Role of Cinnarizine as an adjuvant treatment in cases of postviral hyposmia

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Background
Odor identification is a complex process involving different neuronal mechanisms. It is important from different aspects of quality of life. Postviral neuritis is one of the leading causes of hyposmia. Attention to it has increased in the last year due to the coronavirus disease 2019 pandemic. Systemic steroids are presumed to benefit such cases through its anti-inflammatory mechanism of action. Cinnarizine, being a multimodal mechanism of action drug with a potent cerebral vasodilator effect, is assumed to have a great potential to be used as adjuvant treatment to systemic steroids.

Objective
The aim of the study is to assess if there is any role of Cinnarizine as an adjuvant treatment to steroids in cases of postviral hyposmia.

Patients and methods
This is a single-blinded, randomized, controlled trial including 82 patients with postviral hyposmia. Patients were distributed equally into two groups according to the given therapy with group I receiving 25 mg oral prednisolone per day for 2 weeks along with budesonide nasal spray/64 μg per puff in a dose of two puffs for each nostril twice daily for 1 month, in addition to our drug of study Cinnarizine 25 mg given postoperative TDS for 1 month. Group II received the same but without Cinnarizine. Both groups were compared regarding the number and percentage of patients having their smell identification test score improved either partially or fully back to normal.

Results
Cinnarizine intake as an adjuvant treatment to steroids had a significant effect on improving the smell identification test scores in patients with postviral hyposmia (P<0.05). However, among the improved patients in both groups, there was a nonsignificant difference between the two groups regarding the degree of recovery whether complete or partial (P=0.78).

Conclusion
Cinnarizine has a beneficial effect as an adjuvant treatment to steroids in cases of postviral hyposmia.

Keywords:
anosmia, hyposmia, olfaction Cinnarizine, olfactory, Stugeron

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Introduction

Anosmia or hyposmia, the decreased ability or inability to detect odors, is estimated to affect 3–20% of the population [1]. Many causes exist for hyposmia, including postviral olfactory neuritis, bilateral nasal obstruction, head traumas, tumors of the brain, uncinate fits, or neurodegenerative disorders with increasing risk in the elderly [2].

Hyposmia affects the quality of life in different aspects, including the detection of food flavor, warning odors in the vicinity, and social relationships. This provides a great necessity for the meticulous research regarding the pathophysiology of hyposmia [3].

Postviral neuritis is one of the leading causes of hyposmia [4]. Attention to it has increased in last year due to the coronavirus disease 2019 (COVID-19) pandemic. While there is no gold standard of treatment in postviral hyposmia, many studies have proved that systemic corticosteroids did help in regaining the sense of smell in many patients [5–8].

Cinnarizine has a multimodal mechanism of action. It is a well-known fact that it has an antihistaminic, antiserotonergic, and antidopaminergic effects [9] along with being a good cerebral vasodilator through its calcium channel blocking effect [10], which is our primary focus in this particular study. Cinnarizine belongs to the diphenylmethyl piperazine group [11]. It inhibits smooth muscle cell contraction in the cerebral vasculature by blocking L&T-type voltage-gated calcium channel [10]. It also holds to histamine H1

receptors, muscarinic (acetylcholine) receptors, and dopamine D2 receptors [9]. Cinnarizine inhibits the flow of calcium into red blood cells, which increases the elasticity of the cell wall, thereby increasing their flexibility and making the blood less viscous [12]. This allows the blood to travel more efficiently and effectively through narrowed vessels in order to bring oxygen to the damaged tissue [12]. It boosts up the brain oxygen supply [13] and allows for better cerebral perfusion. The multimodal mechanism of action of Cinnarizine and its contribution to hyposmia is discussed in detail later in the discussion section of this article.

This article concerns postviral hyposmia in general. SARS-COV-2 is one of the respiratory tract viruses that has a higher incidence, in relation to others, to violate olfactory apparatus. Many articles discussed the possible mechanism of olfactory loss in such cases. The majority contributed the olfactory dysfunction to the violation that occurs to the integrity of sustentacular cells of olfactory epithelium with or without accompanying degeneration of olfactory neurons [14]. Further possible mechanisms of olfactory loss in cases of postviral hyposmia are discussed later in this article.

The aim of our study is to assess if there is any role of Cinnarizine as an adjuvant treatment to steroids in cases of postviral hyposmia.

Patients and methods

The current study is a single-blinded, randomized, controlled clinical trial conducted on recruited patients from the outpatient clinics of Zulekha Hospital LLC, Sharjah, UAE, during the period from March, 2019 to March, 2021. All procedures performed were following the ethical standards of the Zulekha Hospital Research Committee and the 1964 Helsinki Declaration and its later amendments. A written consent was obtained from every patient before participation in the study.

