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Original Article

The efficacy of itraconazole, fluticasone and doxycycline in chronic rhinosinusitis

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Abstract: Background: Different treatment strategies for chronic rhinosinusitis (CRS) have been evaluated. Here we aimed to investigate the effects of fluticasone spray alone and in combination with itraconazole or doxycycline. Methods: This is an open-label clinical trial performed in 2020-2021 in Isfahan on patients with CRS. This survey's Iranian Registry of Clinical Trials (IRCT) code was IRCT20200825048515N50 (https://en.irct.ir/trial/60826). Demographic data of all patients including age and gender and duration of CRS, were obtained. The SNOT-22 and Lund-Kennedy questionnaires were evaluated and recorded for the symptomatology of CRS. Patients were randomly assigned to the treatment groups to receive 100 mg of doxycycline with intranasal fluticasone spray, intranasal fluticasone spray alone, or itraconazole 100 mg capsules with intranasal fluticasone spray. After one month of treatment, the scores and patient satisfaction were evaluated and compared. Results: Data of 104 patients was analyzed. Patients had improvements in their symptoms and SNOTT-22 scores. The mean SNOTT-22 score was 55.36±8.36 in all patients. During the study, patients had improvements in their symptoms and SNOTT-22 scores. The mean final SNOTT-22 score was 47.77±7.36 at the end of the survey (P=0.02). Our data also demonstrated significant improvements in the Lund-Kennedy score in all patients during the study (P<0.05). Conclusion: There were no significant differences between the clinical condition of patients receiving intranasal fluticasone, intranasal fluticasone in combination with doxycycline or itraconazole.

Keywords: CRS, fluticasone, doxycycline, itraconazole, SNOT-22

Introduction

Chronic rhinosinusitis (CRS) is an inflammatory disease of the nasal mucosa and paranasal sinuses that lasts for at least 12 consecutive weeks [1]. This disease is one of the most common upper respiratory tract diseases [2]. Symptoms of this disease include purulent rhinorrhea, post-nasal discharge, headache, congestion and inflammation, pain, pressure or a feeling of fullness in the face, and a decreased sense of smell [3, 4]. CRS is not a severe life-threatening factor, but its proximity to the orbit and brain can cause serious problems, such as orbit infections, brain abscesses, and meningitis [5, 6].

Two important phenotypes of CRS include chronic rhinosinusitis without nasal polyps (CRSsNP) associated with mechanical obstruction of the osteomeatal complex [7] and chronic rhinosinusitis with nasal polyps (CRSwNP), known as a diffuse mucosal disease based on eosinophils [8]. Most epidemiological studies on CRS do not distinguish between CRSsNP and CRSwNP [9].

The goal of treatment in patients with CRS is to manage the symptoms of the disease and improve their quality of life. Treatments focus more on improving mucociliary clearance, improving sinus drainage, eradicating local infection and inflammation, and improving access to topical medications [10]. Common treatments for CRS include washing with saline, topical intranasal corticosteroids, antibiotics, oral corticosteroids, and surgical treatment [11]. Many studies have been performed on various treatments for CRS and while many of these treatments may be effective in reducing

the symptoms of the disease, they are not definitive. The usage of itraconazole, fluticasone, and doxycycline have been investigated in previous research, and it has been indicated that each of these agents could significantly improve the disease [12]. Itraconazole is an antifungal medication that could have significant effects on CRS based on the presence of immune system interaction with fungus [13]. Fluticasone could also help reduce CRS's inflammation and symptoms and significantly affect the remission of nasal polyps [14]. The use of doxycycline in CRS has also been approved in recent studies. Based on previous data, doxycycline treatments could significantly improve symptoms by acting on responsible bacteria. The main adverse reactions of doxycycline use are allergic reactions and bacterial resistance [15].

Considering the prevalence and importance of CRS and giving attention to the beneficial effects of itraconazole, fluticasone, and doxycycline, in the present study, we aimed to compare the effectiveness of these agents in combination and alone in the treatment of CRS with nasal polyps.

