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ARTICLE

A COMPARATIVE STUDY OF THERAPEUTIC EFFECTS OF DOXEPIN AND CETIRIZINE IN PATIENTS WITH ALLERGIC RHINITIS: A RANDOMIZED DOUBLE-BLIND CLINICAL TRIAL

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ABSTRACT

Allergic rhinitis is a common disease presenting in 20% of the population. Major symptoms are including sneezing, rhinorrhea, nasal congestion, and nasal pruritus. It is seemed that tricyclic antidepressants blocking histamine receptors might be applied as an effective treatment in allergic rhinitis. In the current clinical trial, a total of 84 subjects with allergic rhinitis were enrolled and randomly assigned to 2 groups. Both groups were administered cetirizine and doxepin for 2 weeks. The subjects were evaluated in terms of sneezing, rhinorrhea, nasal congestion, and nasal pruritus after 2 weeks of taking the aforementioned medications. There was no difference in the clinical score of the patients after 2 weeks (p = 0.261). Sneezing was the only symptom that was affected by the type of remedy, it was significantly different between the groups (p = 0.005). The findings of the present study indicated that there is no substantial difference in taking cetirizine and doxepin in treating seasonal allergic rhinitis symptoms. Administering TCAs with more potency of blocking histamine receptors and larger population are necessary for future studies.

KEY WORDS
Allergic rhinitis, Doxepin, Cetirizine, Treatment

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INTRODUCTION

Allergic rhinitis is a common disease presenting in 20% of the population [1]. Allergic rhinitis is a general term for seasonal allergic rhinitis, perennial allergic rhinitis, and perennial allergic rhinitis with seasonal severity. Seasonal allergic rhinitis and perennial allergic rhinitis are presenting in 20% and 40% of the cases, respectively, while 40% of the subjects have a combination of the aforementioned disorders. As for the high prevalence of allergic rhinitis, and co-morbidities such as atopy and asthma affect the society [2]. The seasonal allergic rhinitis is usually initiated with trees' and plants' allergens. The major symptoms are including sneezing, rhinorrhea, nasal congestion, nasal or pharyngeal pruritus [3]. The histamine is the most effective mediator in the preliminary phase of the disease, presenting of this factor was approved in the most symptoms [4]. The symptoms such as sneezing, pruritus, tearing and rhinorrhea are greatly adjusted by H_1 receptors [5]. There are different remedies for treating allergic rhinitis. The most common treatments for allergic rhinitis are including antihistamines, decongestions, and leukotriene regulators and inhaled corticosteroids [6]. In treating allergic rhinitis, topical corticosteroids including beclomethasone, fluticasone, and mometasone together with new generation of antihistamines including loratadine, cetirizine, fexofenadine, and ketotifen are administered as the first line of treatment [7]. Also, the histamine is considered as an important mediator in creating acute and chronic urticaria [8], the antihistamines are used as the selective treatment of urticaria [9]. The tricyclic antidepressants (TCAs) are effective medications in treating urticaria as well [10].

The TCAs are potent inhibitors of H_1 and H_2 receptors. The biochemical, pharmacological, and behavioral similarities were demonstrated in TCAs and some of the antihistamines. It should be kept in mind that TCAs are categorized in antihistamine medicines [11]. Doxepin hydrochloride is a TCA with the highest activity of antihistaminic feature that is stronger than diphenhydramine and hydroxyzine being 775 and 56 times than that, respectively [12]. Doxepin as an H_2 receptor inhibitor is 6 times stronger than cimetidine [13, 14]. In vitro and in vivo studies indicated that doxepin inhibits histaminic receptors in the wall of smooth muscles of the vessels; this feature can commonly be used to treat chronic pruritus and urticaria [7, 15]. Furthermore, anti-muscarinic, anti-serotonergic, and anti-adrenergic features were observed in doxepin [13, 16]. Literatures indicated that doxepin suppressed induced response by histamine [17].

Given consideration to the known pharmacological effect of doxepin as a tricyclic antagonist of H_1 and H_2 receptors, classic taking and its therapeutic indications in reducing allergic symptoms, also with individual experiences in treating allergic rhinitis, and similarity of the mechanism and interaction of the neurotransmitters in allergic rhinitis and classic therapeutic indications of doxepin (e.g., treating

headaches relating to migraine, tension headaches, pains in face and head, sleep and behavioral disorders, and anxiety disorders) and high prevalence of the aforementioned diseases and their correlation with allergic rhinitis, also low rate of medication's side effects, low and daily dosage, possible effectiveness, and influence on chronic headache, we have decided to compare doxepin and cetirizine effects on patients with allergic rhinitis.

