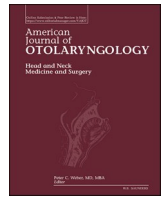


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Effect of nasal corticosteroid in the treatment of anosmia due to COVID-19: A randomised double-blind placebo-controlled study

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ABSTRACT

Objectives: Anosmia is a common debilitating symptom of the novel coronavirus disease 2019 (COVID-19). Currently, there is no satisfactory treatment of anosmia. Therefore, this study was conducted to evaluate the therapeutic effect of nasal betamethasone drops in the recovery of olfaction in COVID-19-associated anosmia.

Methods: The study was designed as a randomised, double-blind, placebo-controlled clinical trial. In total, 276 PCR-confirmed COVID-19 patients who were presented to the outpatient clinic with anosmia were enrolled in the study. In the betamethasone group, 138 participants received nasal drops of betamethasone 3 times daily until recovery for a maximum of one month. Similar dose of 9% NaCl drops was administered to 138 participants in the placebo group.

Results: The median age of participants was 29 years (IQR 23–37). Among them, 198 (71.7%) were females. Ageusia was co-presented with anosmia in 234 (84.8%) of participants. In this study, 83% of participants had recovered from anosmia within 30 days, with a median recovery time of 13 days (IQR 8–18). Compared to placebo, nasal application of betamethasone drops has no significant effect on the recovery time of anosmia (hazard ratio 0.88; 95% CI 0.68–1.14; $P = 0.31$).

Conclusion: The use of nasal betamethasone to facilitate the recovery time of acute anosmia is not advised. In addition, age, smoking status, the duration of anosmia at presentation, and the co-presentation of ageusia with anosmia are important determinant covariates for the recovery time of anosmia. Further clinical trials, which take these covariates into account, will need to be undertaken.

The trial has been registered at [ClinicalTrials.gov](https://clinicaltrials.gov), NCT04569825.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a debilitating pandemic disease that, so far, affected more than 115 million individuals worldwide, as reported by the World Health Organization (WHO) [1]. It is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA virus from the family *Coronaviridae*. Infections with SARS-CoV-2 are mainly transmitted through patients' droplets and aerosols [2]. Therefore, countries around the globe have applied social measures in an attempt to break the chain of virus outbreak. As such, COVID-19 had massive burdens on economic, social, and psychological statuses as well as impacts on health-care systems [3].

Early studies from China, where the disease has first disseminated, reported that non-specific symptoms such as fever, cough, fatigue, and

excessive mucus production are common in COVID-19 patients. Less common symptoms like shortness of breath, pain in joints and muscles, sore throat, and headache were also reported. Most of cases are mild to moderate. Yet, life-threatening lower respiratory complications might develop in small proportion of patients [4,5]. Recently, a multi-centre European study has verified high prevalence of olfactory symptoms, particularly anosmia (loss of sense of smell) in European COVID-19 patients [6]. In fact, it is now widely accepted that anosmia might be an important and common symptom of COVID-19 (ranged from 22 to 68%) [7]. Importantly, it might occur in the absence of other symptoms [8]. Hence, it was suggested for health authorities to consider newly developed anosmia as a potential indicator for SARS-CoV-2 infection [9,10]. Indeed, WHO, Centers for Disease Control and Prevention (CDC), and United Kingdom National Health Service (NHS) as well as other

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health authorities have recommended early intervention in cases when anosmia has recently evolved. To note, in COVID-19 patients, anosmia usually accompanied by gustatory dysfunction, namely ageusia (loss of taste) [11].

