A prospective study comparing Itraconazole and systemic steroids as an adjunct to topical steroids in the post-operative management of Allergic fungal rhinosinusitis

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Abstract

Title: A prospective study comparing Itraconazole and systemic steroids as an adjunct to topical steroids in the post-operative management of Allergic fungal rhinosinusitis ABSTRACT Objectives The objective of this study was to compare the efficacy of Itraconazole and systemic steroids as an adjuvant to topical steroids in post-operative patients with Allergic Fungal Rhinosinusitis (AFRS) using both subjective and objective outcome measurements. Methods A prospective comparative study was conducted in a tertiary care center on 60 patients diagnosed with AFRS. Patients with chronic systemic illness and those undergoing revision surgery were excluded. Post-operative patients were divided into two groups of 30 each which received Itraconazole 400 mg OD or Methylprednisolone in tapering doses over six weeks. The outcomes were measured at the end of 6 weeks -Kupferberg endoscopic staging, Absolute Eosinophilic Count (AEC), Serum Immunoglobulin (IgE), and Sino Nasal Outcome Test - 20 scores. Results Our study showed no statistical significance in outcomes between the two groups treated with Itraconazole and Methylprednisolone regarding recurrence, AEC, IgE, and Quality of Life Assessment ($p<0.01$). Conclusion Itraconazole was comparable to Methylprednisolone in preventing disease recurrence in the post-operative management of AFRS. It may be a viable alternative to replacing systemic steroids where the latter may be contraindicated. Itraconazole given at a dose of 400 mg once daily for six weeks was a safe dose. Keywords: Allergic Fungal Rhinosinusitis, Itraconazole, endoscopy, Quality of Life, Methylprednisolone Key points: * Itraconazole was comparable to systemic steroid (Methylprednisolone) in preventing disease recurrence in the post-operative management of AFRS. * It may be a viable alternative to replacing systemic steroids where the latter may be contraindicated. * Itraconazole given at a dose of 400 mg once daily for six weeks was a safe dose. * Recurrence may be treated safely with Itraconazole than with steroids. * The course may be repeated in case of recurrence with close monitoring.

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ABSTRACT

Objectives

The objective of this study was to compare the efficacy of Itraconazole and systemic steroids as an adjuvant to topical steroids in post-operative patients with Allergic Fungal Rhinosinusitis (AFRS) using both subjective and objective outcome measurements.

Methods

A prospective comparative study was conducted in a tertiary care center on 60 patients diagnosed with AFRS. Patients with chronic systemic illness and those undergoing revision surgery were excluded. Post-operative patients were divided into two groups of 30 each which received Itraconazole 400 mg OD or

Methylprednisolone in tapering doses over six weeks. The outcomes were measured at the end of 6 weeks -Kupferberg endoscopic staging, Absolute Eosinophilic Count (AEC), Serum Immunoglobulin (IgE), and Sino Nasal Outcome Test - 20 scores.

Results

Our study showed no statistical significance in outcomes between the two groups treated with Itraconazole and Methylprednisolone regarding recurrence, AEC, IgE, and Quality of Life Assessment ($p<0.01$).

Conclusion

Itraconazole was comparable to Methylprednisolone in preventing disease recurrence in the post-operative management of AFRS. It may be a viable alternative to replacing systemic steroids where the latter may be contraindicated. Itraconazole given at a dose of 400 mg once daily for six weeks was a safe dose.

Keywords : Allergic Fungal Rhinosinusitis, Itraconazole, endoscopy, Quality of Life, Methylprednisolone

Key points :

- Itraconazole was comparable to systemic steroid (Methylprednisolone) in preventing disease recurrence in the post-operative management of AFRS.
- It may be a viable alternative to replacing systemic steroids where the latter may be contraindicated.
- Itraconazole given at a dose of 400 mg once daily for six weeks was a safe dose.
- Recurrence may be treated safely with Itraconazole than with steroids.
- The course may be repeated in case of recurrence with close monitoring.

Introduction:

Allergic Fungal Rhinosinusitis (AFRS) is a type I and type III mediated hypersensitivity reaction to inhaled fungal antigens, notably Aspergillus species and dematiaceous fungi present in the nasal cavity of immunocompetent individuals.[1]This non-invasive form of fungal sinusitis is notorious for high recurrence rates and is often a topic of intrigue to the treating clinician. Multimodality treatment with primary surgery followed by medical management is the usual norm. The aim of surgery in these cases is to remove the antigenic fungal load and improve the aeration of sinuses. Surgery would facilitate easy access to topical sprays and lavages. Medical therapy with topical and systemic corticosteroids plays a vital role in preventing disease recurrence. However, a steroid-sparing agent with a better side effect profile may be a welcome alternative. The favorable outcomes in patients with Allergic Broncho Pulmonary Aspergillosis(ABPA) treated with Itraconazole have prompted rhinologists to add Itraconazole to the armamentarium against AFRS.[2, 3] However, there is a paucity of studies comparing the effectiveness of Itraconazole and systemic steroids as an adjuvant to topical steroids in post-operative patients, in preventing disease recurrence in AFRS, which was the objective of our study.