Methods and material

Study design

This is an open label clinical trial that was performed in 2020-2021 in Kashani and Al-Zahra hospitals affiliated to Isfahan University of Medical Sciences. The current study was conducted on patients with CRSwNP referred to the ENT clinic of our medical center. The study protocol was approved by the Research Committee of Isfahan University of Medical Sciences and the Ethics committee has confirmed it (Ethics code: IR.MUI.MED.REC.13-99.706, Iranian Registry of Clinical Trials (IRCT) code: IRCT20200825048515N50).

Inclusion and exclusion criteria

The inclusion criteria were age between 15-65 years, diagnosis of CRS by expert otolaryngologists, duration of CRS more than six months, having nasal polyps, and signing the written informed consent to participate in this study. The criteria for CRS were at least two out of four cardinal symptoms (i.e., facial pain/pressure, hyposmia/anosmia, nasal drainage, and nasal obstruction) for at least 12 consecutive weeks, in addition to objective evidence. Patients with the following conditions did not enter the study: Any previous treatments for CRS within the past month before the study initiation, having diabetes, granulomatous, immune deficiency diseases and sensitivity to the studied drugs or any hepatic complications. The exclusion criteria were using other drugs, intolerance to the drugs, lack of sufficient drug compliance, worsening the patient's condition, patient's will to exit the study, and lack of access to follow-up results one month after patient treatment.

Sample size calculation

In this study, using the following sample volume formula at 95% confidence level, 80% test power and considering previous studies on the mean and standard deviation of quality of life in patients with chronic rhinosinusitis with two doxycycline drugs equal to 55.2±24.2 and fluticasone equal to 46±0.77, and the minimum mean difference equal to 9.2, 36 people in each group were estimated. These samples were selected non-randomly.

SNOT-22

108 patients entered the study based on the mentioned criteria. Demographic data of all patients, including age and gender and duration of CRS, were obtained. In addition, the questionnaire SNOT-22 was evaluated and recorded for the symptomatology of CRS [16]. SNOT-22 is designed to assess patients' respiratory status and recovery, including 22 questions regarding the following: need for nasal emptying, nasal congestion, runny nose, sneezing, coughing, post-nasal discharge, concentrated nasal discharge, feeling full, ear pain, dizziness, facial pain, decreased sense of smell and taste, difficulty falling asleep, waking up in the middle of the night, defects and lack of good sleep at night, tired waking up, fatigue during the day, decreased performance and efficiency, decreased concentration, frustration and irritability, sadness, embarrassment and shame in patients. In this questionnaire, each question scores from 0 to 5, so the total scale score is classified from 0 to 110. The higher the score, the more severe the patient's respiratory involvement.

Lund-Kennedy endoscopic scoring

We also assessed the clinical condition of cases using the Lund-Kennedy endoscopic scoring system. This scoring system evaluates the following items:

- Polyps in the middle meatus
- Discharge in the middle meatus
- Edema of the middle meatus
- Crusting in the middle meatus
- Scarring in the middle meatus

Each condition is scored from 0 (absent) to 2 (moderate or severe).

Randomization and interventions

Patients were randomly assigned to the treatment groups using blocks of 5. Patients in the first group received 100 mg of doxycycline twice daily with intranasal fluticasone spray (one puff per nostril every 12 hours), and patients in the second group received intranasal fluticasone spray (one puff per nostril every 12 hours). Patients in the third group received itraconazole 100 mg capsules daily with intranasal fluticasone spray (one puff per nostril every 12 hours). The duration of treatment was 12 weeks for all patients. Patients were followed for two weeks after discontinuing the drugs for possible complications.

Data gathering

Patients were visited after 4, 8 and 12 weeks of treatment and the SNOT-22 questionnaire, Lund-Kennedy score and patient satisfaction were evaluated and re-recorded. It should be noted that the patient satisfaction rate was asked from them based on the licker scale from 0 (dissatisfaction) to 10 (complete satisfaction).

Statistical analysis

The collected information was entered into the Statistical Package for Social Sciences (SPSS) version 24. We used independent t-tests and repeated measure ANOVA to compare data between different time lines and different groups. *P*-value <0.05 was considered as significance threshold.

