

**ROLE OF ITRACONAZOLE IN SINO NASAL POLYPOSIS**Somu L<sup>1</sup>, Prasanna Kumar Saravanam<sup>2</sup>, A. Ravikumar<sup>3</sup>**HOW TO CITE THIS ARTICLE:**

Somu L, Prasanna Kumar Saravanam, A. Ravikumar. "Role of Itraconazole in Sino Nasal Polyposis". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 70, August 31; Page: 12112-12119,

DOI: 10.14260/jemds/2015/1745

**ABSTRACT: OBJECTIVE:** To diagnose fungal disease in Sinonasal Polyposis. To compare the clinical outcome of patients with Sinonasal Polyposis treated with and without Itraconazole. **PATIENTS AND METHODS:** A 2 year, Randomized Case Controlled study in University Hospital. 30 patients with Sinonasal Polyposis were randomly allocated to Study and Control group. All underwent nasal endoscopy, CT PNS, Nasal swab for fungal smear & culture. Study group received Itraconazole, per oral for 2 and 4 weeks in pre & post-operative period. **RESULTS:** 60% of Pre-operative nasal swab were KOH positive for fungal hyphae. Both groups presented with headache and nasal obstruction. Lund Kennedy system used to grade polyps, edema and discharge. Fungus was isolated in 40%; the predominant fungus grown was *Aspergillus flavus*. Histopathology showed 66% inflammatory polyps and 44% allergic polyps. Statistical analysis and comparison of control and study group showed significant lower clinical scores in study (Itraconazole) group in the 1<sup>st</sup> month post-operative in regards to nasal obstruction and recurrence of nasal polyps at 6 months post treatment. The Lund Mackay score for CT scan did not show significant difference. **CONCLUSION:** Fungal disease co exists in a majority of patients with Sinonasal Polyposis. It is not known if it is a causative factor. Itraconazole was found to improve the clinical outcome in patients treated for sinonasal polyposis. No untoward side effects of the drug were indentified in our study.

**KEYWORDS:** Allergy, Nasal Cavity, fungal Sinusitis, Itraconazole.

**INTRODUCTION:** Ahmed Bassiouny et al,<sup>1</sup> have reported allergic fungal sinusitis to be present in 92% of patients with chronic rhinosinusitis and sinonasal polyposis. Laila M Telmesani,<sup>2</sup> has reported histopathological evidence of allergic fungal sinusitis in 12.1% of patients with sinonasal polyposis.

The presence of fungi in sinonasal polyposis has been well documented in literature,<sup>3</sup> but the role of fungi in polyposis is debated. Either it causes polyposis by eliciting an immune response or by invading tissue.<sup>4,5</sup> F Munoz-del-Castillo et al have concluded that nasal colonization by fungi does not induce fungal sensitization.<sup>3</sup> Rains BM et al have suggested that use of Itraconazole in AFS may avoid revision surgery.<sup>6</sup> The use of antifungal medications in sinonasal polyposis needs to be evaluated further.

The present study was carried out to diagnose the prevalence of fungal infection in patients with sinonasal polyposis and to compare the clinical outcome of patients of sinonasal polyposis, treated with and without Itraconazole.

**PATIENTS AND METHODS:** This prospective randomized controlled trial was conducted over a period of two years, from June 2008 to June 2010 in a tertiary care center in South India. Informed consent was taken from all patients, who underwent this study. Adult patients aged between 20 and 60yrs, of both sexes having diagnosed as sinonasal polyposis by clinical, Nasal Endoscopy & CT scan were included in the study. Patients with co-morbid conditions such as diabetes, renal failure, immunocompromised state and atopy were excluded from the study. These patients were randomly allocated into two groups. Group A (Study group) and Group B (Control group).

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The treatment protocol used in this study is shown in table 1. The only difference between the two groups was that the group A patients received tablet Itraconazole (4mg/kg body weight) for two weeks preoperatively and four weeks post operatively. All patients who were started on Itraconazole were monitored for renal and liver functions.

### All these Patients were Evaluated Using:

1. Symptom inventory for subjective evaluation.
2. Diagnostic nasal endoscopy using Lund – Kennedy scoring system.<sup>7</sup>
3. CT- PNS scoring using Lund - Mackay scoring system.<sup>8</sup>

All patients underwent Functional Endoscopic Sinus surgery with polypectomy under general anaesthesia. Post operatively, they were followed up at first, third and sixth month.