Materials and Methods:

The study was approved by the Institutional Ethics committee of our institute and conformed to the ethical standards laid down in the Declaration of Helsinki. This manuscript preparation followed the principles of COPE (Committee on Publication Ethics) and guidelines of STROBE (The Strengthening the Reporting of Observational Studies in Epidemiology) statement. Informed consent was taken from all patients recruited for the study.

The study was a prospective observational study on AFRS patients in a tertiary care teaching hospital. Patients with chronic systemic illness and those undergoing revision surgery were excluded. AFRS was diagnosed based on Bent and Kuhn's criteria.[4] Based on the literature, as it was difficult to fulfill all criteria, especially a positive fungal culture, we came to a diagnosis based on clinical, radiological, and histopathological reports.[5, 6]

Pre-operative assessment:

Complete blood counts, Absolute Eosinophil Count (AEC), and total Serum Immunoglobulin (IgE) levels were assessed, along with a Quality-of-life questionnaire-Sino- nasal Outcome Test (SNOT- 20). The standard reference level of serum IgE in our institute was 0-100 IU/ml, and in AFRS, as per standard,>500 IU/ml was considered elevated. The standard reference range for AEC in our Institute was 40 -440 mm^3. In AFRS, as per standard, a value of more than 500mm^3 was considered elevated. Nasal polyps were graded by endoscopy according to Kupferberg's grading system.[7]Patients were given a course of antibiotics (Roxithromycin 150 mg twice a day for ten days) and a short course of oral steroid (8 mg Methylprednisolone for five days followed by 4 mg methylprednisolone for five days) one week prior to endoscopic sinus surgery.

Intraoperative assessment:

Nasal polyp, fungal debris, and allergic mucin were sampled separately and sent for fungal smear, fungal culture, and histopathology (HPE) to look for Charcot-Leyden crystals, fungal hyphae, allergic mucin, and eosinophils.

Post-operative assessment:

After one week of surgery, patients were divided into two groups by a closed envelope technique of randomization, but no blinding was involved. The Itraconazole group was given oral Itraconazole 400 mg once daily for six weeks. The Methylprednisolone group was given tapering doses of 16mg, 8mg, and 4mg of Methylprednisolone, each taken for two weeks. Both groups were given topical fluticasone nasal spray, one puff (50mcg) each nostril once daily and saline nasal douching for six weeks.

The Itraconazole group had a baseline liver function test repeated every two weeks. In case of alteration of values, the drug was withdrawn. Similarly, in the Methylprednisolone group, baseline blood sugar levels (Fasting Blood Sugar [FBS], Post Prandial Blood Sugar [PPBS], and Glycosylated Hemoglobin [HbA1c]) were checked. People with diabetes receiving Methylprednisolone were monitored every two weeks. In case of poor glycemic control, the drug was withdrawn. At the end of 6 weeks, patients were assessed for post-operative SNOT- 20 scores, Kupferberg endoscopic staging, AEC, and Serum IgE.

The patients who were available for follow-up were followed up at twelve weeks and twenty four weeks even after the study period of six weeks. After six weeks, patients in both groups continued to use Fluticasone nasal spray.

Sample size:

Due to the sparsity of similar studies, a pilot study was conducted in the department on 20 patients. Based on the results of recurrence percentage among patients receiving Itraconazole (10%) and Methylprednisolone (30%) observed in the pilot study and with 80% power and 95% confidence, the minimum sample size required was 62. Sixty patients were recruited (30 in each arm).

Statistical analysis:

The data were analyzed using IBM SPSS version 20.0 software. Categorical variables were expressed using frequency and percentage and numericals using mean and standard deviation. An independent sample t-test was used to test the statistical significance of comparing mean change from baseline of SNOT- 20, Serum IgE, and AEC at one month between two groups. A Chi-square test with continuity correction was used to test the statistical significance of the association of all categorical variables (Predominant symptoms, histopathological findings, and nasal endoscopic grading) between both the groups. P-value < 0.05 was considered to be statistically significant.

Results:

At the end of six weeks, one patient from Itraconazole and two from Methylprednisolone groups were lost for follow-up, leaving behind 57 patients. Hence, out of 57 patients, 29 (50.9 %) belonged to the Itraconazole group, and the rest, 28(49.1%) Methylprednisolone group. Both groups were comparable (Table- 1).