Results

Study population

In the present study, 108 patients were assessed for eligibility to enter the study and divided into three groups each containing 36 patients. During the investigation, four patients were excluded due to lack of follow-up (N=2) and lack of proper compliance with the treatments (N=2). In the end, the data of 104 patients were analyzed. The CONSORT flow chart of the study is indicated in **Figure 1**.

The study population comprised 60 males (57.7%) and 44 females (42.3%) with a mean age of 42.36±12.7 years. The mean duration of CRS was 5.39±1.80 weeks. There were no significant differences between the three groups regarding the above information (P>0.05 for all) (**Table 1**).

Patient's symptoms

Evaluation of the patient's symptoms indicated that the most common symptoms in all patients before the study were nasal congestion (42.3%), facial pain and pressure (41.3%), waking up in the middle of the night (34.6%), fatigue (31.7%), and inability to understand the smell of foods (28.8%), respectively. In the end, nasal congestion (27.8%), facial pain and pressure (24%), and inability to understand the smell of foods (19.2%) were the most common symptoms among patients. There were no significant differences between groups before and after the study (P>0.05) (**Table 2**).

SNOT-22 score

SNOT-22 showed no significant differences between the three groups at the beginning of the study. The mean SNOTT-22 score was 55.36±8.36 in all patients. During the investigation, patients had improvements in their symptoms and SNOTT-22 scores. The mean final SNOTT-22 score was 47.77±7.36 at the end of the survey (P=0.02). We also observed that there were no significant differences between the three groups during and after the study (P>0.05) (**Table 2**).

Lund-Kennedy score

Our data also demonstrated significant improvements in the Lund-Kennedy score in all

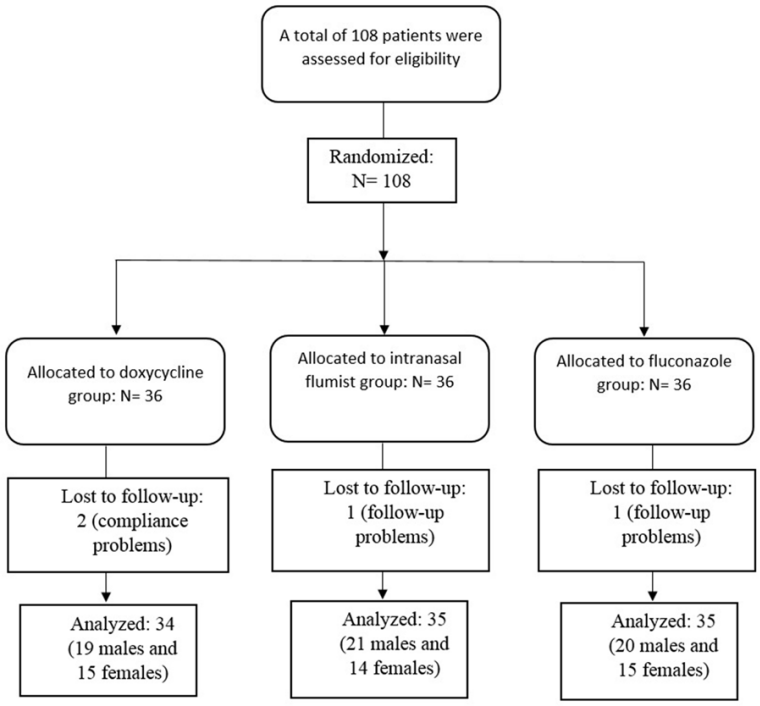

Figure 1. The CONSORT flow chart of the study.

patients during the study (P<0.05). Patients that received Doxycycline had slightly better progress in their scores, but these differences were not statistically significant (P>0.05). Furthermore, the satisfaction score of the patients was 2.63±1.88 at the beginning and improved to 9.07±2.14 at the end of the interventions (P<0.001), but no significant differences were detected between the patients (P>0.05). These data are indicated in **Table 2**. No complications were observed in the studied patients.