**RESULTS:** A total of thirty patients who fulfilled the criteria were included in this study.

Statistical analysis was done using SPSS software (Version 15). The following parameters were assessed. The mean, standard deviation, P values wherever necessary using Mann Whitney U test, Pearson chi square test. p value of <0.05 was considered significant.

The average mean age of the patients was 31.8±10.9. Preoperative KOH fungal smear was positive in 60% of specimens. Fungal culture was positive in 40% of specimens, majority of which grew *Aspergillus flavus* (36.7%) and one grew *Cladosporium oxysporium* (3.3%).

On analysis of the subjective symptom inventory (Table 2) there was significant reduction in scores between the preoperative and postoperative symptom score at 6 months post-operative follow up in both groups. Patients in group A had a statistically significant relief in nasal obstruction in the first post-operative follow up at 1 month.

Endoscopic scores (Lund–Kennedy scoring system,<sup>7</sup>) did not show any significant difference between the two groups. But, the recurrence of polyp was less in group A (Itraconazole) at 6 months that was statistically significant with p value of 0.01. Histopathological study of the specimen showed changes consistent with inflammatory polyp in a majority of these patients. There was no statistically significant difference between the two groups in CT PNS (Lund - Mackay scoring system<sup>8</sup>) scores.

**DISCUSSION:** The etiology of sinonasal polyposis is multifactorial. Many authors have implicated fungi to have a role in ethiopathogenesis of sinonasal polyposis. However the question arises whether fungi play a role in the persistence of polypi, recurrences of polypi and whether they contribute to the persistence of inflammation and edema as in allergic fungal sinusitis (AFRS).

In this study, we have sought to assess the presence of fungi in sinonasal polyposis, its role in persistence of symptoms even after the polypi has been surgically removed. In our study KOH fungal smear was positive in 60% of all patients of sinonasal polyposis. Ponikau et al.,<sup>5</sup> (1999) in a study in patients with chronic rhinosinusitis have detected fungi in 96% of nasal secretion and isolated 40 different fungal species in the sinuses.

In this study, Fungi was cultured in 40% of specimen, *Aspergillus flavus* was the commonest fungi that was cultured in 37% of the isolate, *Cladosporium oxysporium* was cultured in one specimen. In 60% of the specimens there was no growth. P. Kordbacheh et al.,<sup>9</sup> reported a smear positive rate of 9%, culture positive in 9% and the most common fungus was *Aspergillus flavus*. E Razmpa et al.,<sup>10</sup> reported 42% of samples were positive for fungus, 34% of samples showed fungal colonization in culture which includes 30% *Aspergillus flavus* and 4% *Aspergillus fumigatus*.

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The sensitivity of the fungal smear depends on the method of taking the specimen, transit time and environmental humidity. In this study smear and tissue were taken under endoscopic control in the endoscopy room and processed immediately within 20 min.

SNOT 20 has been developed as a useful, comprehensive subjective questionnaire to assess symptomatology and its impact on life across physical, psychological & emotional domains.<sup>11</sup> It does not take into account a very important nasal function, namely, sense of smell, which is severely affected in patients with sinonasal polyposis. Hence in this study, we have concentrated only on three major symptoms, such as nasal obstruction, headache and sense of smell which form the basis of our symptom inventory.

On comparison between the two groups, group A patients who had received Itraconazole had a significant improvement in the 1<sup>st</sup> month for nasal obstruction (p value 0.05). There was no significant difference between the two groups in the 3<sup>rd</sup> & 6<sup>th</sup> month follow up. Both groups had equally significant improvement in all the three symptoms during follow up with no difference in the degree of relief between the two groups. Chan KO et al.,<sup>12</sup> in their study of effectiveness of Itraconazole in allergic fungal infections showed that 28% significant improvement, 28% moderate improvement and 44% no change following administration of Itraconazole for refractory allergic fungal sinusitis.

Diagnostic Nasal Endoscopy was performed pre operatively and post operatively at 1, 3, 6 months post-surgery to check for polyp, edema, discharge using Lund Kennedy System.<sup>7</sup> In this study, we found there was a statistically significant reduction in recurrence of polyp in group A when compared with the group B (p value 0.01) at 6 months. There was a statistical improvement in overall scoring at 6 month follow up (p value 0.04) in both groups when compared with pre op scores. However, there was no significant changes in 1<sup>st</sup> and 3<sup>rd</sup> month follow up.

CT paranasal sinus was done pre operatively and post op at 6 months and graded using Lund Mackay system.<sup>8</sup> Both the groups improved at 6 months but there was no statistical difference between both groups (p value 0.02).