After six weeks of treatment, serum IgE was found to be normalized (< 500 IU/mL) in 51.7% and 64.3% of Itraconazole and Methylprednisolone groups, with no statistical difference between both groups. (p=0.34). The AEC was normalized in 82.8% and 89.3% in Itraconazole and Methylprednisolone groups with no statistical difference between both groups(p=0.74) (Tables- 2, 3). Pre-operatively, all patients had grade 3 nasal polyps on nasal endoscopy. At six weeks after surgery, recurrence (Kupferberg Grade more than 1) was seen in 2 patients (6.9 %) in the Itraconazole group and 4(14.3%) patients in the Methylprednisolone group. The difference was not statistically significant (p=0.6).

At 12 weeks, 24 out of 29 from the Itraconazole group and 17 out of 28 from the Methylprednisolone group were available for follow-up. Of which, 5(20.8%) in the itraconazole group and 6(35.3%) in the methylprednisolone group showed recurrence in endoscopy, which was not statistically significant (p=0.6).

At 24 weeks, 20 of the 29 patients in the Itraconazole group and 17 of the 28 patients in the Methylprednisolone group were available for follow-up. Of which, 5(25 %) in the itraconazole group and 7(41.2%) in the methylprednisolone group showed recurrence in nasal endoscopy (p=0.3).

Discussion:

Optimal medical management to prevent recurrence in post-operative patients of AFRS is still controversial. The International Consensus Statement on Allergy and Rhinology: Rhinosinusitis 2021 has recommended modest benefits from systemic antifungals in AFRS in improving endoscopic scoring and time to recurrence.[8]The dearth of well-designed trials for studying the efficacy of oral antifungals was also emphasized. Given the potential systemic toxicity with long-term systemic steroids, the possibility of utilizing Itraconazole in the post-operative care of AFRS, its repeatability, and safety in long-term use form the basis of the current study.

Though Bent and Kuhn's criteria have been widely used since its inception for the diagnosis of AFRS, fungal detection could be problematic, attributing factors being the sparse distribution of fungus within mucin unless highly sensitive methods of detection are used.[5,6]In a study by Reda et al. only 6 out of 60 patients showed fungal hyphae and Charcot- Leyden crystals. A positive fungal culture was excluded by them, as it was inconclusive.[9]Similarly, Rains et al. had included patients without histologic evidence of fungus.[10] In our study, allergic mucin was seen in 54 out of 57 patients, of which 28(96.5%) were from the Itraconazole group, and 26 (96.8%) were from the Methylprednisolone group. A positive fungal stain was seen in 31(54.3%) out of 57 patients, 13(72.4%) in the Itraconazole group, and 18(79.3%) in the Methylprednisolone group. Eosinophil with Charcot- Leyden crystals was seen in 48 out of 57 patients, twenty-three (79.3%) patients in the Itraconazole group, and 25 (89.2%) in the Itraconazole Methylprednisolone group. Culture positivity for fungus was seen only in 9 (15.8%) out of 57 patients, five patients in the Itraconazole group and 4 in the Methylprednisolone group. As reported by Tyler et al., neither a positive fungal culture confirmed the disease nor did a negative fungal culture exclude the diagnosis of AFRS because there is always a question of an isolated fungus being an air contaminant.[11] This aspect was further explained in a study conducted by Buzina et al. in 233 patients, which showed that nasal mucus collected either by saline flushing or by endoscopic sinus surgery from both patients and healthy volunteers had the same proportion of fungal elements.[12] Thus, many of the studies on AFRS have not strictly adhered to all the criteria mentioned in Bent and Kuhn.

Patients with AFRS should ideally have a raised IgE as this is an IgE-mediated immune response to an extra mucosal fungus. With surgery and adequate post-operative care, IgE should theoretically show a decreasing trend as the antigenic load decreases. All patients showed a reduction in IgE values after treatment (Table-2). It was observed that 51.7% of Itraconazole and 64.3% of the Methylprednisolone group had normalized IgE (<500IU/ml) after treatment. However, the difference in pre-operative and post-operative IgE values between both groups was not significant. Moreover, all patients who recurred had an elevated IgE pre-operative value of more than 1000IU/ml, and post-operative value never decreased below 500IU/ml.

Serum eosinophilia is part of the minor criteria in AFRS.[4] A raised eosinophil count can be seen associated with conditions like atopy; hence a high value in a patient need not be indicative of AFRS alone. Similarly,

for the same reason, a fall in the absolute eosinophil count is not necessary with just the treatment for AFRS, and a patient can continue to have a persistent raised AEC even with treatment. In our study, AEC was raised in all patients pre-operatively, and 82.8% of patients who took Itraconazole and 89.3% who took Methylprednisolone had AEC<500 mm^3 post-treatment. Though a definite decrement was seen in post-treatment patients in both groups, there was no statistically significant correlation between relapse and fall in AEC counts.