Before COVID-19 era, the prevalence of olfactory dysfunctions, anosmia and hyposmia (decrease in the sense of smell), was around 3 to 20% of the population [12]. Common causes of anosmia include nasal and paranasal sinus diseases, viral infections, trauma, aging, and neurodegenerative diseases such as Parkinson's and Alzheimer's diseases [13]. Viral infection by SARS-CoV, another family member of coronavirus which caused the epidemic severe acute respiratory syndrome outbreak in 2003, was also reported to cause anosmia [14]. Similar to SARS-CoV-2, SARS-CoV invades affected cells by a mechanism that involves binding of its spike proteins to angiotensin-converting enzyme 2 (ACE2) receptors on the surface of host cells [15]. ACE2 receptors are highly expressed in nasal mucosa including olfactory epithelial cells [16]. Brann et al. [17] have demonstrated that ACE2 receptors are expressed on supportive olfactory epithelial cells but not on olfactory sensory neurons. The authors anticipated that infection of non-neuronal supportive cells by SARS-CoV-2 could be the primary mechanism of anosmia in COVID-19 patients. In addition, Torabi et al. [18] have detected high levels of the proinflammatory cytokine tumour necrosis factor α (TNF- α) in the olfactory epithelium of COVID-19 patients, proposing that direct inflammation plays a pivotal role in the pathogenesis of anosmia. However, Maria de Fátima et al. [19] suggested that injury to the intracranial olfactory neurons, particularly olfactory bulbs, causes anosmia in patients with COVID-19. Given the novelty of COVID-19, the precise mechanism underlying anosmia is yet to be determined. To note, this topic grabs the attention of many researchers, thereby relevant studies are still emerging.

In general, post-viral anosmia is often treated by intranasal and/or oral corticosteroids as well as other remedies [20]. In mild to moderate cases of COVID-19, the use of systemic corticosteroids is not recommended due to potential immunosuppression [21]. On the other hand, the therapeutic potential of intranasal corticosteroids to alleviate anosmia in COVID-19 patients is controversial (reviewed by Vroegop et al. [22]). Therefore, the aim of the current study was to evaluate the therapeutic effect of intranasal corticosteroids, particularly betamethasone, to alleviate anosmia in COVID-19 patients.

2. Methods

2.1. Study design

The current study is an investigator-initiated, randomised, double-blind, parallel-arm, placebo-controlled clinical trial which was designed to evaluate the therapeutic effect of nasal betamethasone drops to facilitate the recovery from anosmia in COVID-19 patients. The study was conducted in accordance with the principles of good clinical practice and the ethical principles disclosed in the Declaration of Helsinki. The ethical approval was obtained from the Ethical Approval Committee, University of Anbar (REF: 62). The trial has been registered at ClinicalTrials.gov, NCT04569825.

2.2. Patients and intervention

Polymerase chain reaction (PCR)-confirmed mild to moderate COVID-19 patients were recruited from August 1, 2020 to September 31, 2020 at two Otolaryngology outpatient-clinics in Al-Ramadi Teaching Hospital and Tikrit Hospital, Iraq. All participants have provided written informed consents. Patients were randomly allocated in 1:1 ratio to receive intranasal betamethasone sodium phosphate drops (0.1 mg/mL), or placebo drops (0.9% NaCl solution) 3-times daily until recovery for a maximum of one month. Betamethasone drops were prepared by transferring a pharmaceutically available formulation (Ophatamesone® sterile drops for eye, ear, and nose; Dar Al Dawa, Na'ur, Jordan) into a

plain container at aseptic conditions. At similar conditions, 0.9% NaCl intravenous solution was used to prepare placebo drops. Drops were prepared by a pharmacist who was not involved in the study. Treatment arms were concealed to patients and investigators.

The inclusion criteria were PCR-confirmed SARS-CoV-2 infection, age ≥ 18 years, and recent developed of anosmia. The exclusion criteria included pregnancy, the presence of psychological disorders, history of anosmia before COVID-19 era, severe sinonasal diseases, previous sinonasal surgery, and anosmia for more than 15 days. Clinical data including age, sex, time for first onset anosmia to treatment initiation, nasal symptoms (nasal obstruction, rhinorrhea, sneezing, and facial pain), and previous sinonasal abnormalities and surgery were taken from each participant.