Our study included 82 adult patients diagnosed with organic hyposmia following immediately an upper respiratory tract infection and characterized by being of sudden onset. Adult patients with an age range from 18 to 60 years were selected to allow a broader experience for odor identification and better cooperation. Patients with a history of posttraumatic anosmia, having other neurological disorders or manifestations, with hyposmia/anosmia lasted more than 6 months, received previous treatment for their current hyposmia/anosmia, had any contraindications to any of the used medications or took a prolonged course of systemic steroid in last 3 months were excluded from the study.

All patients were assessed by history taking and complete otorhinolaryngology examination, including endoscopic nasal examination to exclude any visible intranasal pathology which may be a cause for the hyposmia.

Computed tomography of the nose and paranasal sinuses was done for some patients to confirm suspicious nasal pathology. Any patient confirmed to have chronic sinonasal pathology was excluded from the study.

The degree of hyposmia was assessed using the smell identification test with hyposmia graded as mild (scores of 30–33) in men/scores of 31–34 in women, moderate (scores of 26–29) in men/scores of 26–30 in women, and severe (scores of 19–25). Anosmia considered with scores (6–18) while normosmia considered with scores of more than 33 in men/scores of more than 34 in women.

Patients got randomly distributed among two equal groups utilizing the block randomization method. Group I included 41 patients who received a course of systemic corticosteroids in the form of 25 mg oral prednisolone per day for 2 weeks together with local nasal corticosteroids in the form of budesonide/64 μg per puff in a dose of two puffs for each nostril twice daily for 1 month, in addition to our drug of study Cinnarizine (Stugeron, Janssen Pharmaceuticals headquartered in Beerse, Belgium and wholly-owned by Johnson & Johnson.) by Janssen Pharmaceutica 25 mg given postoperative TDS for 1 month. Group II included 41 patients who received a course of systemic corticosteroids in the form of 25 mg oral prednisolone per day for 2 weeks together with local nasal corticosteroids in the form of budesonide/64 μg per puff in a dose of two puffs for each nostril twice daily for 1 month.

The author was blinded to the clinical progress of each patient within both groups as the senior resident, who is already blinded to the treatment protocol, was invited to perform the smell identification test for each patient before and after treatment. Results were collected and projected to the author at a later stage for statistical analysis and interpretation of data.

Outcomes

Primary outcomes include comparison between the two groups regarding the number and percentage of patients having there smell identification test score improved either partially or fully back to normosmia. Also, any possible side effects from the drugs were assessed.

Results

The current study included 82 patients distributed equally between two groups. Group I included

41 patients with 27 males and 14 females and an age of 38.41±12.41 years. Group II included 41 patients with 32 males and nine females and an age of 39.95±9.61 years. There was a nonsignificant difference between the two groups regarding age and sex (P=0.58 and 0.22, respectively) (Table 1).

In the current study, there was a nonsignificant difference between the two groups regarding the presenting degree of hyposmia and the presenting duration of hyposmia (P=0.78 and 0.44, respectively) (Table 2).

In the current study, there was a nonsignificant difference between the two groups regarding if the postviral hyposmia was COVID-19 induced or not (P=0.44) (Table 3).

In the current study, there was a significant difference between the two groups regarding the number and percentage of patients, who had their smell identification test score improved posttreatment (P<0.05) favoring group I. However, among the improved patients in both groups, there was a nonsignificant difference between the two groups regarding the degree of recovery whether complete or partial (P=0.78) (Table 4).

Twenty patients out of 41 patients in group I (48.8%) experienced minor side effects related to the use of Cinnarizine in the form of drowsiness and dry mouth, which did not lead to cessation of treatment. There was no recorded extrapyramidal side effects of Cinnarizine use on any of our patients during the study period. Eighty-two (100%) patients in both groups experienced 'to a variable degree' the common side effects related to prolonged oral steroid intake and all those symptoms disappeared after its discontinuation.

Table 1 Demographic data of both study groups

Items	Group I (41)	Group II (41)	Statistical test	*P*
Age (Mean±SD)	38.41±12.41	39.95±9.61	Z=−0.55644	0.57548
Sex [*n* (%)]				
Male	27 (65.9)	32 (78.05)	χ^2=1.5107	0.219035
Female	14 (34.1)	9 (21.95)		

χ^2, χ^2 test; Z, Z value of Mann–Whitney U test.

Discussion

All individuals in their lifetime have experienced loss of smell at some point due to flu, while in most of the cases the sense of smell returns back to normal gradually; in few patients there is permanent hyposmia [15,16].