It is essential to slash down long-term or repeated usage of corticosteroids given the plethora of complications it can bring on, especially in the Asian population, where the metabolic syndrome is one of the leading causes of morbidity and mortality.[13] In our study, we used oral Methylprednisolone in tapering doses of 16mg, 8mg, and 4mg over 2weeks each for six weeks. Twelve patients had transient weight gain, 8 had gastritis despite using proton pump inhibitors, and none developed steroid-induced DM. All our patients completed therapy without a treatment break.

A therapeutic dose of Itraconazole 400 mg once daily for six weeks was given in our study. All our patients had grade 3 polyps pre-operatively. In the Itraconazole group, 2 out of 29 (6.9%) patients had a recurrence. The rest who received Itraconazole had definite clinical improvement in QOL and endoscopy. Similar results in recurrence between the groups were observed by Rojita et al.[14]None of our patients on Itraconazole developed transaminitis or liver failure.

Rains et al. 10, in the retrospective analysis of patients with recurrent AFRS treated with high dose Itraconazole, topical nasal steroids, and low burst steroids, showed that only 20.5% of the patients with recurrence required revision surgery after this treatment. We followed up with patients for 24 months, and none required revision surgery. There was recurrence in terms of endoscopic staging, but SNOT- 20 score had reduced.

Not many studies have compared the effectiveness of both steroid and Itraconazole in AFRS. Though Kupferberg did compare steroids and antifungals in his trial, endoscopic evaluation was the only method employed as a comparison tool between the groups.[7]Also, the basis of division into groups was unclear. However, we had 30 patients in each arm and used subjective (QOL questionnaire) and objective outcome measures (IgE, AEC, Endoscopic grading).

In a study by Rojita et al., 14 patients received oral prednisolone 30 mg once daily for one month, followed by topical nasal steroids for six months. The other group received only Itraconazole 100 mg twice daily for six months. So topical nasal steroid was given only to the group that received oral steroids. Outcome parameters were measured at the end of 6 months, showing no statistical difference in the recurrence percentage. In contrast, our study compared oral steroids and Itraconazole as adjuncts to topical steroids. Hence all our patients (in both groups) received topical nasal sprays. Also, the drug regimen used in our study differed in that Itraconazole was given in a dose of 400 mg once daily and Methylprednisolone16 mg, 8 mg, and 4mg tapered over two weeks each for a total of 6 weeks. Our study evaluated outcome parameters at a shorter follow-up duration of 6 weeks, which was the decided study period planned for the study. However, we could follow up with 20 out of 29 patients in the Itraconazole group and 17 out of 28 patients from the Methylprednisolone group at six months. Recurrence was noticed in 6.9% (2 out of 20) and 14.3% (4 out of 17) of Itraconazole and Methylprednisolone groups, respectively, with no statistical significance between the two groups. In both groups, recurrence was treated by increasing the topical steroid dose. Efficacy of Itraconazole in refractory AFRS was cited by Chan et al. 15 and reported significant clinical improvement in 28% of cases. Some authors have reported no significant benefit with post-operative Itraconazole.[16, 17] Lack of benefits may be due to the inability to identify fungi in the specimen or since Itraconazole may fail to reach the minimal inhibitory concentration in mucous when taken systemically.

In our experience, Itraconazole was found to be effective as a steroid-sparing agent in a distinct cohort of patients who underwent surgery. Further karyotyping and endotyping may be required to identify this subset. Robust studies with a longer duration of follow-up may be ideal for comparing the effectiveness in the long run.

Limitations:

The short duration of the follow-up period, small sample size, sinus surgery and concomitant use of topical steroid sprays are limiting factors. Also, in some patients whose pre-operative and post-operative IgE values showed a plateau trend with only a reduction in SNOT- 20 score raise the question of a possible overlap between AFRS and EMRS(Eosinophilic mucin rhinosinusitis) as the symptomatic relief could attributed to reduced antigenic load after surgery.

Conclusions:

Itraconazole was comparable to Methylprednisolone in preventing disease recurrence in the post-operative management of AFRS. It may be a viable alternative to replace systemic steroids where the latter may be contraindicated. An oral dose of 400 mg once daily of Itraconazole given for six weeks was safe.

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Conflict of interest: None to declare.

Data Availability Statement:

The data supporting this study's findings is available from the corresponding author at reasonable request.

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Legends for tables

Table- 1: The baseline characteristics of both the study groups are comparable.

Table 2: Both study groups showed similar improvement in terms of symptoms, SNOT- 20, AEC, and serum IgE in the first week

Table 3: At the end of 6 weeks, both the Itraconazole and steroid groups had similar scores in SNOT- 20. The AEC and serum IgE had become normal in a majority of patients.

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