CLINICAL EVALUATION OF EFFECTIVENESS OF ITRACONAZOLE IN PREOPERATIVE AND REFRACTORY POSTOPERATIVE PATIENTS OF ALLERGIC FUNGAL SINUSITIS

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ABSTRACT

BACKGROUND

Allergic Fungal Sinusitis (AFS) is a noninvasive type of fungal sinusitis, clinically and pathologically a unique entity of chronic rhinosinusitis. The aetiology, pathogenesis, and treatment of AFS are subject to controversy. In spite of aggressive endoscopic surgery, pre- and postoperative steroids and immunotherapy recurrence rates are high. Many additions are made to its original description and management since its early description in 1980. The aim of the present paper was to evaluate clinically. The response to high-dose itraconazole before endoscopic sinus surgery and in refractory postoperative patients. Related literature was reviewed in the light of the present study.

MATERIALS AND METHODS

A 2 year prospective study conducted on 68 AFS patients divided into two groups to clinically evaluate the results after using oral itraconazole preoperatively in one group and in refractory postoperative period in another.

RESULTS

The mean age of patients with typical AFS was 36±3.9 years. Patients with AFS with an average follow up of 21 months were included. Recurrence was 6/34 (17.64%) in itraconazole group and revision FESS done in 3/34 (08.82%). Recurrence in patients without itraconazole was 16/34 (47.05%) and refractory to conventional treatment, but responded to itraconazole in 14/16 (87.50%). Revision surgery required in 2/16 (12.50%) after starting oral itraconazole. No side effects or reactions were observed in a total of 7920 doses administered.

CONCLUSION

Itraconazole is well tolerated by patients and effective in shrinking the polyposis preoperatively with low recurrence. Postoperative refractory AFS is amenable in (87.50%) of patients avoiding repeat FESS. Overall, low recurrence rate and minimizing revision surgery when compared to patients treated without itraconazole was evident in the study.

KEYWORDS

Allergic Fungal Sinusitis, Itraconazole, Fungal mucin, Mucosal oedema, Hypersensitivity, Polyposis, and Fluticasone.

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INTRODUCTION: Allergic Fungal Sinusitis (AFS) was described by Millar et al in1981 as Aspergillosis of paranasal sinuses.[1] AFS was described as a new form of allergic reaction to fungal antigen by Katzenstein et al.[2] The incidence of the disease varies from region to region and estimated between 7 to 25%.[3] Individuals with atopy evolve type I hypersensitive reaction and a type III immunity reactions to fungal antigens resulting in local mucosal oedema. Mucosal oedema and anatomical variations like septal deviations, turbinate hypertrophy, blockage of Ostiomeatal Complex (OMC) and sinuses perpetuates the entrapment and wide exposure of antigens of fungi as well as fungal proliferation.

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This vicious cycle results in fungal mucin collection later on deposition of heavy metals like magnesium and iron with calcium salts gives a characteristics variegated appearance on CT scan of PNS. In MRI scans, fungal mucin appears as hypointense areas in T2 images. Expansile nature of the fungal mucin gives thinned out appearance to the sinus walls, but rarely destruction of the sinus walls. The most widely accepted diagnostic criteria are from Bent and Kuhn.[4], which includes nasal polyposis, type I and III allergic reactions, typical CT scan signs, eosinophilic mucin, and positive fungal culture or smear.

For a long-term effective control and eradication of the disease, FESS should always be combined with nasal steroids, immunotherapy, antifungal therapy.[5] The essentials of FESS is to enlarge the natural ostia of sinuses allowing more dependent, natural drainage, and complete removal of fungal debris and mucin without damaging the normal mucous membrane. This type of nasalisation of the sinuses gives wider access for inspection postoperatively and for medication to reach the sinuses.

Introduction of image-guided FESS helps in precisely localising the landmarks, which are destroyed either by the disease or previous surgeries. Chan and Javer showed use of oral itraconazole as a useful adjunct for AFS patients as it has anti-inflammatory property and inhibitor of steroid metabolism.[6] Bent and Kuhn.[4] found that MIC levels can be achieved with anti-fungal agents on intranasal usage. Rains and Mineck.[7] proposed short burst of low-dose oral steroids, use of itraconazole, and combined with FESS as a safe and clinical effective regimen in the treatment of AFRS. The present prospective random longitudinal study of two groups of independent subjects with confirmed criteria of AFS were administered oral itraconazole preoperatively in one group and postoperatively in refractory period showing recurrence with conventional treatment in another group.

