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ORIGINAL ARTICLE

The Role of Systemic Itraconazole in Management of Allergic Fungal Rhinosinusitis

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ABSTRACT

Background: Management of allergic fungal sinusitis after surgery is difficult and prolonged steroid use has significant side effects and there are a group of patients who are unresponsive to standard treatment with corticosteroid. Other modalities are suggested as adjunct to steroid in the treatment of AFRS including Oral itraconazole which is an antifungal agent that seems to be benefit to patients with AFS. The aim of the present study is to study the effect of post-operative use of systemic Itraconazole as an adjunct to local steroids in management of patients of Allergic fungal rhino sinusitis.

Methods: This prospective study was conducted in Otorhinolaryngology Department, Faculty of Medicine, Zagazig University. This study included 18 patients with AFRS met the inclusion and exclusion criteria in our study.

Results: In our study there was no statistically significant difference in the affected nasal sinus between the two studied groups, there was statistically significant decrease in IgE post-operatively in both groups. there was no statistically significant difference preoperatively and six-month post-operative in both groups.

Conclusions: Systemic Itraconazole can be considered as an effective treatment alternative to the systemic steroid for postoperative management of AFRS,especially when there is intolerance, decrease response or contraindication to system steroid.

Keywords: Systemic Itraconazole, Allergic Fungal Rhinosinusitis, allergic fungal sinusitis

INTRODUCTION

Allergic fungal rhinosinusitis (AFRS) is a subset of chronic rhinosinusitis with nasal polyps characterized by antifungal IgE sensitivity, eosinophil-rich mucus (i.e., allergic mucin), and characteristic computed tomographic and magnetic resonance imaging findings in paranasal sinuses [1]. Most patients with AFS have history of allergic rhinosinusitis, approximately 5-10% of patients affected by chronic rhinosinusitis actually carry a diagnosis of allergic fungal sinusitis (AFS). The incidence of AFS appears to be impacted by geographic factors. Review of the world's literature reveals the majority of sites reporting cases of AFS to be located in temperate regions with relatively high humidity [2].The standard treatment for control of AFRS is endoscopic sinus surgery followed by systemic and/or topical steroids. Although most of patients are usually improved by this treatment, recurrence was noticed in many patients even in the early postoperative period [3].Itraconazole is a synthetic triazole antifungal agent. It inhibits the cytochrome P-450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes. Bent and Kuhn showed that many of the fungi in AFRS have in vitro susceptibility to itraconazole [4].

Follow up of AFS patients show high recurrence despite of corticosteroid using in these patients. So another method of AFStherapy is Systemic antifungal therapy is suggested. Antifungal therapy often was used in an attempt to provide some degree of control over recurrence of AFS [2].The aim of the present study is to study the effect of post-operative use of systemic Itraconazole as an adjunct to local steroids in management of patients of Allergic fungal rhino sinusitis.

METHOD

This prospective study was conducted in Otorhinolaryngology Department, Faculty of Medicine, Zagazig University .Between September 2018 to July 2019 . this study included 18 patients who clinicaly diagnosed with Allergic fungal Rhinosinusits were included .Written informed consent was obtained from all participants' parents and the study was approved by the research ethical

committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.Patients were divided into 2 groups: 1st group: received systemic corticosteroid in form of prednisolone (20 mg/ day) for 3 months then tapered over 2 weeks and local steroid spray.2nd group received systemic itraconazole (100 mg twice daily) for 3 months in addition to local steroid spray. The Mean age for the 1st group was (21.6±5.84) and the 2nd group Mean age was (21.22±3.82). ***Inclusion criteria:*** Patients with AFRS who are diagnosed according to Bent-Kuhn's criteria Elevated IGE level, characteristic CT findings, eosinophilic mucin, positive fungal smear or culture, and nasal polyposis.***Exclusion criteria:***Patients with impaired kidney or liver functions, patients who will not tolerate anti-fungal therapy, diabetic patients, patients with invasive fungal rhinosinusitis, allergic to itraconazole.