Itraconazole was used only for 6 weeks in group A (15 patients) and the follow up was for 6 months only. No guidelines exist about duration of treatment of Itraconazole. None of the patients in this study developed toxicity to the drug. Liver functions were monitored monthly while they were on treatment. K Seiberling et al, Wormald et al reported elevated liver enzymes in 3 patients among 23 patients who were treated with Itraconazole.

In our study we noted a statistically significant improvement in nasal obstruction in 1 month and also significant decrease in recurrence of polyps in 6 months for patients who were treated with Itraconazole. Itraconazole may have reduced the fungal load and thus there could have been a significant reduction in nasal obstruction and recurrence of polyps.

The authors acknowledge that the sample size in this study is less. The duration of Itraconazole therapy was 6 weeks and follow up was for 6 months. There is a need for further evaluation of role of antifungal medication in sinonasal polyposis in a larger group of patients with a longer follow up.

**CONCLUSION:** This study shows the presence of fungi in sinonasal polyposis, as evidenced by 60% positivity in fungal smear and 40% positivity in fungal culture. However it does not prove the role of fungi in ethiopathogenesis of sinonasal polyposis. It is possible that fungi may play a part in recalcitrant/chronicity of disease. This will require further large scale randomized control trial.

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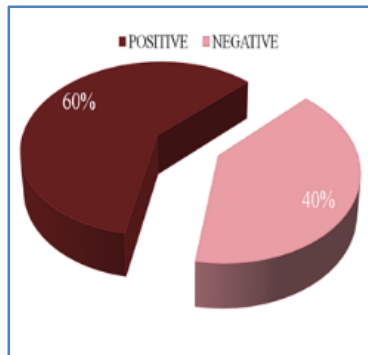
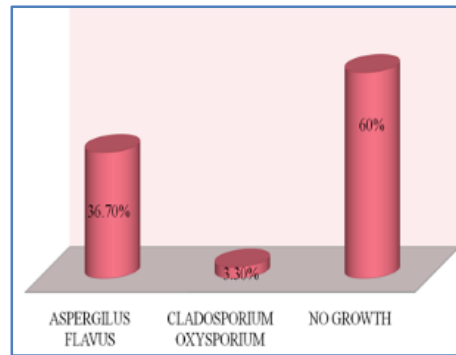
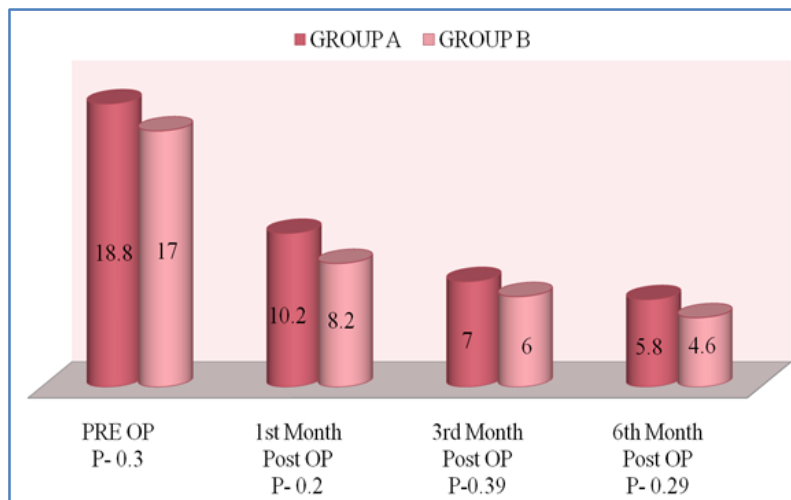
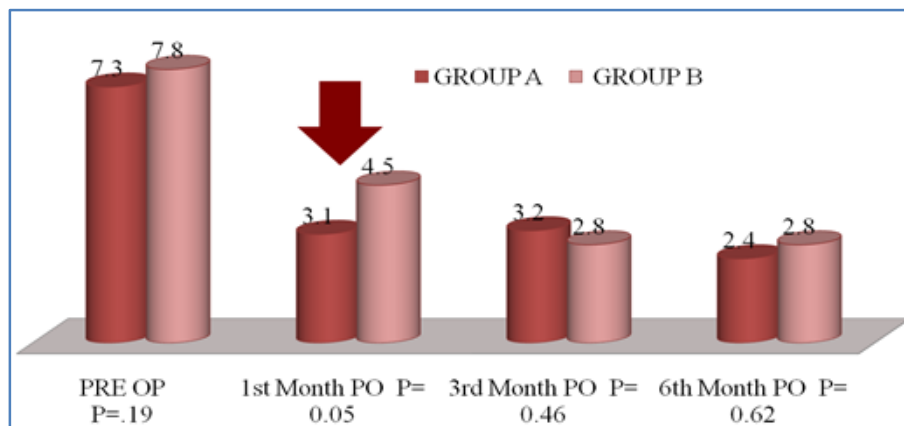
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Itraconazole probably improves the clinical outcome in patients undergoing surgical treatment for sinonasal polyposis, and plays a useful role in the pre and post-operative therapy resulting in early resolution of symptoms and decreased recurrence rates.

