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Original Article

Effectiveness of itraconazole on clinical symptoms and radiologic findings in patients with recurrent chronic rhinosinusitis and nasal polyposis

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Abstract

Background: This study was done to evaluate the effect of itraconazole on clinical symptoms and radiologic findings in patients with chronic rhinosinusitis and nasal polyposis after surgery.

Materials and Methods: In a clinical trial which was conducted in Alzahra and Kashani hospitals, from November 2011 to December 2012, 22 patients with recurrent postsurgical chronic sinusitis and polyposis entered the study. At the start of the study demographic data, subjective clinical symptoms (severity of rhinorrhea, nasal obstruction, hyposmia, and dyspnea), quality of life (QoL) by sinonasal outcome test-20 (SNOT-20), serum immunoglobulin E (IgE), and score of computed tomography (CT) scan (by Lund-Mackay) were recorded. Itraconazole (100 mg, twice per day) prescribed for 3 months and patients were followed in the 1st, 3rd, and 6th months. Liver enzyme tests and side effects were evaluated monthly.

Results: Severity of rhinorrhea, nasal obstruction, hyposmia, dyspnea, and QoL (by SNOT-20) improved during 3 months of treatment. Serum IgE was 265 (±277) at the start of the study, and decrease to 193 (±183) after 3 month. After 3 month, Lund-Mackay score of CT scan lowered from 19 (±4) to 15 (±6) ($P < 0.05$). At the 6th month, severity of clinical symptoms except dyspnea and QoL were better than first evaluation.

Conclusion: This study showed the beneficial effect of 3-month itraconazole treatment on clinical symptoms and radiologic findings and QoL in patients with recurrent postsurgical chronic rhinosinusitis and nasal polyposis.

Key Words: Chronic rhinosinusitis, itraconazole, nasal polyposis

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INTRODUCTION

Chronic rhinosinusitis (CRS) is identified by nasal and paranasal sinus mucosal inflammation,[1] which lasted for at least 12 consecutive weeks.[2,3] CRS has so much negative effects on community QoL,[4] and waste about 58 billion dollars per year in USA.[5]

Underlying mechanisms of CRS and sinonasal polyposis are still unclear, but the role of fungi has been suggested.[6] There had been a big controversy about pathophysiology of CRS. It has been supposed that fungal colonization is a major factor for lasting inflammation in CRS with or without plyposis.[7] Previous reports demonstrated the high incidence of fungal colonization in both normal and patient groups that was between 91.3-100%.[7,8]

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The clinical importance of these findings is under debate, and it is possible that clinical symptoms are a consequence of eosinophilic aggregation and degranulation in CRS patients.[9]

As a vast majority of underlying factors and causes which are related to CRS, deciding about the appropriate treatment is complex. There are a lot of potential factors which influence in mucosal inflammation, and treatment options address removal of predisposing elements, inflammatory responses, or both.[10]

There is a continuous contact with fungi every day, but in most people fungal colonization do not evoke an inflammatory response. Few vulnerable people are oversensitive to inflammatory response and react to fungal elements.[7,8,11,12]

The traditional treatment for allergic fungal CRS and polyposis is surgery and following usage of steroids, for modulating immune response to fungi, but longtime application of oral steroids have a lot of known side effects, so an alternative treatment to steroids is needed. Some people do not respond to standard treatment. The role of antifungal agents are unknown in CRS treatment.[13] Because of the possible role of fungi in nasal polyposis, antifungal agents have been proposed as an alternative option for surgery in patients with polyposis and reduce recurrence and its severity after functional endoscopic sinus surgery (FESS). Early studies showed useful effect of amphotericin B solution following FESS.[7,14,15]

One study on 50 patients showed no benefits for topical antifungal agents such as amphotericin B solution over normal saline in the treatment of polyposis following FESS.[16] Some studies suggested that using itraconazole in allergic fungal CRS, acts as an adjunct medication and useful in these patients.[13] But the role of itraconazole in recurrent CRS and polyposis after surgical implementation is not proved yet.