Preoperative assessment:nformation regarding the study and consent was explained to patients. All studied subjects were subjected to: ***Full history taking.Personal history:*** *Age, sex, marital state, residence and special habits.****Nasal symptoms:*** History about two main complaints (nasal obstruction and nasal discharge) and other nasal symptoms, (sneezing, post-nasal drip, headache, nasal itching , facial pain and hyposmia).

Present and past history of ENT:diseases including: ***Nose:*** Other nasal symptoms as sneezing epistaxis, allergy, lacrimation, previous, surgery.. etc.

Ear: pain, deafness , discharge , tinnitus , vertigo , ... etc.

Throat and larynx: Sore throat, dysphagia, cough , hoarseness of voice..... etc.

B. Ophthalmological diseases including Proptosis, visual loss.

C. Systemic disease, drugs or previous operations. Diabetes, asthma, hypertention, drug allergy, aspirin intolerance.Complete physical examination for all patients.External and internal nasal examination. Nasal endoscopy was done in each patient using (0° Hopkin rods) after decongestion of the mucosa by Oxymetazoline soaked cotton pledgets and topical anaesthesia by xylocain spray for the assessment of nasal mass, nasal polyp, allergic mucin, and nasal discharge.

Computer tomography in axial , coronal and sagittal planes of nose and PNS is performed in all patients for evaluation of the nasal cavity, asses the extent of disease and any bony defect in the region of lamina papyracea or skull base.Routine laboratory investigations.Haematological evaluation (complete blood count, absolute eosinophil count), Total serum IgE. Patients were given systemic steroid (30mg/ Day) for 7 days followed by (20mg/Day) for another 7 days prior to ESS.Patients were also given antibiotics and topical steroid 7 to 10 days before endoscopic sinus surgery to improve the condition of paranasal sinuses as a preoperative preparation.***Surgical intervention:***Patient Nose was prepared by oxymetazoline spray half hour before surgery.

Endoscopic sinus surgery (ESS):

All the patients underwent Endoscopic Sinus Surgery (ESS) under general hypotensive anasthesia . Every effort was done to clear all the sinuses from allergenic fungus debris , polyps and eosinophilic mucin. This restores ventilation of the sinuses and establishes a widened pathway for drainage and access of post-operative medication and irrigation . The surgical procedure of functional endoscopic sinus surgery was tailored to each patient according to the different sinus involvement revealed in the C.T scan.

Intra-operatively, nasal tissue were taken for cytological evaluation of charcot-layden crystals, fungal hyphae, allergic mucin, mast cells, eosinophils and basophil. The specimen (allergic mucin, debris, polyp) were sent for fungal microscopy, fungal culture and sensitivity and histopathological evaluation.At the end of surgery and assurance of heamostasis , nasal packs in the form of lubricated finger gloves were inserted & pt allowed to recover from GA.***Postoperative care:*** Pack removal after 24 hour.Broad spectrum antibiotics for one week.Analgesics (as needed).

Nasal decongestants three times daily for 5 days.

Close observation for nasal and postnasal bleeding or other complications.Nasal saline irrigation douches through out the follow up period.

Patients were divided randomly into two groups:

First group included (Nine patients) who received systemic corticosteroid in form of prednisolone (20 mg/day) for 3 months then tapered over 2 weeks and local steroid spray (once daily) ;whereas the scond group included (nine patients) who received systemic itraconazole (100 mg twice daily) for 3 months in addition to local steroid spray.

In addition, in the second group the pre-operative steroid dose tapered over 2 weeks post oprative.

Follow up*:* All cases were followed up to 6 months after surgery.Patients were asked to visit the OPD one week, 2 weeks ,one month and then monthly for 6 months postoperatively. They were checked using nasal endoscopy at each visit to assess any recurrent polypi, allergic mucin, nasal discharge, mucosal edema, debris . Every effort was done to clear the nose and sinus from any crustations or secretions during each visit. CT & IGE level were done 6 months postoperatively for

all patients. Patients in both groups were compared .The main parameters of comparison were:
Improvment in symptoms. Recurence of the Nasal polyps & Allergic mucin.IGE level .CT findings . Monitoring of the Liver and Kidney functions was done routinely for patients in the Itraconazole group and sign of Corticosteroid side effects were also considered for the first group.

STATISTICAL ANALYSIS

Data were collected, tabulated and analyzed by SPSS 20, software for Windows. The significance level was set at $P < 0.05$.