MATERIALS AND METHODS: 68 patients attending the ENT Department of RIMS Kadapa, Andhra Pradesh, India were included in the present study. After a thorough history taking and ENT examination, direct endoscopic examination of the nasal cavity was done to confirm the diagnosis. Patients with history of allergic bronchitis and bronchial asthma were included in the study. Diagnosis of AFS was based on Kuhn's criteria and patients with bilateral nasal polyposis, mucosal oedema, presence of allergic mucin, eosinophilic mucin raised titres of Ag specific IgE and typical CT scan signs were included. Two treatment protocols were formulated in group A patients. Oral methylprednisolone 4 mgs twice daily, oral phenylephrine HCl 10 mgs once daily, oral levocetirizine 5 mgs + 5 mgs of Montelukast daily, intranasal azelastine with fluticasone furoate metered-steroid spray (Twice daily each dose of 75 micrograms), oral azithromycin 500 mgs once daily (6 days), and oral itraconazole 150 mgs twice daily for one month given preoperatively. After one month, patients of this group were subjected to DNE followed by FESS.

Operative parameters like grading of the polypi, convenience of delineation of anatomical landmarks, and amount of bleeding were recorded. Postoperatively, the antifungal group continued to receive oral itraconazole 150 mgs twice daily for the first 3 months and 100 mgs twice daily for the next 3 months. Intranasal spray with azelastine and fluticasone furoate and levocetirizine 5 mgs + Montelukast 5 mgs was continued for 6 months. In group B, 34 patients who underwent operative procedure (FESS) without antifungal agent itraconazole in the preoperative period and presenting with recurrence of polyposis and refractoriness for conventional treatment of AFS were included. DNE was done in these patients to assess the polyposis before inclusion. These patients were given oral itraconazole 150 mgs twice daily for the first 3 months and 100 mgs twice daily for the next 3 months. Going through the records during the FESS procedure, status of the polyposis, bleeding, and disease clearance in this group was noted. All the patients were periodically examined at monthly intervals and parameters like mucosal oedema, synechia, crusting, recurrence of polypi, and sense of smell were recorded. Revision surgery conducted in patients of both the groups not responding to treatment. Follow up of patients was done for 21 months. All the data was analysed using standard statistical methods using student's t test with P value taken as $P<0.05$.

OBSERVATIONS: This study has ethical committee review and permission at the General Hospital of RIMS, Kadapa, Andhra Pradesh. An informed consent was taken from the patients. The study consisted of 68 patients who presented for the study between May 2010 and September 2012. Out of 68 patients, there were 38 (55.8%) males and 30 (44.11%) females. The male patients in group A were 19 (55.88%) and females were 15 (44.11%). In group B, the males were 20 (58.82%) and the females were 14 (41.17%).

In group A, youngest patient was 24 years old and the eldest was 54 years with a mean age of 36±3 (Table 1). In group B, patients belonged to the age group between 16 and 49 years with mean age of 39.8±6. In group A, history of allergic rhinitis was observed in 15 (44.11%), bronchial asthma in 26 (76.47%) of the patients. In group B, allergic rhinitis was seen in 20 (58.82%), bronchial asthma in 22 (64.70%) of the patients. History of anosmia was given by 18 (52.94%) of the patients of group A and 20 (58.82%) of the group B patients. Eosinophilia was observed in 13 (38.23%) of the group A and 15 (44.11%) of group B patients (Table 2). Grade III polyposis was observed on DNE in 23 (67.64%) of group A and 23 (67.64%) of the group B patients. Allergic mucin showed eosinophils in 14 (41.17%) of group A and 19 (55.88%) of group B patients. Raised IG E titres more than 400 units/mL was found in 11 (32.35%) of the group A and 15 (44.11%) of the group B patients. CT scan signs were seen in 30 (88.23%) of the group A and 31 (91.17%) of the group B patients (Table 3).

Group	Group A	Group B
Male	21 (63.63%)	25 (69.44%)
Female	12 (36.36%)	11 (35.55%)
Anosmia	18 (54.54%)	20 (55.55%)
B. Asthma	26 (37.68%)	22 (61.11%)
Allergic Rhinitis	15 (45.45%)	20 (55.55%)
Eosinophilia	13 (39.39%)	15 (41.66%)

Table 1: Showing the Symptoms of Allergic Fungal Sinusitis (n=33, 36=69).

In group A, after the initial treatment with itraconazole and regular protocol, the patients were subjected to DNE to evaluate the polyposis. Grade III polyposis was changed to grade I in 13/23 (56.52%) of the patients of this group A. Patients with grade III converted to grade II were 10/23 (43.47%), grade II to I were 8/8 (100%), and from group I to no polyposis in 3/3 (100%) of patients. Whereas in group B, grade III to I were 06/23 (26.08%), grade III to grade II were 05/23 (21.73%), grade II to grade I were 2/7 (28.57%) and grade I to no polyposis were 1/4 (25%).