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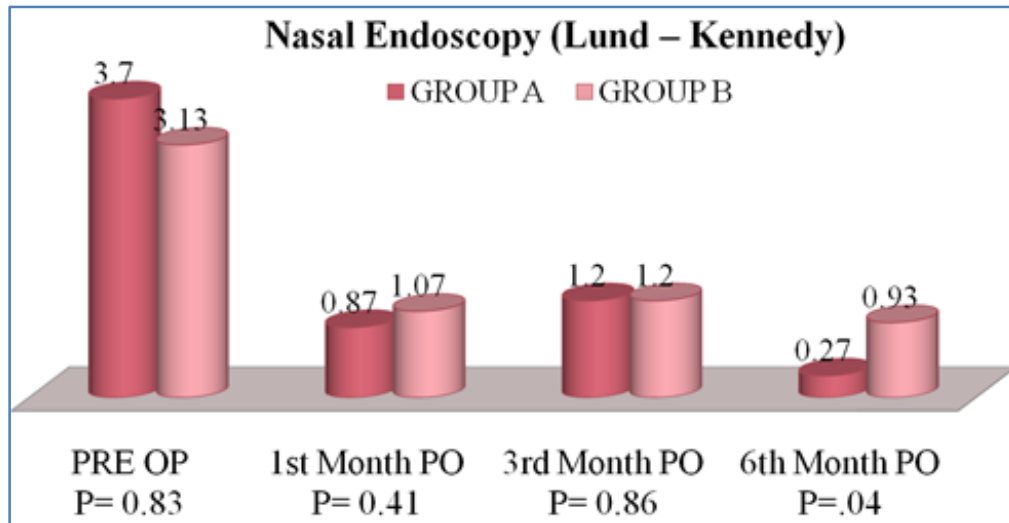
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**Fig. 1a):** Graph showing fungal smear & **b) Fungal culture** in both group.**Fig. 1a****Fig. 1b****Fig. 2:** Subjective assessment scores.**Fig. 2****Fig. 3:** Subjective assessment: nasal obstruction scores.**Fig. 3**

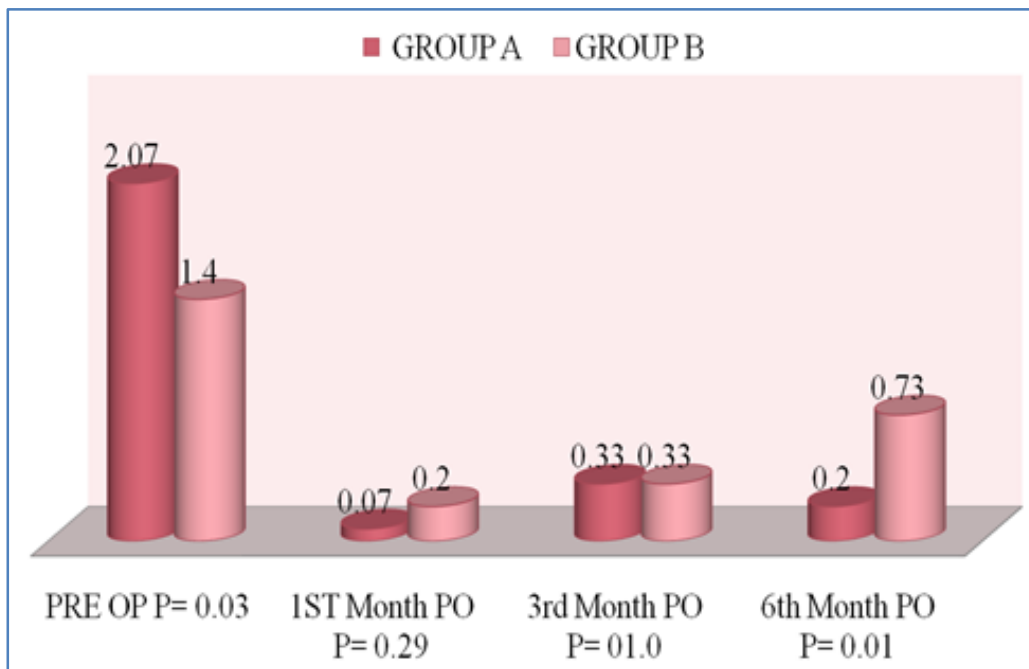
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**Fig. 4:** Diagnostic nasal endoscopy scores (Lund Kennedy scoring system).