RESULTS

Table (1) and fig (1) showed that the age of studied groups ranged from 13 to 30 years and there was no statistical significant difference between the two groups regarding age and sex. Table (2) showed that there was no statistical significant difference between the two groups in pre-operative symptoms and signs with (100.0%) of patients having nasal obstruction or congestion, headache, nasal polyps and allergic rhinitis. Table (3) showed that there was no statistical significant difference between the two groups regarding the side invaded by the disease and regarding the affected side with (33.3% and 44.4%) of cases had bilateral involvement in 1st and 2nd group respectively. Table (4) showed that there was no statistically significant difference in the affected nasal sinus between the two studied groups with the ethmoid sinuses the most affected in both groups. Table (5) and fig (2) showed that there was an statistical significant decrease in IgE post-operatively in both groups with high decrease in 1st group from (709±176.6) pre-operatively to (415.1±92.6) at 6 months post-operative and decreased in the 2nd group from (736±221.1) pre-operatively to (399.5±73.8) at 6 months post-operative. Also, there was no statistical significant difference in the degree of improvement of pre and post-operative IgE between the two groups. Table (6) and fig. (7) showed that there was statistically significant decrease in Lund-Mackay score post-operatively in both groups with decrease in 1st group from (16.6±4.1) pre-operatively to (0.22±0.6) at 6 months post-operative and decreased in the 2nd group from (17.6±1.3) pre-operatively to (0.44±0.5) at 6 months post-operative. Also, there was no statistical significant difference in pre-operative and post-operative Lund-Mackay score between the two groups. Table (7), showed that there was no statistically significant difference preoperatively and six month post-operative between both groups, with high improvement in all symptoms In general here was statistically significant improvement in all symptoms at 1st month and at 6 months post-operatively in the two groups. Comparing between two groups, there was only one case (11.1%) had nasal obstruction and recurrence of nasal polyps in the1st group and two cases (22.3%) in the 2nd group had recurrence of nasal polyp at 6 months post-operatively

Table 1: comparison between the two studied groups regarding socio-demographic characteristics:

Variable	1st group (9) mean ± SD (Range) median	2nd group (9) mean ± SD (Range) median	t- test	p-value
Age	21.6±5.84 (13-30) 22	21.22±3.82 (16-27) 21	1.6	0.5
Variable	**1st group No(9) %**	**2nd group No(9) %**	**χ^2**	**p-value**
Sex **Male** **Female**	3 33.3% 6 66.7%	5 55.5% 4 44.4%	FET	0. 6

FET= Fischer Exact test.

Table 2: Comparing pre-operative symptoms and signs between the two studied groups:

Symptoms	1st group No(9) %	2nd group No(9) %	χ^2	p-value
Nasal obstruction or congestion	9 (100.0%)	9 (100.0%)		
Nasal discharge	9 (100.0%)	8 (88.9%)		
Postnasal drip	5 (55.6%)	6 (66.7%)		

Symptoms	1st group No(9)	%	2nd group No(9)	%	χ^2	p-value
Headache	9	(100.0%)	9	(100.0%)	1.4	0.07
Nasal polyp	9	(100.0%)	9	(100.0%)		
Smell abnormalities/ anosmia	3	(33.3%)	4	(44.4%)		
Allergic rhinitis	9	(100.0%)	9	(100.0%)		
Proptosis	2	(22.2%)	1	(11.1%)		

Table 3: Comparing affected side of nasal cavity between the two studied groups:

Symptoms	1st group No(9)	%	2nd group No(9)	%	χ^2	p-value
Bilateral	3	(33.3%)	4	(44.4%)	0.9	0.8
Right side	2	(22.3%)	1	(11.2%)		
Left side	4	(44.4%)	4	(44.4%)		

Table 4: Comparing perioperative affected nasal sinuses in the two studied groups:

Variable	1st group No(9)	%	2nd group No(9)	%	χ^2	p-value
Maxillary	7	(77.7%)	8	(88.8%)	0.27	0.99
Ant. ethmoid	9	(100.0%)	9	(100.0%)		
Post. ethmoid	9	(100.0%)	9	(100.0%)		
Sphenoid	4	(44.4%)	3	(33.3%)		
Frontal	6	(66.6%)	7	(77.7%)		

