

META-ANALYSIS

Efficacy of topical steroids for the treatment of olfactory disorders caused by COVID-19: A systematic review and meta-analysis

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Abstract

Objectives: The aim of this study was to assess the effect of topical steroids on acute-onset olfactory dysfunction in patients infected with COVID-19.

Design and Setting: Systematic review and meta-analysis of cohort studies.

Participants: Patients infected with COVID-19.

Main outcome measures: PubMed, Embase, the Web of Science, SCOPUS, Cochrane database and Google Scholar were searched for articles up to September 2021. We analysed studies comparing the improvement of olfactory dysfunction between topical steroid treatment and control groups (placebo or no treatment). In addition, we performed a subgroup analysis by study type.

Results: The improvement of olfactory score at 2 (standardised mean difference [SMD] = 0.7272, 95% confidence interval = [0.3851, 1.0692], $p < .0001$, $I^2 = 62.1\%$) and 4 weeks post-treatment (SMD = 1.0440 [0.6777, 1.4102], $p < .0001$, $I^2 = 61.2\%$) was statistically greater in the treatment than control group. However, there was no significant difference (odds ratio [OR] = 1.4345 [0.9525, 2.1604], $p = .0842$, $I^2 = 45.4\%$) in the incidence of fully recovery from anosmia/hyposmia between the treatment and control groups. In subgroup analysis, there were no significant differences in the improvement of olfactory score at 4 weeks post-treatment (OR = 0.6177 [0.1309, 1.1045] vs. 0.1720 [0.8002, 1.5438], $p = .0761$) or the incidence of full recovery from anosmia/hyposmia (OR = 1.8478 [0.6092, 5.6053] vs. 1.3784 [0.8872, 2.1414], $p = .8038$) between randomised and non-randomised controlled trials.

Conclusions: Although this meta-analysis found that topical steroids improved the acute-onset olfactory dysfunction caused by COVID-19, there was no difference in the rate of full olfactory recovery between treated and control patients.

KEYWORDS

coronavirus infections, nasopharynx, saliva, specimen handling, treatment outcome

1 | INTRODUCTION

Since the onset of the global COVID-19 pandemic caused by the SARS-CoV-2 virus, otolaryngologists have noted olfactory dysfunction in COVID-19-infected people.^{1,2} Olfactory disorder is a

common clinical symptom, appearing in 22%–68% of mild disease cases.³ It is widely accepted that loss of smell is an important symptom of COVID-19.⁴ The clinical course of the olfactory impairment caused by COVID-19 varies significantly, with recovery rates of between 4% and 89% reported within 1 month after the onset of

anosmia.⁵ Given the high global prevalence of COVID-19, olfactory dysfunction may also be an important issue in otolaryngology, and long-lasting loss of smell lead to comorbidities such as depression and cognitive impairment.⁵ For this reason, there is a need to identify effective treatments that promote spontaneous recovery of olfactory function.⁶

No intervention shows a clear (i.e. evidence-based) benefit, although olfactory training is generally effective in improving olfaction in COVID-19 patients.⁷ Oral or topical corticosteroids are typically used to treat olfactory disorders.⁸ However, systemic corticosteroid for COVID-19 patients is not recommended due to the potential for immunosuppression or delayed viral clearance.⁹ Meanwhile, the effect of topical corticosteroids on olfaction recovery in patients with olfactory impairment caused by COVID-19 is still controversial.^{10,11} Despite these clinical controversies, no systematic review of studies examining the effects of topical steroids on olfactory dysfunction in COVID-19 patients has been published. Therefore, the purpose of this study was to evaluate olfactory recovery and the efficacy of topical steroids for COVID-19 patients with olfactory dysfunction.

2 | MATERIALS AND METHODS

2.1 | Search strategy

We searched the PubMed, SCOPUS, Embase, Web of Science, Google Scholar and Cochrane databases for relevant studies. We retrieved all prospective articles published in English prior to September 2021. COVID-19, SARS-CoV-2, anosmia, hyposmia, olfactory, smell, olfactory disorders, olfactory dysfunctions, recovery, olfactory test, steroid therapy, nasal spray, corticosteroids and treatment were the search terms and keywords (Table S1). Two independent researchers reviewed and screened the titles and abstracts of all identified studies, and excluded those not related to topical steroids in patients testing positive for COVID-19 and having acute-onset (<2 weeks) olfactory dysfunction. If the abstract alone was not sufficient to determine whether to include a study, the full text was checked. Studies were excluded if they described long-lasting olfactory dysfunction that onset after more than 3 weeks. In Figure 1, we present a flow chart of the study selection process. The study protocol was registered at the Open Science Framework (<https://osf.io/m5gkd/>). This study was prepared in accordance with the recommendations of the Priority Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines.