MATERIALS AND METHODS

This study is a clinical trial performed on the allergic rhinitis patients referred to the ENT clinic of Amir-Kabir hospital. At the first stage, the patients filled out the consent form and enrolled in the study. The subjects were randomly assigned to 2 groups based on block design. Both groups were administered 10 mg cetirizine and 10 mg doxepin daily for 2 weeks, respectively. The Total Nasal Symptom Score (TNSS) of the patients was recorded based on the severity and duration of the allergic rhinitis symptoms after diagnosing allergic rhinitis, the symptoms of allergic rhinitis are including rhinorrhea, nasal pruritus, sneezing, and nasal congestion. This score is in the range of zero to three (zero: no sign, one: The symptoms less than 30 minutes per day, two: The symptoms from 30 minutes to 2 hours per day, three: The symptoms more than 2 hours per day) [18-20]. After 2 weeks of treating the subjects, the symptoms were re-assessed based on TNSS in each group. To observe the blindness, the classifying of the groups and administrating medications were carried out by ENT specialist, documenting the clinical symptoms was undertaken by the author via calling to the subjects. Finally, the data obtained were analyzed by SPSS software version 19 via t-tests and compared by one-tailed variance.

The inclusion criteria were patients aged from 8 to 55 years old, history of allergic rhinitis for at least 2 years. The exclusion criteria were patients with the history of asthma, acute sinusitis, upper respiratory tracts infection, taking antihistamines in 2 weeks previously, patients with deformity of nose such as polyp, pregnant and feeder women, history of psychological disorders including schizophrenia, Post-Traumatic Stress Disorder (PTSD), and mania, also allergy to doxepin, mono-amino oxidase inhibitors and cimetidine.

RESULTS

A total of 84 patients with allergic rhinitis were enrolled in the current clinical trial, then, they were randomly assigned to 2 groups, and were administered doxepin and/or cetirizine. Forty five patients were female (53.6%) and the remainder were male. In the view of gender, there was no significant difference between two groups (p=0.512). The mean of age in doxepin and cetirizine groups was estimated as being 33.16 ± 11.06, and 33.42 ± 13.88, respectively. In terms of age, there was no significant difference between two groups (p=0.54).

The patients were assessed in terms of rhinorrhea, nasal pruritus, and sneezing, as well as nasal congestion, afterwards, the severity of the symptoms was recorded. The data obtained, indicated that there is no significant difference between two groups in terms of symptoms severity. The maximum score was 12 including all of the symptoms, the score 0 was considered for the patients with no symptom. There was no substantial difference between two groups in terms of score mean before receiving medication (p=0.385). Furthermore, the findings demonstrated that there is no significant difference between two groups in terms of score 2 weeks after receiving medication (p=0.261). The score mean in doxepin and cetirizine groups was 4.40 ± 3.43, and 2.59 ± 3.19, respectively. Moreover, the findings indicated that there is no significant difference between two groups in terms of gender segregation (males: p=0.390, and females: p=0.488).

The subjects were also evaluated in terms of symptoms. Firstly, rhinorrhea was investigated 2 weeks after receiving medication. In doxepin group, rhinorrhea was not observed in 18 subjects (42.9%), rhinorrhea was observed in 5 (11.9%), 8 (19%), and 11 (26.2%) patients less than 30 minutes, from 30 to 120 minutes, and more than 120 minutes, respectively. In cetirizine group, rhinorrhea was not observed in 18 subjects (42.9%) 2 weeks after treatment, whereas rhinorrhea was observed in 14 (33.3%), 3 (7.1%), and 7 (16.7%) patients less than 30 minutes, from 30 to 120 minutes, and more than 120 minutes, respectively. The data obtained showed that there is no significant difference between two groups in terms of rhinorrhea (p=0.06) [Table 1]. In doxepin group, nasal pruritus was not observed in 14 subjects (33.3%), while nasal pruritus was observed in 8 (19%), 10 (23.8%) and 10 (23.8%) patients less than 30 minutes, from 30 to 120 minutes, and more than 120 minutes, respectively. In cetirizine group, nasal pruritus was not observed in 24 subjects (57.1%), whereas nasal pruritus was observed in 8 (19%), 4 (9.5%), and 6 (14.3%) patients less than 30 minutes, from 30 to 120 minutes, and more than 120 minutes, respectively. There was no significant difference between two groups in terms of nasal pruritus (p=0.102).

Table 1: The severity of rhinorrhea in doxepin and cetirizine groups

Groups	Lack of rhinorrhea N (%)	Less than 30 min N (%)	Between 30 to 120 min N (%)	More than 120 min N (%)

Doxepin	18 (42.9)	5 (11.9)	8 (19)	11 (26.2)
Cetirizine	18 (42.9)	14 (33.3)	3 (7.1)	7 (16.7)
Total	36 (42.9)	19 (22.6)	11 (13.1)	18 (21.4)

In doxepin group, sneezing was not observed in 13 subjects (31%), while sneezing was observed in 9 (21.4%), 13 (31%), and 7 (16.7%) patients less than 30 minutes, from 30 to 120 minutes, and more than 120 minutes, respectively. In cetirizine group, sneezing was not observed in 29 subjects (69%), whereas sneezing was observed in 6 (14.3%), 5 (11.9%), and 2 (4.8%) less than 30 minutes, from 30 to 120 minutes, and more than 120 minutes, respectively. There was no significant difference between two groups in terms of sneezing (p=0.005) [Table 2].