Table 5: Comparing pre and post-operative IgE in the two studied groups:

Variable	1st group (9) mean ± SD (Range) median	2nd group (9) mean ± SD (Range) median	M.W test	p-value
Preoperative IgE (IU/ml)	709±176.6 (410-960) 760	736±221.1 (510-1200) 620	1. 3	0.2
6 months Postoperative IgE (IU/ml)	415.1±92.6 (230-520) 450	399.5±73.8 (280-555) 400	0.2	0.8
p-value (Paired t-test)	**0.001****	**0.001****		

** Statistically highly significant difference (P ≤ 0.001)

Table 6: Comparing pre and post-operative Lund-Mackay score in the two studied groups:

Variable	1st group (9)mean ± SD(Range)median	2nd group (9)mean ± SD(Range)median	t-test	p-value
Preoperative Lund-Mackay score	16.6±4.1(9-22)15	17.6±1.3(12-22)18	0.8	0.7
6 months postoperative Lund-Mackay score	3.4±0.6 (0-7)2.1	5.6±1.5(0-9)3.4	0.5	0.2
p-value (Paired t-test)	0.001**	0.001**		

** Statistically highly significant difference (P ≤ 0.001)

Table 7: Comparing pre and post-operative symptoms and Nasal polyp recurrence in the two studied groups:

	1st group		2nd group		χ^2	p-value
	No(9)	%	No(9)	%		
Pre-operative						
Absent	0.0	(0.00%)	0.0	(0.00%)		
Present	9	(100.0%)	9	(100.0%)	FET	1
One month Post-operative						
Absent	9	(100.0%)	9	(100.0%)	FET	1
Present	0.0	(0.00%)	0.0	(0.00%)		
Six months Post-operative	8	(88.9%)	7	(77.7%)		
Absent	1	(11.1%)	2	(22.3%)		
Recurrence (Nasal obstruction & Nasal polyp)					0.4	0.5
p-value	**0.001****		**0.001****			

** Statistically highly significant difference ($P \leq 0.001$)

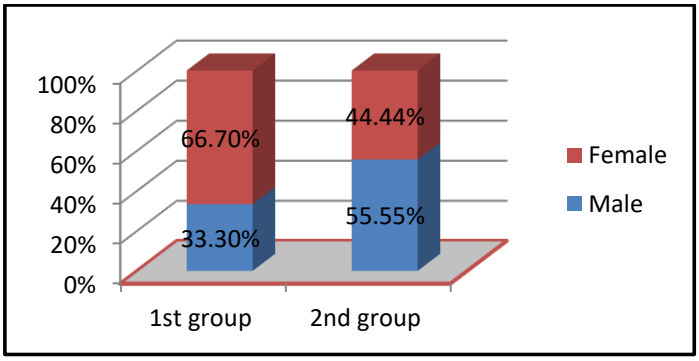

Figure 1: Bar chart for sex distribution in the two studied groups

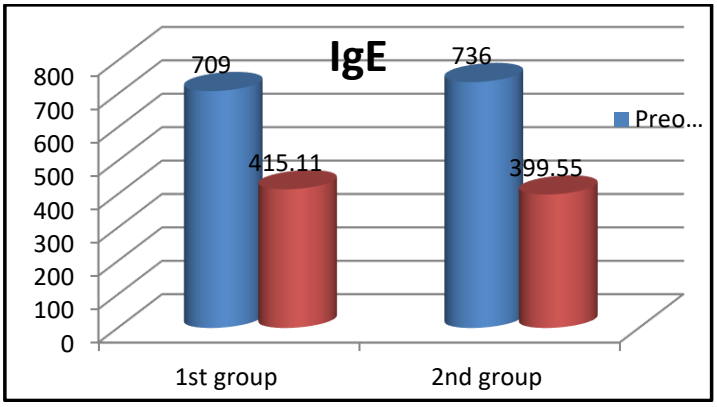

Figure 2: Bar chart for comparing pre and post-operative IgE in the two studied groups