2.2 | Data extraction and risk of bias assessment

We extracted the following data from the eligible studies: number of patients, scale used for analysing olfactory disorders, incidence (percentage) of patients showing a full recovery from olfactory

Key Points

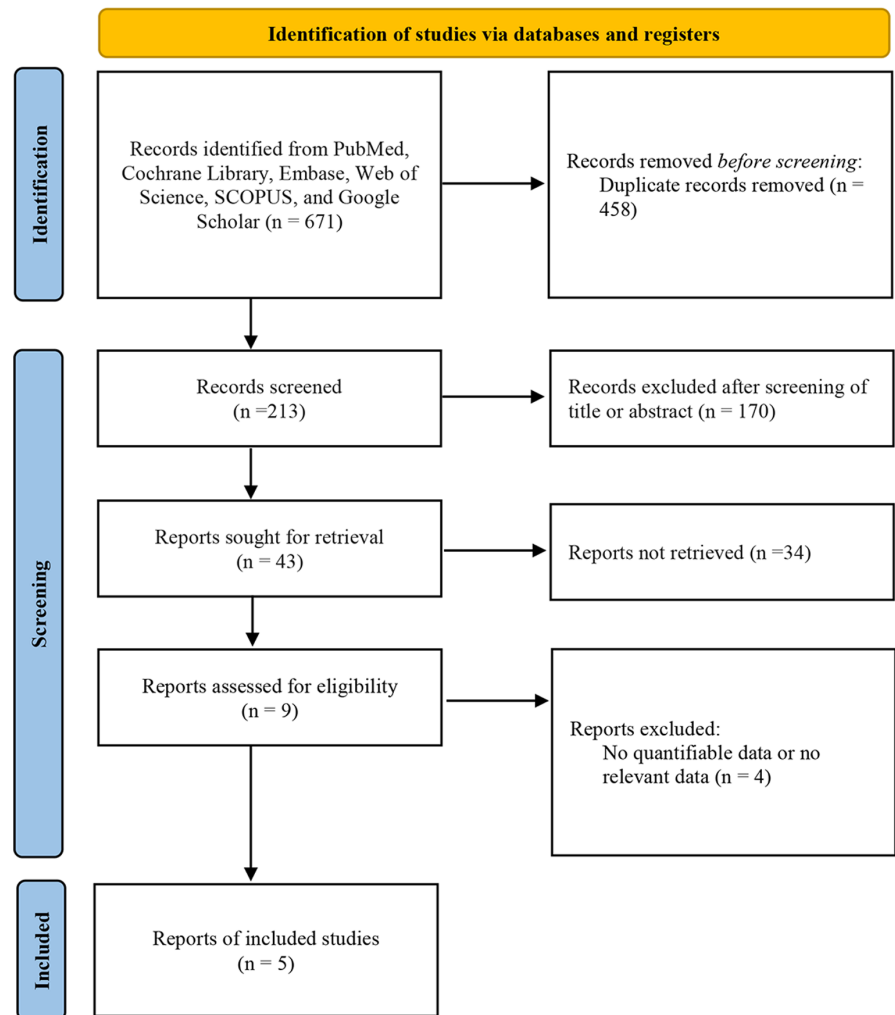
- The prevalence of olfactory disorders due to COVID-19 is high.
- No intervention shows a clear benefit in improving olfaction in COVID-19 patients.
- Systemic corticosteroid for COVID-19 patients is usually not recommended.
- Topical steroids could improve the acute-onset olfactory dysfunction caused by COVID-19.
- No significant difference in olfactory score in the endpoint after topical steroids treatment.

dysfunction and *p*-values for comparisons between topical steroid and control groups. The data were organised using a standardised format.^{4,12} The outcomes of interest were the post-treatment olfactory score (2 and 4 weeks after the initiation of treatment were analysed referring to the common analysis time point of the included papers) and percentage of patients with a full recovery.^{7,10,11,13,14} These outcomes were compared between the treatment (topical steroid) and control groups; the latter were administered either saline or nothing. When the original data were expressed as continuous variables, the meta-analysis was performed using the standardised mean difference (SMD). In our study, this method was chosen to calculate effect sizes due to the absence of a standardised scale used across all studies to assess olfactory function (self-reported olfactory score system, VAS, Iranian version of UPSIT and Sniffin' Sticks tests). The individual mean difference (treatment outcome minus control outcome) is assessed with the size and standard deviation of each study. This method allows a precise estimate of the treatment effect and summates it into a single outcome (SMD). An effect size of approximately 0.2 is considered a small effect, while 0.5 is considered a medium effect and 0.8 a large and clinically significant effect. The quality assessment of the included randomised controlled studies was conducted using the Cochrane Risk of bias tool.¹⁵ The Newcastle-Ottawa Scale was used to assess non-randomised controlled studies with scores ranging from 0 to 9.