Once randomised to one of the treatment groups, patients were instructed to apply the nasal drops in Mecca position with a dose of 3 drops for each nasal cavity 3-times daily until the recovery of anosmia for a maximum of one month. Patients were asked to self-report the time of recovery from anosmia by phone. In addition, patients were followed-up by phone every 5 days to confirm the clinical condition, adherence to treatment, or the development of side effects. The primary outcome of the current study was the time taken for anosmia to resolve, in days, following the initiation of treatment.

2.3. Sample size

Sample size was estimated based on the assumption that median time to clinical recovery from anosmia is 7 days as previously reported by Lee et al. [23]. The calculated number in each group, which would provide 80% power and a 5% significance level, was 214 participants (428 for both groups), assuming a withdrawal rate of 10%. However, in the current study, recruitment was stopped at 276 randomised participants due to constraints in the time of enrolment.

2.4. Statistical analysis

The primary outcome of the current study, time of recovery from anosmia, was analysed on an intention to treat basis for all randomly assigned participants. No clinical improvement at the end of the follow-up period was considered as right censored at day 30. Time to clinical improvement from anosmia was represented by Kaplan-Meier plot and compared with a log-rank test. Cox proportional hazards model was used to assess the effect of covariates on the time of recovery indicator. Results are expressed as median (interquartile range; IQR) or number of patients (%). Statistical differences between treatment groups were assessed using chi-square test and Mann-Whitney *U* test, as appropriate. IBM SPSS Statistics software, version 25, was used to perform the analysis and a *P* value <0.05 was considered to represent a significant difference.

3. Results

Between August 1, 2020 and September 30, 2020, 304 individuals were screened for eligibility, of whom 276 were enrolled in the study. All participants had mild or moderate forms of COVID-19, which was confirmed by PCR. One-hundred and thirty-eight patients were assigned to each treatment arm, the betamethasone group and the placebo group. Fourteen (10.1%) and thirteen (9.4%) patients were lost to follow-up in the betamethasone and placebo groups, respectively, 5 days following the initiation of the study. Those patients were included in the intention to treat analysis (Fig. 1). No patients were enrolled after September 30 as per the protocol of the study.

As depicted in Table 1, there was no difference in the baseline characteristics between the groups with regard to age, gender, clinical onset of anosmia to involvement, smoking status, the coincidence of ageusia, and the history of sinonasal diseases. However, more patients with nasal symptoms (nasal obstruction and/or rhinorrhoea) are in the

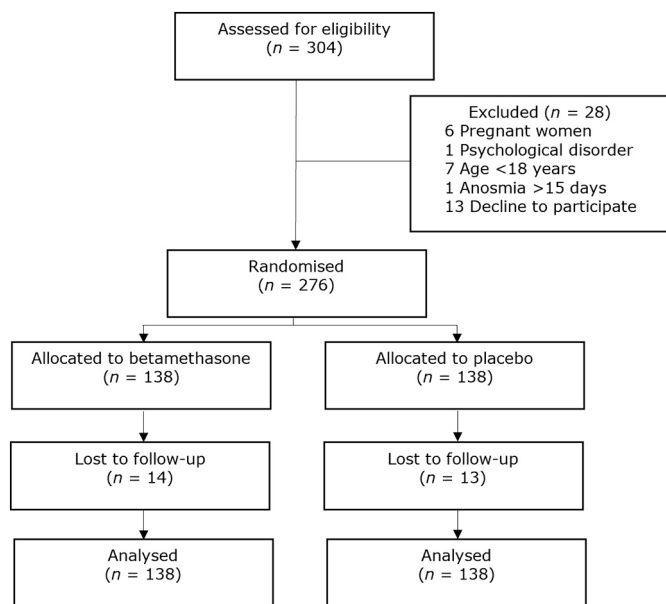


Fig. 1. Study flow diagram.

Table 1
Baseline characteristics of patients with anosmia due to COVID-19.