Calculating the significance between these two groups statistically by using chi-square test, it was found significant with P value 0.044 (With P<0.05 taken as significant), (Table 3). Mild bleeding was seen in 52.94%, moderated bleeding in 32.35%, and severe bleeding in 14.70% (Bleeding was graded by loss of blood more than 350 mL and difficulty in visualizing the operative field).

Reduction in fungal mucin was seen in 64.70%. Kupferberg's grading of postoperative FESS endoscopic examination of group A showed grade I in 20.58%, grade II in 14.70%, and grade III in 02.94% of the patients. Similarly, the grading in group B showed grade I in 29.41%, grade II in 47.05%, and grade III in 23.42% of the patients.

Group	Group A	%	Group B	%
Fungal Mucin Eosinophils	14	41.17	19	55.88
Raised IgE titres >400 units/mL	11	32.35	15	44.11
Grade I polyposis	03	8.82	04	11.76
Grade II polyposis	08	23.52	07	20.58
Grade III Polyposis	23	67.64	23	67.64
C T Scan Signs:				
Hyperattenuation	12	35.29	11	32.35
Variegated appearance	11	32.35	14	41.17
Expansile sinus walls	07	20.58	06	17.64

Table 2: Showing the Signs of Allergic Fungal Sinusitis (n=33, 36=69)

The incidence of synechia was 20.58% in group A and 41.17% in group B patients. Recovery of sensation of smell was observed in 41.17% in both the groups (Table 4). (Kupferberg's classification consisted of grade 0 - No evidence of disease. Grade 1 - Oedematous mucosa. Grade 2 - Polypoidal mucosa. Grade 3 - Frank polyps or caseous debris).

Group ⇨	Group A	%	Group B	%	T value	P value
IG E Titres	07	20.58	10	29.41		
Fungal mucin Eosinophils	10	29.41	11	32.35		
Eosinophils	09	26.47	11	32.35		
Grade III to Grade I	13/23	56.52	6/23	26.08		
Grade III to Grade II	10/23	43.47	5/23	21.73		
Grade II to Grade I	08/08	100	02/07	28.57		
Grade I to No polypi in the nasal cavity	03/03	100	01/04	25.00	2.137	0.044
Bleeding						
Mild	18	52.94	13			
Moderate	11	32.35	10			
severe	05	14.70	11			
Reduction in Fungal mucin	22	64.70	14	41.17		

Table 3: Showing the Effect of Itraconazole in Patients on Polyposis and Operative Findings during FESS (n=34x2=68)

DISCUSSION: Allergic fungal sinusitis is the commonest fungal sinus disease with a high rate of recurrence rate despite ever changing treatment protocols and advance FESS techniques. The main hindrance for total eradication of the disease is the allergic phenomenon for which the patient should be monitored and treated.

Group ⇨	A	%	B	%
Kupferberg's grading				
Grade I	07	20.58	10	29.41
Grade II	05	14.70	16	47.05
Grade III	01	02.94	08	23.52
Synaechiae	07	20.58		
Recovery in Anosmia	14	41.17		41

Table 4: Showing the Post FESS follow up findings in both groups (n =34X2 =68)

T value 2.137 and P value 0.049.

The present prospective study was conducted on 68 patients presenting with Kuhn's clinical criteria of AFS divided into 2 groups to evaluate the response to itraconazole preoperatively in group A and postoperatively in recurrent polyposis of group B. It is found in atopic individuals with chronic sinusitis and nasal polyps who develop an allergic immune response to extra mucosal fungal hyphae histologically seen as fungal mucin.[8] CT scan of PNS shows hyperattenuation invariably, which is due to deposition of heavy metals like iron and calcium sulphates and phosphates in the necrotic areas of the disease, which clinches the diagnosis.[9] The present study showed patients with CT scan signs of hyperattenuation in 35.29% of group A and 32.35% of group B patients. Variegated appearance of CT PNS opacity found in 32.35% of group A and 41.17% of group B patients. Expansile sinus walls were observed in 20.58% of group A and 17.64% of group B patients.

A significant diagnosis of AFS could be made in 88.23% of group A and 99.17% of group B patients in this study. Khali Y et al in their study to assess the effect of systemic and topical antifungal agents - both separately and in combination - in preventing recurrence of AFRS following functional endoscopic sinus surgery (FESS) concluded that the recurrence rate of AFS in patients is low.[10] AFS represents a type 1 and type III hypersensitivity reaction to the fungal hyphae 4. But, recently some studies, however, report good result with the use of systemic itraconazole therapy. Initially, use of antifungal therapy was theoretically proposed to prevent progression of AFS to invasive forms. Subsequently, due to high rate of residual disease following FESS alone, antifungal therapy was used to provide get control over recurrence of AFS.

