon and mycological analysis has been done by the same mycologist as an attempt to ensure uniformity in the surgical and culture isolation techniques to avoid bias. However, there was lack of

placebo control for the control group, grading, scoring done by a single author, absence of blinding, and lesser sample size put limitations to the study.

This study concludes that itraconazole when given as an adjuvant in AFRS improves cavity conditions in endoscopic and radiologic examinations along with improving symptomatology scores compared to steroid alone, and the effects are even more profound when itraconazole is administered preoperatively.

Hence, itraconazole can be taken as an adjuvant therapy with promise for cases of AFRS.

Author Contributions

Sourabha K Patro: collected data. Compiled and did statistical calculations and prepared the manuscript.

Abhilash Alex Francis: collected data.

Roshan Verma: Operated the cases, edited the manuscript, conceptualized and mentored the study.

Naresh K Panda: Provided inputs for data interpretation, edited and guided the manuscript.

Arunaloke Chakrabarti: planned the mycological and histopathological analysis for the study and did mycological analysis of the specimens.

Paramjeet Singh: did radiologic analysis of patients included in the study.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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