	Total (n = 276)	Betamethasone group (n = 138)	Placebo group (n = 138)
Age, years	29 (23–37)	29 (23–35)	30 (24–38)
Gender	Male	42 (30.4%) (28.3%)	36 (26.1%)
	Female	198 (71.7%)	102 (73.9%)
Clinical duration of anosmia to involvement, days	4.5 (3–6)	5 (3–6)	4 (3–7)
Smokers	Yes	32 (11.6%)	12 (8.7%)
	No	244 (88.4%)	126 (91.3%)
Nasal symptoms; nasal obstruction and/or rhinorrhoea	32 (15.6%)	28 (21.0%)*	14 (10.1%)
Ageusia	Yes	234 (84.8%)	118 (85.5%)
	No	42 (15.2%)	20 (14.5%)
History of sinonasal diseases	20 (7.2%)	10 (7.2%)	10 (7.2%)

Data are presented as median (interquartile range) or number of patients (%). Differences between treatment groups were assessed by chi-square test and Mann-Whitney U test, as appropriate.

* P < 0.05.

betamethasone group than placebo group (P = 0.019). The median age of participants was 29 years (IQR 23–37) and sex distribution was 42 (30.4%) men versus 96 (69.6%) women in the betamethasone group and 36 (26.1%) versus 102 (73.9%) in the placebo group. All most all participants had the clinical symptoms of anosmia for more than 3 days before being involved in the study (median of 4.5 days; IQR 3–6). In addition to anosmia, most of the participants had ageusia; 118 (85.5%) in the betamethasone group and 116 (84.1%) in the placebo group. Among the participants, 32 (11.6%) were smokers; 20 (14.5%) in the betamethasone group and 12 (8.4%) in the placebo group.

Final follow-up was on October 30, 2020. In the intention to treat population, the time to clinical improvement from anosmia in the

betamethasone group was not significantly different to that of the placebo group. The median time of recovery from anosmia following the intervention in the betamethasone group was 7 days (IQR 5–14) versus 7 days (IQR 4–12) in the placebo group (hazard ratio 0.88; 95% CI 0.68–1.14; P = 0.31; Fig. 2). The median recovery time from the onset of anosmia for all participants was 13 days (IQR 8–18). Overall, 83% of participants had recovered from anosmia within the follow-up period; 82% in the betamethasone group versus 84% in the placebo group.

Table 2 shows the effect of covariates on the recovery time of anosmia in each treatment arm. To note, age has a remarkable effect on the recovery time. It seems that younger participants recover from anosmia faster than older participants in both groups. In addition, as the time of anosmia to involvement increases, days of anosmia elapsed before participation, the recovery is decreased in the placebo group (P = 0.014) but not in the betamethasone group (P = 0.94). In the betamethasone group, participants who had anosmia and ageusia have significantly higher recovery than participants with anosmia alone (P = 0.026). However, it seems that the coincidence of ageusia has no significant effect on the recovery of anosmia in the placebo group. Also, it appears that smoking has negative effect on the recovery from anosmia. This effect was numerically significant in the betamethasone group (P = 0.009), but not in the placebo group (P = 0.058). Other covariates such as sex, the presence of nasal symptoms, and a previous history of sinonasal diseases have no significant effect on the recovery in both groups.

4. Discussion

Since the earliest days of COVID-19 era, many otolaryngologists described an extremely high number of sudden anosmia with or without other symptoms. In fact, anosmia has caught the attention of otolaryngologists all over the world with a growing body of research on this abnormality. However, the exact mechanism of smell abnormalities is yet to be determined. Currently, there is no satisfactory treatment of anosmia. Herein, the effect of local corticosteroids, particularly betamethasone, on the recovery of olfaction in COVID-19-associated anosmia was explored.