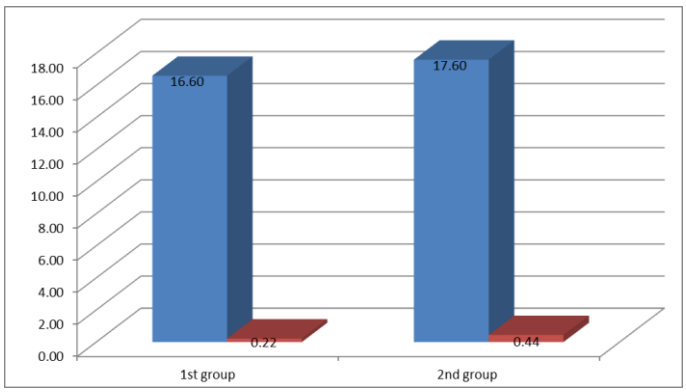

Figure 3: Bar chart for comparing pre and post-operative Lund-Mackay score in the two studied groups

(A) (B)

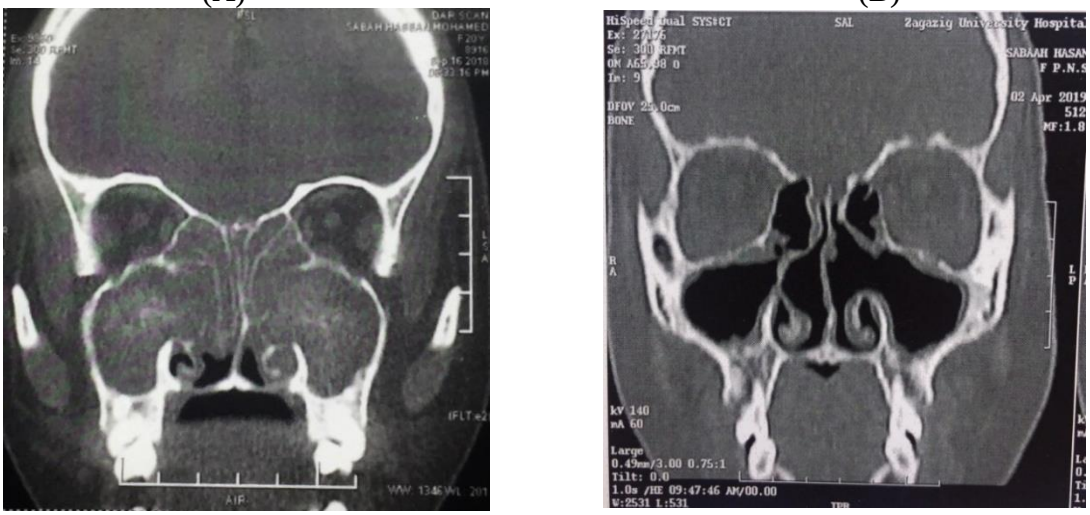

Figure 4: Computed tomographic scan on nose and PNS showing a case of allergic fungal rhinosinusitis treated by oral Corticosteroids for 6 months in addition to local steroids nasal spray after surgery (a) preoperatively and (b) 6 months postoperatively.

(A) (B)