2.3 | Statistical analysis

Meta-analyses were conducted using R statistical software (R Foundation for Statistical Computing). Continuous variables were analysed using the standardised mean difference (SMD). We used this method to calculate the effect sizes because, among the included studies, no standardised measure was used for evaluating olfactory function, such as self-rated scores, a visual analogue scale, or the Sniffin' Sticks test. In all other cases, odds ratios (ORs) were calculated. We also conducted sensitivity analyses to assess the effect of each study on the overall meta-analysis results.

FIGURE 1 Diagram showing the study selection process



3 | RESULTS

Of 696 articles initially identified, 5 were included in the final analysis; the study characteristics are listed in Table 1, and bias assessment results are presented in Table S2 and S3. We did not evaluate publication bias because the number of studies included was not sufficient to generate a funnel plot or perform advanced regression analyses.

3.1 | Post-treatment olfactory scoring

The treatment group showed a significantly higher olfactory score at 2 (SMD = 0.7272, 95% confidence interval = [0.3851, 1.0692], $p < .0001$, $I^2 = 62.1\%$) and 4 weeks post-treatment (SMD = 1.0440 [0.6777, 1.4102], $p < .0001$, $I^2 = 61.2\%$) compared with the control group (Figure 2). There was significant inter-study heterogeneity ($I^2 > 50$) in the results. The included studies were of two types: randomised controlled trials (RCTs) and non-randomised, prospective studies (non-RCTs). The effects of topical steroids might vary depending on the study type; therefore, we conducted a subgroups analysis to assess the topical steroids by study type. There was no significant difference in the olfactory score improvement at 4 weeks

post-treatment (0.6177 [0.1309, 1.1045] vs. 1.1720 [0.8002; 1.5438], $p = .0761$) between the RCT and non-RCT subgroups.

3.2 | Rate of full recovery from olfactory dysfunction: comparison between the treatment and control groups

There was no significant difference (OR = 1.4345 [0.9525, 2.1604], $p = .0842$, $I^2 = 45.4\%$) in the rate of full recovery from anosmia/hyposmia between the treatment and control groups (Figure 3). Also, in subgroup analysis, there was no significant difference in the rate of full recovery from anosmia/hyposmia (1.8478 [0.6092, 5.6053] vs. 1.3784 [0.8872, 2.1414], $p = .8038$) between the RCT and non-RCT subgroups.

3.3 | Sensitivity analyses

We performed a sensitivity analysis to evaluate the effects on the outcomes of the meta-analysis of excluding individual studies. In all cases, the results were consistent with those described above.

TABLE 1 Summary of included studies

Study (year)	Sample size (treatment/control)	Age/sex (M:F)	Study design	Administration methods	Outcome measure analysed/time point
Yildiz 2021	150 (59/71)	38.5 ± 10.5/84:66	RCT	Intranasal saline and triamcinolone irrigation treatment (nasal steroid spray 2*2 puffs/each nose/Triamcinolone acetate 0.055% for 1 month)	<ul style="list-style-type: none"> • Olfactory score (self-reporting score; VAS: 0 = no odour at all, and 10 = full odour)/initial, 2 and 4 weeks
Kasiri 2021	77 (39/38)	35.4 ± 9/39:38	RCT	Mometasone furoate (0.05% nasal spray) at an appropriate dose (100 µg) twice daily in each nostril for 4 weeks	<ul style="list-style-type: none"> • Olfactory score (self-reporting score; VAS: 0 = no odour at all, and 10 = full odour)/initial, 1, 2, 3 and 4 weeks • UPSIT: anosmia [0–9], severe microsmia [10–13] mild microsmia [14–18] and normosmia [19–24])/initial and 4 weeks • Rate of fully recovered (normosmia [19–24]) patients from olfactory dysfunction/4 weeks
Ahmed Abdelalim 2021	100 (50/50)	29.0 (IQR 21.75–38.0)/46:54	RCT	Mometasone furoate nasal spray (2 puff (100 µg) once daily in each nostril for 3 weeks)	<ul style="list-style-type: none"> • Olfactory score (self-reporting score; VAS: 0 means total loss of smell and 10 refers to completely normal smell sensation)/initial, 1, 2, and 3 weeks • Rate of fully recovered patients from olfactory dysfunction (score 10 refers to completely normal smell sensation)/3 weeks or later (mean follow up: 26.29 ± 6.76)
Ali Rashid 2021	276 (138/138)	29 (IQR 23–37)/78:198	RCT	Intranasal betamethasone sodium phosphate drops (0.1 mg/ml) (Mecca position with a dose of three drops for each nasal cavity 3-times daily until the recovery of anosmia or a maximum of 1 month)	<ul style="list-style-type: none"> • Rate of fully recovered patients from olfactory dysfunction (self-reporting score)/initial, 5, 10, 15, 20, 25 and 30 days
Saussez 2021	93 (22/71)	37.1 ± 11.9/62:90	Pros	1 month of nasal corticosteroids (mometasone furoate spray, two sprays in each nostril once daily)	<ul style="list-style-type: none"> • Sniffin' Sticks tests: anosmia [0–8], hyposmia [9–11] and normosmia [12–16]/initial, 1, and 2 months • Rate of fully recovered (normosmia [12–16]) patients from olfactory dysfunction/2 months