In this clinical trial, 276 patients with COVID-19-related anosmia were randomised into two groups, 138 participants in each treatment arm. The baseline characteristics of participants revealed that the majority of participants were young females (Table 1). This might confirm that olfactory dysfunction is more prevalent in younger participants and females as previously reported by other investigators [24–27]. Our data broadly support the hypothesis that younger patients have better local

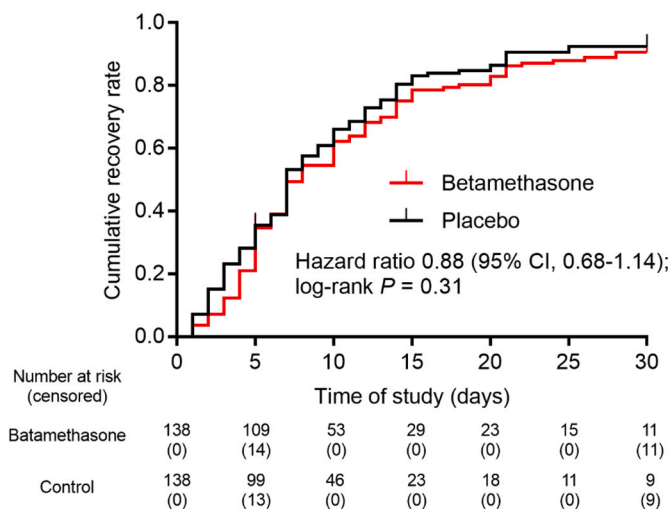


Fig. 2. Kaplan-Meier curves for the time of recovery from anosmia in COVID-19 patients treated with betamethasone nasal drops and 9% NaCl drops (placebo).

Table 2
Effect of covariates on the recovery time of anosmia over the study period.

Covariate	Hazard (recovery) ratio (95% CI)	
	Betamethasone	Placebo
Age	0.97 (0.95–0.99)**	0.98 (0.96–0.99)**
Male gender	0.85 (0.57–1.23)	0.88 (0.58–1.34)
Time of anosmia to involvement	0.94 (0.87–1.01)	0.90 (0.82–0.98)*
Smoking	0.46 (0.26–0.83)**	0.50 (0.24–1.03)
Nasal symptoms; nasal obstruction and/ or rhinorrhoea	0.84 (0.52–1.35)	1.49 (0.84–2.66)
Ageusia	2.03 (1.09–3.80)*	1.09 (0.66–1.81)
History of sinonasal diseases	1.11 (0.52–2.39)	1.20 (0.58–2.46)

Cox proportional hazards model was used to assess the effect of covariates on the recovery in each treatment arm. Data are presented as hazard ratio (95% Confidence Interval).

* $P < 0.05$.

** $P < 0.01$.

immunological response, which produces a stronger local inflammatory reaction and thereby manifested as olfactory dysfunction [25,28]. The higher presentation of anosmia in females could be attributed to the fact that women are more sensitive to changes in the sense of smell than men [29]. Another important characteristic of our study population is the high association of anosmia with gustatory dysfunction, ageusia, which presented in 84.8% of the patients (Table 1). Similar trends were also highlighted in previous reports [30,31]. Also consistent with the literature [24,25,32], low proportion of the participants in the current study was smokers (Table 1).

In general, most patients with COVID-19-associated olfactory dysfunction recovered within 1–4 weeks, with a median recovery time of 1–2 weeks [23,24,33,34]. Indeed, in the current study, 83% of participants had recovered from anosmia within the follow-up period (30 days), and the median recovery time from the onset of anosmia was 13 days. Some cases, however, didn't recover within the follow-up period. The short recovery time in the majority of COVID-19 related anosmia suggests that the primary mechanism of olfactory disorder could be temporary disturbance of olfactory epithelial cells, whereas neuronal damage in some cases could cause long-lasting anosmia. Similar mechanisms were previously suggested for anosmia due to viral diseases other than COVID-19 [35].