The main treatment option for nasal polyposis is eradication of background etiology, and surgery is an additive treatment to medical management in refractory cases. Recurrence after surgery is high, and the possibility of complications remain, so finding an effective medical treatment for recurrent CRS and polyposis is essential.[1,17]

Itraconazole is an antifungal agent, and its absorption increases with food and gastric acidity.[18] Liver function tests should be monitored in patients with previous liver disease, and patients who used itraconazole for more than 1 month. Its metabolism interacts with cytochrome 450, so decrease the synthesis of ergosterol (the main role of fungal cell membrane) and prohibits the synthesis of fungal cell membrane.[19]

This study was done to evaluate the effect of itraconazole on clinical symptoms and radiologic findings in patients with recurrent chronic rhinosinusitis and nasal polyposis after FESS.

MATERIALS AND METHODS

This self-control clinical trial was carried on 22 patients with recurrent postsurgical chronic sinusitis and polyposis. Sampling was carried out by simple convenient type method.

The inclusion criteria contained patients at least 15 years old without history of hepatic disease and heart failure, without allergy to itraconazole, and usage of interacting medications (cisapride, dofetilide, ergot derivatives, levomethadyl lovastatin, midazolam (oral), nisoldipine, pimozide, quinidine, simvastatin, or triazolam). Exclusion criteria of the study were no compliance for follow-up, side effects of itraconazole like rising in hepatic enzyme, nausea, vomiting, or starting a new treatment during the study.

The study was conducted in Alzahra and Kashani hospitals, from November 2011 to December 2012.

At the start of the study; demographic data, clinical symptoms (severity of rhinorrhea, nasal obstruction, hyposmia, dyspnea), quality of life (QoL) by sinonasal outcome test-20 (SNOT-20),[20] serum immunoglobulin E (IgE), and score of computed tomography (CT) scan by Lund-Mackay[21] were recorded. Severity of rhinorrhea, nasal obstruction, hyposmia, dyspnea was asked from the patients by the score of none, mild, moderate, and severe.

Itraconazole capsule of 100 mg, twice per day prescribed for 3 months (Rose Daru, Tehran, Iran). Patients were followed-up in the first month for clinical symptoms, and then at the 3 and 6 month regarding to clinical symptoms (as primary end point), QoL (by SNOT-20), and serum IgE and score of CT scan (by Lund-Mackay) as an additional analysis.

At the 6th month, patients were evaluated for clinical symptoms again. Liver enzyme tests and side-effects were evaluated monthly.

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The number of cases was calculated by the formula $n = (z1 + z2)^2.s^2/d^2 = (1.96 + 0.84)^2.s^2/0.6^2 = 22$. Every patient signed a written informed consent after thorough explanation of the study. The study protocol has been registered in Iranian Registry for Clinical Trials (IRCT201211062106N4).

At the end of the study, data were analyzed by SPSS version 20 by Friedman analysis, *t*-test, and Spearman's and Wilcaxon tests.

RESULTS

This study contained 22 patients aged 22 to 70 years old were started on oral itraconazole. Sixteen (72.7%) were men and 6 (27.3%) were women, out of which nine patients had asthma.

Severity of rhinorrhea, nasal obstruction, hyposmia, dyspnea, and QoL (by SNOT-20) is described in Tables 1-5. By Freidman and Wilcaxon tests, there is a significant improvement in rhinorrhea, nasal obstruction, hyposmia, dyspnea, and QoL (by SNOT-20) in 3 month of follow-up.

At 6th month 5 patients excluded from the study: 3 patients had aggravation of symptoms that indicated surgical implementation. One patient did not follow and; and one patient continued Itraconazole out of our protocol [Figure 1].

At the 6th month, there was a recurrence in dyspnea, but other symptoms (rhinorrhea, nasal obstruction, and hyposmia) and QoL was better than first evaluation.

Serum IgE was 265.7 (±27.97) at the start of the study and there was a decrease to 193.8 (±183) after 3 months. IgE was not in normal distribution, so Wilcaxon test was used ($P = 0.001$).

Lund-Mackay score of CT scan before treatment was 19.8 (±4.2). After 3 month of treatment Lund-Mackay score of CT scan lowered to 15.6 (±6.5). Because of abnormal distribution of CT score, Wilcaxon test was used and *P* value was 0.001.