The exact mechanism behind the postviral hyposmia is no yet clearly understood. Studies have suggested that there is damage to the layer of mucous membrane of olfactory epithelium containing olfactory receptors and neurons in the olfactory bulb that supplies those receptors. The olfactory epithelium is a self-renewing tissue, so any viral pathology that impairs neuroepithelial regeneration from basal stem cells may result in olfactory loss [17,18]. Therefore, basal cells are a logical therapeutic target for particular olfactory losses. In addition, postviral damage to the olfactory receptor neurons leads to vasoconstriction of the olfactory area microcirculation.

Multiple studies done recently in times of COVID-19 pandemic have come up with some evidence to suggest a similar mechanism in postviral olfactory hyposmia caused by COVID-19, but more studies are required in this regard for better acceptance of this hypothesis [14].

The present study focusses on the role of Cinnarizine in postviral olfactory loss restoration based on its multimodal central mechanism of action. Knowing its effect for decades in improving cases of inner ear dysfunction [19] led us to research and study any similarities in the pathophysiology of inner ear dysfunction (tinnitus in particular) and hyposmia. Tinnitus is not a single entity produced by a single cause, it is a multifactorial phenomenon. The common pathology is damage and loss of the tiny sensory hair cells in the cochlea like that of olfactory cells in hyposmia. Tinnitus also occurs due to vascular insufficiency affecting the cochlea [20], which has seen also in olfactory area in cases of hyposmia. Cinnarizine by virtue of being a potent cerebral and labyrinthine vasodilator improves blood flow in the inner ear and prevents the constriction on these vessels and reduces the symptoms of tinnitus.

There are other cerebral vasodilators apart from Cinnarizine, the effect of which have already been

Table 2 Comparison between the two groups regarding the degree of presenting hyposmia and duration of presenting hyposmia

	Group I (41)	Group II (41)	Statistical test	*P*
Degree of presenting hyposmia [*n* (%)]				
Mild	3 (7.3)	4 (9.7)	χ^2=0.4914	0.782171
Moderate	20 (48.8)	17 (41.5)		
Severe	18 (43.9)	20 (48.8)		
Duration of presenting hyposmia (days) (mean±SD)	43.54±21.88	48±24.17	Z=−0.77438	0.4413

χ^2, χ^2 test; Z, Z value of Mann–Whitney U test.

studied thoroughly in olfactory dysfunction and tinnitus treatment. Ginkgo biloba extract was one of them. It increases microperfusion by increasing red blood cell deformability and decreases whole blood viscosity. Also it protects mitochondria from oxidative stress and improves energy metabolism, thus attenuating damage to cochlear cells, thus reducing the tinnitus [21,22]. Similar mechanism of action of ginkgo biloba extract has also been found useful in the treatment of hyposmia. Its cerebral vasodilator and antioxidant effects help in the restoration of olfactory loss [23,24].

Cinnarizine is known for being a calcium channel blocker. This led us to study in depth the role of calcium in olfaction. Calcium plays different roles in the cilia of olfactory sensory neurons. An increase in intracellular calcium ions is involved both in odorant-induced excitation and adaptation. In the excitation phase there is odorant-induced calcium entry into the cilia through cAMP-gated channels [25,26]. The role of calcium in adaptation mainly occurs through a negative feedback causing the desensitization of cAMP-gated channels through calcium ions and calmodulin [27]. The extrusion of calcium ions from the cilia is caused by sodium/calcium exchanger that returns the cytoplasmic calcium ion concentration to basal levels after stimulation [28]. Therefore, calcium ion concentrations need to be tightly regulated to allow the olfactory neuron to convey to the brain a reliable response to odorants from the external environment [29]. Cinnarizine neither has a role on cAMP-gated channels nor on sodium/calcium exchanger. Cinnarizine, by blocking L&T-type voltage-gated calcium channels, reduces the calcium influx in the smooth muscles of the cerebrovascular wall leading to vasorelaxation of the blood vessels, better red blood cell's deformability and improvement in olfactory perfusion. This carries better nutrients, better oxygen, and better coadministered systemic medications (steroids in our scenario) to the affected olfactory apparatus [12,13].

Cinnarizine has also an antihistaminic effect. The studies regarding the role of histamine in olfactory apparatus are very limited. One study by Yu *et al.* [30] demonstrated that H1 receptors, H2 receptors, and H3 receptors are strongly expressed in rat olfactory receptor neurons. Mammalian olfactory receptor neurons form the primary elements of the olfactory system. The specific localization of these receptor subtypes in the olfactory epithelium suggests that histamine may also play an important role in olfactory transmission. This role is proven to be inhibitory in insect's antenna lobe (which is the functional analog to olfactory bulb in mammals) [31] and in lobsters [32,33], but still no good evidence about this inhibitory role in mammals. It was previously demonstrated that Levocetrizine, a potent second-generation H1 antagonist, could improve the loss of smell in persistent allergic rhinitis, which is not correlated with improvement in nasal obstruction [34]. This study [30] highlights the presence of histamine receptors in the olfactory apparatus and also the role of antihistamines in olfaction improvement either through blocking the inflammatory effect of histamine on the olfactory mucosa or blocking the assumed central inhibitory effect of histamine on the olfactory pathway. This further supports the role of Cinnarizine in hyposmia.