The most important finding to emerge from the analysis of our data is that intranasal betamethasone made no significant difference to the recovery time of anosmia compared to placebo ($P = 0.31$). In fact, although not statistically significant, it seems that participants who received betamethasone had slower recovery from anosmia than those who received placebo (hazard ratio 0.88; 95% CI 0.68–1.14; Fig. 2). This observation might support the hypothesis that anosmia is predominantly caused by olfactory epithelial damage [18] where the use of corticosteroids could impede the regeneration of olfactory epithelium as previously demonstrated for gastric [36], airway [37], and corneal [38] epithelial cells. Further, in accordance with the present results, a recent randomised controlled trial by Abdelalim et al. [39] have demonstrated that nasal administration of mometasone furoate to patients with post COVID-19 anosmia did not enhance the clinical recovery of anosmia. However, our data are contrary to that of Singh et al. [40] who found that fluticasone nasal spray can significantly improve the olfactory function in COVID-19-associated anosmia. To note, Singh's data should be interpreted with caution as the study has important limitations. These include very short follow-up period and the lack of randomisation and blinding [40].

In this trial, the effect of covariates on the recovery time of anosmia was assessed in each treatment arm. Apparently, age is an important discriminative factor affecting the recovery time in the betamethasone group ($P = 0.001$) and placebo group ($P = 0.006$; Table 2). It seems that

younger participants recover faster than older participants. This finding is consistent with that reported by Abdelalim et al. [39]. This result may be explained by the fact that the regeneration of the olfactory epithelium is more efficient in young individuals [41]. However, Lee and colleagues have reported that COVID-19-associated anosmia persists longer in young patients [23]. Further studies are required to elucidate this discrepancy.

In addition, this study found a negative correlation between the duration of anosmia before intervention, in days, and the recovery time (Table 2). This can be interpreted as patients who had longer presentation of anosmia before the start of the study experienced more persistence anosmia. This effect was numerically significant in the placebo group ($P = 0.014$) but not in the betamethasone group ($P = 0.94$). It seems that betamethasone has a therapeutic effect in patients with relatively long-lasting olfactory disorders. A further study with more focus on the duration of anosmia before the initiation of corticosteroids is therefore suggested.

The results of the current study suggest that smoking can adversely affect the recovery time of anosmia (Table 2). Similar effect can be extrapolated from the study of Amer et al. [42] who reported that significant proportion of smoking patients was not recovered within one month from the onset of COVID-19-associated olfactory dysfunction. This could be attributed to the negative impact of smoking on the regeneration of olfactory epithelium as previously demonstrated in mice [43]. To note, in our study, smoking has remarkable effect on the recovery of patients in the betamethasone group ($P = 0.009$), whereas the effect was not significant in the placebo group ($P = 0.058$). This could be due to the difference in the number of smoking participants between groups; 20 (14.5%) in the betamethasone group versus 12 (8.4%) in the placebo group (Table 1). Another important highlight of this study is that the co-presentation of anosmia and ageusia had a positive significant effect on the recovery time of anosmia in the betamethasone group ($P = 0.026$; Table 2). However, this effect was not significant in the control group ($P = 0.729$). This effect reveals the need for further investigation in patients who presented with both symptoms, anosmia and ageusia. Other covariates such as sex, the presence of nasal symptoms, and a previous history of sinonasal diseases were not found to have a significant effect on the time of recovery in both groups.

The limitations of the current study include the use self-reported assessment of smell, short term follow-up, and the relatively small sample size.

5. Conclusion

In conclusion, in this clinical trial, it was shown that nasal application of betamethasone had no significant effect on the recovery time of anosmia in COVID-19 patients. Therefore, the evidence from this study suggests that the use of nasal betamethasone to facilitate the recovery time of acute anosmia is not advised. In addition, age, smoking status, the duration of anosmia at presentation, and the co-presentation of ageusia with anosmia are important determinant factors for the recovery time of anosmia. Further clinical trials, which take these factors into account, will need to be undertaken.

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Declaration of competing interest

None.

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