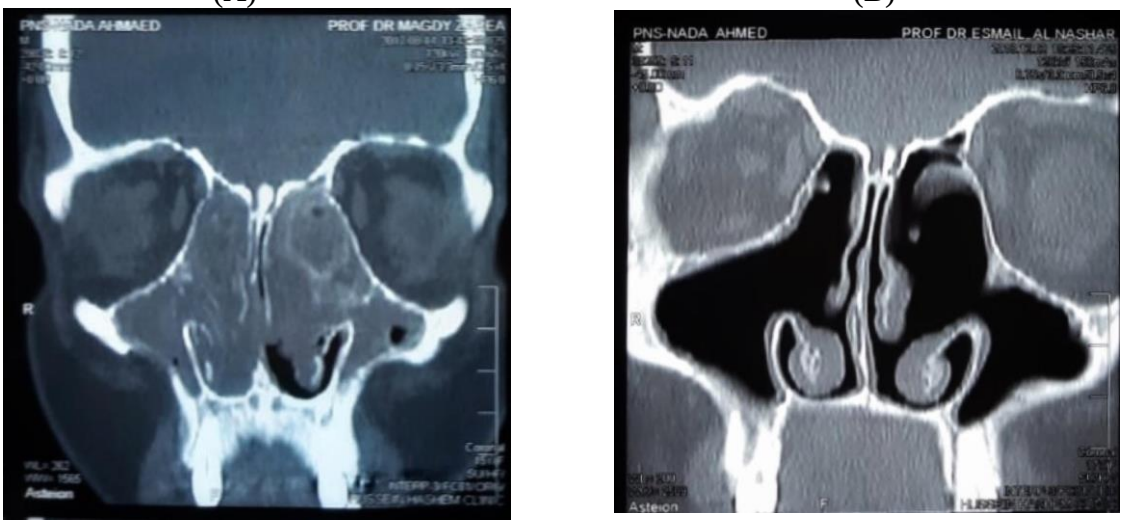

Figure 5: Computed tomographic scan on nose and PNS showing a case of allergic fungal rhinosinusitis treated by oral itraconazole for 6 months in addition tolocal steroids nasal spray after surgery (a) preoperatively and (b) 6 months postoperatively.

Conflict of Interest: Non
Financial Support: Non

DISCUSSION

Management of AFRS is often considered a challenge to the rhinologist in spite of its specific clinical, radiological and histopathological findings. Although Bent-Kuhn's criteria [6] is considered as the gold standard for clinical diagnosis for AFRS, yet it is difficult to produce it in routine clinical practice as majority of patients who exhibit classical features like presence of allergic mucin, IgE mediated hypersensitivity and eosinophilia fail to show positive fungal cultures [(6)].The current study, showed that there was no statistical significant difference in pre and post-operative IgE between the two groups at 6 months post-operative (Table 5). These results were in agreement with the study of Rojita et al [7] and Denning et al. [8] where they studied the effect of systemic itraconazole in patients with allergic bronchopulmonary aspergillosis (ABPA) and demonstrated no statistically significant difference in pre and post-operative regarding total IgE.

In our study, there was a high statistical significant in comparison between the pre and post-operative Lund-Mackay score in both groups at 6 months post-operative, there was statistically significant decrease in Lund-Mackay score post-operatively in both groups, with decrease in 1st group from (16.6±4.1) pre-operatively to (0.22±0.8) at 6 months post-operative and decreased in the 2nd group from (17.6±1.3) pre-operatively to (0.5±0.5) (Table 6). which in agreement with the study of Hashemi et al. [9] who reported Lund-Mackay score of CT scan before treatment was 19.8 (±4.2). After 6 month of treatment Lund-Mackay score of CT scan lowered to 15.6 (±6.5) with a high significant difference (P < 001). In our study, Comparing pre and post-operative symptoms and Nasal polyp recurrence there was no statistically significant difference preoperatively and six month post-operative between both groups, with high improvement in all symptoms, but there was a statistical significant improvement in all symptoms at at 6 months post-operatively in the two groups (table 7). These results were in agreement with the study of Reda et al. [10] who reported that all patients postoperatively were clinically asymptomatic at the end of the sixth months, and there was no recurrence of nasal polyps at the end of sixth months, Similarly Patro et al. [11]in there study reported that none of the patients showed any evidence of recurrence until 6 months of follow-up. On the contrary Nikakhlagh et al.[(2)] found 28% of group A had recurring polyp in one or both sides versus 64% of group B, also 20% of group A had radiological evidence of recurrence versus 12% of group B. Our study found that itraconazole may be of benefit as an adjunct in the management of refractory AFS. And prolong the time of recurrence, which in agreement with the study of Chan et al. [12] study also found that itraconazole was effective in a good percentage of patients of AFRS who had surgery and were refractory to prednisone, intranasal steroids, and amphotericin B nasal sprays were improved by using itraconazole.

Recommendations: We recommend that this study be extended to involve a bigger sample and long term follow up to provide us with adequate results to demonstrate it is effectiveness. Also, another studies which include the use of both medications (Systemic corticosteroids and itraconazole) together can be considered.Conclusion: Systemic Itraconazole can be considered as an effective treatment alternative to the systemic steroid for postoperative management of AFRS, especially when there was intolerance, decrease response and contraindication to system steroid.

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