Discussion

In the present study, by evaluating 104 patients, we indicated that all patients improved after the treatments. No significant differences between patients regarding the SNOT-22 questionnaire and patient satisfaction could be observed. These data showed similar effects of the following regimens in CRS patients: doxycycline with intranasal fluticasone spray, intranasal fluticasone spray alone, and itraconazole tablets with intranasal fluticasone spray.

The use of different agents for treatments of CRS has been evaluated in various studies. Still, intranasal corticosteroid sprays with long-term efficacy have been a fundamental treatment option in CRS, mainly due to the inflammatory basis of this disease. According to recent studies, intranasal corticosteroid sprays may have high clinical effectiveness in cases of CRS, particularly those associated with polyps and even asthma [17], but patients' lack of adherence to this therapy may be the main reason for failure [18]. Based on our findings, using intranasal corticosteroid sprays was associated with significant improvements in patients. In 2016, a study was conducted by Phillips and colleagues in the United States on 40 patients with CRS. It was indicated that CRS severity is negatively associated with asthma control in patients with asthma and CRS [17]. This could be a clarifying issue on the effects of intranasal corticosteroid sprays in CRS. These data were consistent with our findings. In 2020, Hoy reviewed the CRS with polyps and showed that intranasal corticosteroid sprays were generally well tolerated and could improve nasal polyp size, sinus opacification, and health-related quality of life (HR-QOL). They also mentioned that these treatments could relieve the significant symptoms of CRSwNP (nasal congestion or obstruction, nasal discharge, and loss of smell) and reduce the use of systemic corticosteroids and the need for nasal polyp surgery [19]. As a result, intranasal corticosteroid sprays could be widely used in patients with CRS with polyps and in patients with associated asthma disease. The results of our study were in line with these findings showing the effectiveness of intranasal fluticasone spray in CRSwNP patients.

Another study by Chong and colleagues in 2016 reviewed 18 RCTs with 2738 participants. They showed that intranasal corticosteroid sprays could improve all patient symptoms, with a moderate-sized benefit for nasal blockage and a small benefit for rhinorrhea [20]. These effects are mediated by reducing inflammation and inflammatory responses in the body and could significantly relieve patients' symptoms

Table 1. Comparison of demographic data among groups

Variable		Doxycycline (N=34)	Intranasal fluticasone (N=35)	Itraconazole (N=35)	*p*-value
Age (yeas) (mean ± SD)		42.32±12.54	43.68±11.27	42.90±10.62	0.22*
Weight (kg) (mean ± SD)		71.27±9.87	73.21±9.41	72.69±8.32	0.44*
Height (m) (mean ± SD)		172.36±12.69	171.54±13.72	172.28±12.58	0.31*
BMI (kg/m^2) (mean ± SD)		23.97±1.28	24.64±1.60	24.33±1.82	0.17*
Duration of CRS (month) (mean ± SD)		9.10±1.62	9.16±1.07	9.22±1.47	0.26*
Gender (N (%))	Female	15 (47%)	14 (40%)	15 (42.9%)	0.47**
	Male	19 (53%)	21 (60%)	20 (57.1%)	

*using One-way ANOVA, **using Chi-square test.

Table 2. Comparison of SNOT-22, Lund-Kennedy scores and satisfaction between groups