Table 2: The severity of sneezing in doxepin and cetirizine groups

Groups	Lack of rhinorrhea N (%)	Less than 30 min N (%)	Between 30 to 120 min N (%)	More than 120 min N (%)
Doxepin	13 (31)	9 (21.4)	13 (31)	7 (16.7)
Cetirizine	29 (69)	6 (14.3)	5 (11.9)	2 (4.8)
Total	42 (50)	15 (17.9)	18 (21.4)	9 (10.7)

Lastly, the nasal congestion was investigated in two groups. In doxepin group, nasal congestion was not reported in 31 subjects (73.8%), while nasal congestion was reported in 3 (7.1%), 5 (11.9%), and 3 (7.1%) patients less than 30 minutes, from 30 to 120 minutes, and more than 120 minutes, respectively. In cetirizine group, nasal congestion was not reported in 35 subjects (83.3%), whereas nasal congestion was reported in 3 (7.1%), 3 (7.1%), and 1 (2.4%) patients less than 30 minutes, from 30 to 120 minutes, and more than 120 minutes, respectively. There was no significant difference between two groups in terms of nasal congestion severity (p=0.628).

DISCUSSION

Comparison of doxepin and cetirizine effects was carried out on patients with allergic rhinitis. This is the first study, to our knowledge, investigated the effect of an antihistamine and a TCA on treating allergic rhinitis. The findings of the current study indicated that there is only significant difference between two groups in terms of sneezing. In this case, cetirizine had a more substantial effect than doxepin. Our findings demonstrated that cetirizine had a more remarkable impact than doxepin in reducing clinical symptoms score (cetirizine score as being 2.59 as compared to 4.40 for doxepin). Thus, there was insignificant difference between scores. Cetirizine as an antihistamine is the most common used medication for treating the symptoms resulted from over-release of histamine. In a study of comparing cetirizine and fexofenadine effects upon patients with seasonal allergic rhinitis, the same findings were reported [20]. A similar study was carried out by Charpinetal. on comparing azelastine nasal spray and cetirizine on reducing seasonal allergic rhinitis symptoms, the findings were reported the same [21]. In the study of Salmun et al. on comparing somnolence and motivation after taking loratadine and cetirizine, cetirizine led to more somnolence than loratadine as well as lower motivation [22]. Nevertheless, the effects of cetirizine and loratadine were evaluated in terms of reducing pruritus. More significant effects of hydroxyzine and doxepin versus cetirizine on reducing chronic pruritus were reported in the study of Shohratietal. [19].

Doxepin as a TCA has a potency in blocking H_1 and H_2 receptors. The studies reported more strength of doxepin than diphenhydramine and hydroxyzine in blocking H_1 receptors being 775 and 56 times than that, respectively [13]. In a study of comparing the effects of doxepin, hydroxyzine, and cyproheptadine as well as cinnarizine on patients with idiopathic cold urticaria by Neittaanmäki et al., more acceptable effect and lower side effect of doxepin than other medications were reported [23]. It should be noted that, low dosages of doxepin was administered in the most studies, although high dosages of this medication might lead to obscurity, dry mouth, constipation, and bladder outlet obstruction. In a study, the correlation of allergic rhinitis and migraine was surveyed, these disorders are the common factors of headache and facial pain involving inflammatory mediators with vasoactive feature, the prevalence of migraine without aura incidence in patients with allergic rhinitis was higher than subjects without allergic rhinitis [24].

As for diagnostic interference, the migraine was reported as the source of sinus pain as being 86% based on criteria of International Headache Society. Other studies reported migraine stimulators such as climate change (83%), seasonal change (75%), and allergens (62%), these factors are interfering with allergies and stimulating nasal lining. As for common mediators including histamine, IgE, alpha-peptide tumor necrosis factor depended on calcitonin gen, intestinal vasoactive peptide, D2 and F2 prostaglandins, interleukin and nitrous oxide between migraine and allergic rhinitis, doxepin can play an important role in preventing migraine incidence, taking of this medication is suggested in this study and other literatures [25, 26].

CONCLUSION

The same effects of doxepin and cetirizine were reported in the current study, approximately. It is seemed that administration of higher dosages of doxepin might lead to more prevention of allergic rhinitis symptoms. However, higher side effects of higher dosages should be considered. It is suggested to administer doxepin tablet for patients with the symptoms of the allergic rhinitis, tension headaches, migraine, depression, and anxiety disorders. It is also suggested to administer doxepin for patients with allergic rhinitis and various headaches.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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The authors report no financial interests or potential conflicts of interest.

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