Cinnarizine has also an antidopaminergic effect. In a study by Huisman *et al.* [35], a remarkable increase in the number of dopaminergic cells in the olfactory bulbs of Parkinson patients is reported. This is contrary to what is known about excessive degeneration of dopaminergic neurons in Parkinson's disease. Studies have shown that excessive dopaminergic neurons degeneration in the pars compacta of substantia nigra is accompanied by flourished formation in other areas, one of those areas is the olfactory bulb. This was evidenced by a significant increase (>100%) of tyrosine hydroxylase immunoreactive cells there [35]. Because dopamine is known to inhibit olfactory transmission [8,36–39], this dopamine overdose in the olfactory bulb may be responsible for the olfactory dysfunction in Parkinson patients. This study [35]

Table 3 Comparison between the two groups regarding if the hyposmia was coronavirus disease 2019 related or not

Items	Group I (41)	Group II (41)	Statistical test	*P*
COVID-19-related hyposmia [*n* (%)]				
Yes	23 (56.1)	27 (65.9)	χ^2=1.6457	0.439157
No	13 (31.7)	12 (29.2)		
Not sure	5 (12.2)	2 (4.9)		

χ^2, χ^2 test; COVID-19, coronavirus disease 2019.

Table 4 Comparison between the two groups regarding the number and percentage of improved smell identification test score cases and degree of recovery of hyposmia

	Group I (41)	Group II (41)	Statistical test	*P*
Improvement of smell identification test score [*n* (%)]				
Yes	30 (73.2)	21 (51.2)	χ^2=4.2011	0.040397
No	11 (26.8)	20 (48.8)		
Degree of recovery of hyposmia [*n* (%)]				
Complete recovery (normosmia)	16 (53.3)	12 (57.1)	χ^2=0.0724	0.787867
Partial recovery	14 (46.7)	9 (42.9)		

χ^2, χ^2 test.

reinforces the inhibitory role of dopamine in olfaction and the possible benefit of antidopaminergic effect of Cinnarizine in hyposmia.

So, after thorough evaluation of the multimodal mechanism of action of Cinnarizine on the olfactory apparatus and the similarities in pathophysiology between olfactory dysfunction and tinnitus along with evaluating the efficiency of other cerebral vasodilators like ginkgo biloba in the treatment of hyposmia, it can be very well proposed that Cinnarizine presents itself as a potential drug which can be used as an additional treatment in cases of postviral hyposmia.

To the authors' knowledge there has been no article until now discussing the value of immediate treatment of early presented cases of postviral hyposmia compared with the treatment of lately presented ones, although treatment protocols are there for immediate interference in sudden sensorineural hearing loss or sudden facial nerve paralysis, which are both a cranial nerve disorder, with good evidence that delayed interference in both disorders depriving the patient from good chances of recovery. The olfactory apparatus is the only central nervous element that has the capability to regenerate throughout life, which explains why we can still see cases of delayed olfactory recovery [24].

We have faced three limitations in our study, The first was that we did not get a chance to do a study of Cinnarizine on the animal model, so we can have a look on the E/M picture of the animal's olfactory membrane pretreatment and posttreatment, which will add a lot to our knowledge on how this medicament can benefit the olfactory membrane at a histological level. The second limitation was that we did not include a third nontreated control group in our study to eliminate the time healing factor (spontaneous recovery) on our treated groups. This was because our Institutional Ethics Committee refused to deprive any patient included in our study from basic treatment. The third limitation was that we did not do a third olfactory assessment with smell identification test at 6 months posttreatment, so we can detect more improved cases in both groups, this is because our study was not funded and the patients had to self-pay both smell identification test kits pretreatment and posttreatment. However, this limitation was somehow beneficial, as the results of olfactory reassessment 6 months posttreatment will be greatly affected by the time healing factor on both groups and we cannot attribute those added improvements to any of the treatment protocols.

Conclusion

Cinnarizine has a beneficial effect on improving the smell identification test score of hyposmic patients through its multimodal central mechanism of action. This is considered as a valuable add-on to steroids in the treatment of patients suffering from postviral hyposmia, especially in this challenging time of worldwide COVID-19 pandemic where there are numerous cases of postviral hyposmia left after.

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Conflicts of interest

There are no conflicts of interest.

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