There were no side effects such as liver enzyme rising, nausea, vomiting, and allergic response in this study group.

Table 1: Severity of rhinorrhea

Score	Start number (%)	First month number (%)	3rd month number (%)	6th month number (%)
None	1 (4.5)	4 (18.2)	9 (40.9)	3 (17.6)
Mild	4 (18.2)	10 (45.5)	6 (27.3)	3 (17.6)
Moderate	6 (27.3)	5 (22.7)	6 (27.3)	7 (41.2)
Severe	11 (50)	3 (13.6)	1 (4.5)	4 (23.5)
P value (by Wilcaxon test)		0.002	<0.001	0.047

P<0.001 by Freidman test after the 6th month

Table 2: Severity of nasal obstruction

Score	Start number (%)	First month number (%)	3rd month number (%)	6th month number (%)
None	0	2 (9.1)	6 (27.3)	2 (11.8)
Mild	0	8 (36.4)	6 (27.3)	3 (17.6)
Moderate	1 (4.5)	4 (18.2)	1 (4.5)	3 (17.6)
Severe	21 (95.5)	8 (36.4)	9 (40.9)	9 (52.9)
P value (by Wilcaxon test)		0.001	<0.001	0.017

P <0.001 by Freidman after the 6th month

Table 3: Severity of hyposmia

Score	Start number (%)	First month number (%)	3rd month number (%)	6th month number (%)
None	0	1 (4.5)	5 (22.7)	1 (5.9)
Mild	0	3 (13.6)	5 (22.7)	2 (11.8)
Moderate	1 (4.5)	6 (27.3)	2 (9.1)	4 (23.5)
Severe	21 (95.5)	12 (54.5)	10 (45.5)	10 (58.8)
P value (by Wilcaxon test)		0.004	0.002	0.015

P=0.001 by Freidman after the 6th month

Table 4: Severity of dyspnea

Score	Start number (%)	First month number (%)	3rd month number (%)	6th month number (%)
None	6 (27.3)	7 (31.8)	10 (45.5)	7 (41.2)
Mild	5 (22.7)	7 (31.8)	5 (22.7)	2 (11.8)
Moderate	6 (27.3)	6 (27.3)	3 (13.6)	5 (29.4)
Severe	5 (22.7)	2 (9.1)	4 (18.2)	3 (17.6)
P value (by Wilcaxon)		0.03	0.02	0.59

P=0.02 by Freidman test after the 3rd month, and *P*=0.32 after 6th month)

Table 5: Quality of life (QoL) by SNOT-20 (sinonasal outcome test-20)

Score	Start number (%)	First month number (%)	3rd month number (%)	6th month number (%)
Not bothered	0	1 (4.5)	5 (22.7)	2 (11.8)
Bothered but not much	0	4 (18.2)	6 (27.3)	2 (11.8)
Bothered more than a little, but not a lot	1 (4.5)	5 (22.7)	1 (4.5)	1 (5.9)
Bothered a lot	4 (18.2)	3 (13.6)	3 (13.6)	1 (5.9)
Extremely bothered	17 (77.3)	9 (40.9)	7 (31.8)	11 (64.7)
P value (by Wilcaxon test)		0.001	<0.001	0.017