Early institution of amphotericin B was replaced by use of less toxic antifungal drugs like itraconazole, fluconazole. But, the in vivo antifungal activity towards dematiaceous fungus found to be not so ineffective.[11, 12] Denning et al demonstrated use of itraconazole in patients with ABPA resulted in fall in total IgE (Used as a marker of disease severity) and in systemic corticosteroid requirements.[13] In the present study, at the end of 4 weeks, group A patients on DNE showed regression of polypi from grade III to I in 56.52% and from grade III to II in 43.47%. In group B without itraconazole regression from grade III to I was in 26.08% and from grade III to grade II was 21.73%. Applying student T test, it showed a statistical significance between these two treatment regimens with P value 0.044 with P <0.05. There was reduction in fungal mucin in 64.70% of the patients. There was no change in the eosinophil count, fungal mucin, eosinophils, and IgE titres.

Bent and Kuhn in their in vitro study revealed that minimal inhibitory concentrations can be achieved effectively with topical application of antifungal agents towards commonly occurring fungi. Unlike amphotericin B, itraconazole and fluconazole offer a slightly safer form of antifungal therapy, but still may give rise to drug-induced cardiac dysrhythmias, hepatic dysfunction, urticaria, and anaphylaxis[4]. Kwai-Onn Chan, Krista A Genoway et al in their pilot study using itraconazole in refractory cases of AFS found that itraconazole can be useful adjuvant in the treatment of AFS.[7] B Manrin Rains, Corey W Mineker et al in their study to characterise patients with AFS and treating them with high dose of itraconazole found that a typical patient with AFS presented at 42.8 years of age was female and has 3.5 positive fungal cultures. Revision surgery was required in 20.5% of the patients and there were no adverse side effects over more than 36000 doses prescribed. They concluded that use of itraconazole, short burst of low dose steroids, topical steroids, and endoscopic surgery is a safe and clinically effective regimen in treating AFS. [14] Dening D W, O'Driscoll BR in their study found no severe adverse events were observed, but seven patients developed adverse events requiring discontinuation, five in the antifungal group.[13] Kristin Seiberling et al in their study of effect of itraconazole in recalcitrant fungal sinusitis stated that using itraconazole for 6 months (100 mg b.i.d.) in patients not responding to maximal medical and surgical therapy resulted in a prolonged period of next recurrence and decrease the usage of steroids and/or stop them.

The present study showed that group B patients of post FESS showed Kupferberg's grade I polyposis in 29.41%, grade II in 47.05%, and grade III in 23.52% of the patients in comparison to group A patients who showed 20.58% group I, 14.70 % group II, and 02.94% in group III patients. Student t test applied to this data for calculating significance levels and it was found that the P-value is 0.049 and the T-value was 2.34 (Table 4). EngCemGan, Andrew Thamboo et al[15] identified from their review study 6 medical modalities for AFS. Use of nonstandard topical steroids, oral antifungal drugs, and immunotherapy are options in cases of refractory AFS and found that the antifungal agents can be beneficial in recurrent and recalcitrant cases of AFS.[15] In the present study of group B patients after adding itraconazole in the postoperative treatment, it was found that the polyposis responded well with conversion of Kupferberg's grade III to grade I in all except 4 patients.

The recurrence rate of polyposis among the group A patients was 17.64% (Grade II + grade III) when compared to the recurrence rate of group B, it was 16 patients (47.05%). After initiating itraconazole, the disease clearance was seen in 14/16 patients (87.50%) and revision fess required in 2/16 patients (12.50%) in group B. Only 3 patients out of 34 required revision surgery in group A patient (08.82%).

CONCLUSIONS: Proper selection of patients with AFS based on Kuhn's classification and use of itraconazole in addition to the conventional treatment prior to FESS was beneficial in terms of reduced polyposis, symptomatic improvement of nasal obstruction, anosmia, and low recurrence rate. During the procedure of FESS, the surgeon's clearance of the disease fields improved as the bleeding was less than in patients who were not treated with itraconazole. There was statistical significance between the two groups at the end of 4 weeks regimen with and without itraconazole in terms of clearance of polyposis with a P value 0.044.

Similarly, a statistical significance noted after FESS between the groups using Kupferberg's classification to assess postoperative polyposis with a P value at 0.049.

The recurrence rate following FESS in patients using itraconazole was 17.64%. Only 3 patients required revision surgery (8.82%). Patients in whom itraconazole was not used preoperatively had based on their operative notes showed clearance of polyposis was difficult due to bleeding. The recurrence rate was high (70.57%), (grade II and III). The refractory polyposis postoperatively responded after starting itraconazole and avoiding revision surgery in 20/24 patients (83.33%).

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