**Fig. 4**

**Fig. 5:** Diagnostic nasal endoscopic scores for polyp.



**Fig. 5**

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	<b>GROUP A</b>	<b>GROUP B</b>
<b>Day1</b>	<ul style="list-style-type: none"> <li>• Clinical examination</li> <li>• Self-scoring questionnaires</li> <li>• Nasal swab for KOH</li> <li>• Standardized medication               <ul style="list-style-type: none"> <li>➤ <b>Tab Itraconazole 4mg/kg/day x 2 weeks</b></li> <li>➤ Tab Prednisolone 2mg/kg/day x 1week</li> <li>➤ Tab Amoxicillin + Clavulanicacid 40mg/kg/day x 2 weeks</li> <li>➤ Tab Fexofenadine 120mg/day x 1 week</li> <li>➤ Fluticasone nasal spray 200µg BD x 2 weeks</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Clinical examination</li> <li>• Self-scoring questionnaires</li> <li>• Nasal swab for KOH</li> <li>• Standardized medication               <ul style="list-style-type: none"> <li>➤ Tab Prednisolone 2mg/kg/day x 1week</li> <li>➤ Tab Amoxicillin + clavulanicacid 40mg/kg/day x 2 weeks</li> <li>➤ Tab Fexofenadine 120mg/day x 1 week</li> <li>➤ Fluticasone nasal spray 200µg BD x 2 weeks</li> </ul> </li> </ul>
<b>Day 2</b>	DNE – Lund Kennedy grading system	DNE – Lund Kennedy grading system
<b>Day 7</b>	CT-PNS – Lund Mackay grading system	CT-PNS – Lund Mackay grading system
<b>Day 14</b>	FESS with Polypectomy Intra Operatively ➤ Histopathology	FESS with Polypectomy Intra Operatively ➤ Histopathology
<b>Day 15</b>	Post of Medications <ul style="list-style-type: none"> <li>➤ <b>Tab Itraconazole 4mg/kg/day x 4 weeks</b></li> <li>➤ Tab Amoxicillin + Clavulanicacid 40mg/kg/day x 1 week</li> <li>➤ Tab Fexofenadine 120mg/day x 1 week</li> <li>➤ Fluticasone nasal spray 200µg BD x 4 weeks</li> </ul>	Post of Medications <ul style="list-style-type: none"> <li>➤ Tab Amoxicillin + Clavulanicacid 40mg/kg/day x 1 week</li> <li>➤ Tab Fexofenadine 120mg/day x 1 week</li> <li>➤ Fluticasone nasal spray 200µg BD x 4 weeks</li> </ul>
<b>Post Op 1<sup>st</sup> Month</b>	<ul style="list-style-type: none"> <li>✓ Self-scoring questionnaires</li> <li>✓ DNE</li> <li>✓ LFT, RFT</li> </ul>	<ul style="list-style-type: none"> <li>✓ Self-scoring questionnaires</li> <li>✓ DNE</li> <li>✓ LFT, RFT</li> </ul>
<b>Post Op 3<sup>rd</sup> Month</b>	<ul style="list-style-type: none"> <li>✓ Self-scoring questionnaires</li> <li>✓ DNE</li> <li>✓ LFT, RFT</li> </ul>	<ul style="list-style-type: none"> <li>✓ Self-scoring questionnaires</li> <li>✓ DNE</li> <li>✓ LFT, RFT</li> </ul>
<b>Post Op 6<sup>th</sup> Month</b>	<ul style="list-style-type: none"> <li>✓ Self-scoring questionnaires</li> <li>✓ DNE</li> <li>✓ LFT, RFT</li> <li>✓ Post-operative CT PNS</li> </ul>	<ul style="list-style-type: none"> <li>✓ Self-scoring questionnaires</li> <li>✓ DNE</li> <li>✓ LFT, RFT</li> <li>✓ Post-operative CT PNS</li> </ul>
	✓	✓

Table 1: Methodology

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### **FINANCIAL OR OTHER**

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Date of Submission: 21/08/2015.  
Date of Peer Review: 22/08/2015.  
Date of Acceptance: 25/08/2015.  
Date of Publishing: 28/08/2015.