Variable		Doxycycline (N=34)	Intranasal fluticasone (N=35)	Itraconazole (N=35)	Total scores	*p*-value[1]	*p*-value[2]
SNOT-22	Before	56.47±9.87	53.39±8.21	54.10±7.17	55.36±8.36	0.47	0.11
	After 4 weeks	48.34±7.17	50.22±6.71	50.18±8.13	50.62±6.27	0.46	
	After 8 weeks	45.29±6.12	47.31±7.20	47.91±8.47	48.14±7.39	0.52	
	After 12 weeks	44.91±7.11	46.07±6.74	46.31±8.24	47.77±7.36	0.06	
p-value[3]		0.02	0.03	0.02	0.02		
Lund-Kennedy score	Before	8.16±1.55	7.91±2.30	8.08±2.27	8.05±2.18	0.29	<0.001
	After 4 weeks	6.33±2.41	6.72±2.14	6.18±1.40	6.59±2.63	0.63	
	After 8 weeks	4.04±1.33	4.62±2.63	4.41±1.14	4.58±2.36	0.34	
	After 12 weeks	3.04±1.52	3.40±1.71	3.62±1.88	3.28±1.71	0.06	
p-value[3]		0.001	0.002	0.001	0.001		
Satisfaction	Before	2.12±1.26	3.09±1.13	2.57±1.92	2.63±1.88	0.33	<0.001
	After 4 weeks	4.20±2.07	4.10±1.25	4.39±1.66	4.36±1.62	0.29	
	After 8 weeks	6.13±1.62	5.83±2.57	6.24±2.02	5.95±2.51	0.66	
	After 12 weeks	8.87±1.22	9.21±2.83	8.09±1.41	9.07±2.14	0.48	
p-value[3]		<0.001	<0.001	<0.001	<0.001		

P1: Kruskal-Wallis H test, P2 and P3: repeated measurements.

[21, 22]. The results of our study were in line with these findings. Based on the results of our research, the patients that received only intranasal fluticasone spray significantly improved SNOT-22 scores and satisfaction.

Another finding of our study was that patients treated with doxycycline associated with intranasal fluticasone spray significantly improved their clinical status. Still the effects of the treatment combination of intranasal fluticasone spray and doxycycline had similar results compared to intranasal fluticasone spray alone, which could cast doubt on the clinical usage of doxycycline. In a study by Parasher and others in 2019, the role of doxycycline in the management of CRSwNP was evaluated. By assessing 49 patients, it was reported that no significant differences were observed between these cases and patients treated with placebo in terms of SNOT-22 score and pain [23]. These data might indicate that the use of doxycycline might not be very useful in CRS patients. There have also been some different reports. In 2020, Lees and colleagues evaluated the effects of doxycycline on the CRS condition. Based on this study, doxycycline inhibits the activity of matrix metalloproteinases in CRSwNP and, as a result, improvements are observed in these cases [15]. The results of our study were in line with these findings. In another study by De Schryver and colleagues in 2017, they showed that administration of systemic antibiotics and anti-inflammatory agents could improve the effect on the eosinophilic inflammation and clinical outcome of patients [24]. As demonstrated in our study, the usage of systemic antibiotics could alleviate the patient's conditions. Therefore, these data are consistent with our findings.

Another finding of our study was similar effects of itraconazole tablets with intranasal fluticasone spray compared to the other groups of patients. Our data showed that patients receiving itraconazole tablets with intranasal fluticasone spray had similar improvements in the intranasal fluticasone spray group. A study was conducted that evaluated the possible therapeutic options for CRS. It was discussed that oral itraconazole could significantly affect patients with fungal rhinosinusitis [25]. Hashemian and colleagues evaluated data of 54 CRS patients and showed that the use of antifungal treatment for patients with CRS was not shown to be significantly effective [26]. These data are in line with the findings of our study. We believe that the administration of intranasal fluticasone spray was our study's most effective therapeutic strategy.

Our study emphasized that administrations of intranasal fluticasone spray was associated with significantly improved symptoms in patients. However, associations with doxycycline and itraconazole did not change the clinical presentations in patients. Clinical relevance of this issue could be that physicians should pay more attentions to the beneficial effects of intranasal fluticasone in the first stage.

Our study supported the use of intranasal fluticasone spray on patients with CRSwNP. We also showed that administration of doxycycline and itraconazole did not significantly change the symptoms. However, the limitations of our study were limited study population and short follow-up duration. But the main point of our study was to compare three treatment strategies in 104 patients with CRS. We suggest that further studies on larger populations should be conducted.

Conclusion

Based on our data, intranasal fluticasone spray significantly affected patients with CRSwNP. In the present study, significant improvements were observed in all patients regarding Lund-Kennedy score and satisfaction, but all patients had similar scores, and no differences were observed between groups. These data emphasize the effectiveness of all three treatment strategies.

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Disclosure of conflict of interest

None.

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