P <0.001 by Freidman after the 6th month

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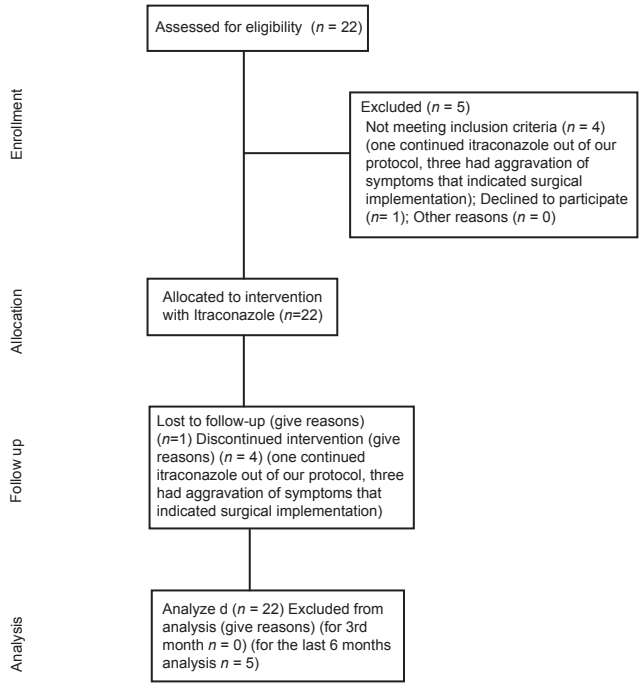

Figure 1: Consort flow diagram

DISCUSSION

This study had shown the benefit of itraconazole in decrease severity of rhinorrhea, nasal obstruction, hyposmia, dyspnea, and a marked improvement in QoL (by SNOT-20) in 3 months of follow-up, and it had considerable effect even after 3 months of itraconazole discontinuation.

A 12-year retrospective review on 139 patients with allergic fungal sinusitis (AFS), suggested that high dose postoperative itraconazole, combined with oral and topical steroids could avoid revision surgery. In their study the dose of itraconazole was 400 mg/day for 1 month, 300 mg/day for 1 month, 200 mg/day for 1 month, or until clear by endoscopy.[22] We used lower dose that was 100 mg BID of itraconazole, and had considerable improvement in this dose; that decreases the expense and side effects.

In a review of 23 patients with AFS and nonallergic rhinitis with eosinophilia syndrome (NARES) who received 100 mg twice daily itraconazole for 6 months, 83% of patients improved in symptoms and endoscopic findings and 48% had complete response.[23] In current study, at the 6th month, (3 months after stopping itraconazole) there was a recurrence in dyspnea, but other symptoms (rhinorrhea, nasal obstruction, and hyposmia) and QoL was better than first evaluation.

Clinically, itraconazole can be regarded as a steroid-sparing or reductive agent of oral steroids in order to control inflammation and polyps.[24]

Some reports did not confirm the benefit of other antifungal agents such as terbinafine in chronic rhinosinusitis. They explained the possibility of inadequate therapeutic levels of terbinafine in the nasal secretions or presence of other pathologic factors.[10]

It has been demonstrated that the addition of itraconazole in corticosteroid-dependent allergic bronchopulmonary aspergillosis, improved their symptoms without increasing toxicity, and decreased the level of IgE.[25]

In the study of itraconazole treatment in 32 allergic fungal rhinosinusitis after surgery that were refractory to prednisone, steroid, and amphotericin B nasal sprays, 12 cases improved endoscopically, but 15 cases had no difference, and five got worse after 3 months; posttreatment IgE levels decreased.[13] Similarly, in our study the serum IgE decreased after 3 months of itraconazole.

Chan and collaborates reported 28% subjective improvement, 28% moderate, and 44% little or no change. Subjective and endoscopic changes had no correlation.[13] We observed upgrading of clinical findings and QoL, also imaging studies; and after 3 month of treatment Lund-Mackay score of CT scan lowered.

It is appreciable that there were no side-effects in this selected population that makes it greatly superior to corticosteroids. Previous reports with itraconazole did not show any side-effects;[22] but up to 13% in different studies had elevated liver enzyme.[23,24] Systemic corticosteroid have a lot of proved benefit in chronic sinusitis and polyposis, but its side-effects limited its usage as a treatment of choice.

The optimum duration of treatment is questionable and should be studied in further researches. This study was not placebo controlled, and more reliable results as a double-blinded randomized clinical trial, especially to use as low dose as 100 mg daily. It is valuable to compare itraconazole to FESS, according to some factors such as QoL or recurrence for further studies.

CONCLUSION

We suggest itraconazole for selected patients with recurrent chronic sinusitis and polyposis after FESS that are not candidate for surgery again, or willing for medical treatment. Three-month treatment of itraconazole has dramatic effect on clinical and radiologic findings, even after discontinuation.

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