Abbreviations: IQR, interquartile range; Pros, prospective cohort study; RCT, randomised controlled study; VAS, visual analogue scale.

FIGURE 2 Comparison of the topical steroid and control groups based on the standardised mean difference. Olfactory scores at 2 (A), and 4 (B) weeks post-treatment

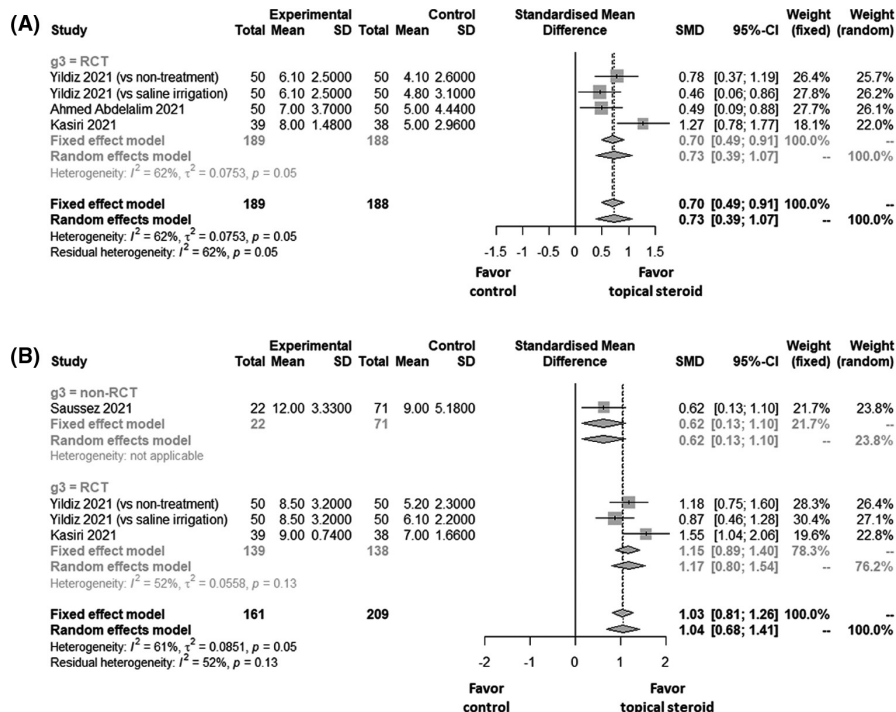
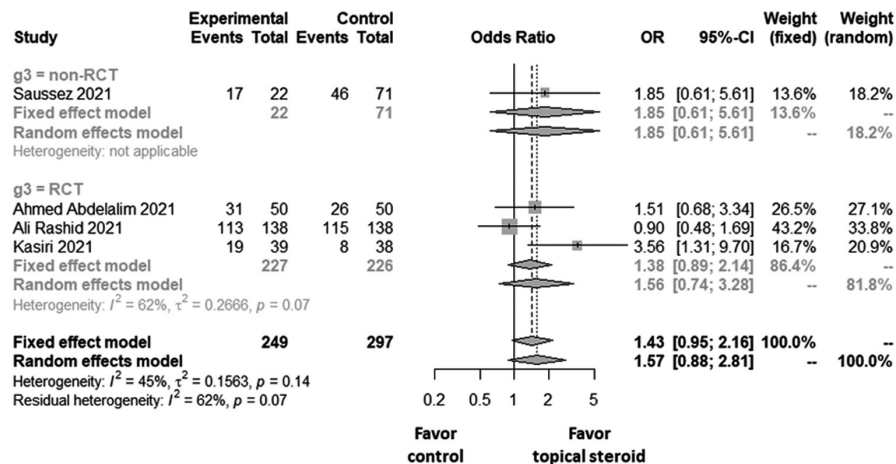


FIGURE 3 Comparison of the topical steroid and control groups based on odds ratios. Percentage of patients showing a full recovery from olfactory dysfunction



4 | DISCUSSION

Anosmia induced by an upper respiratory viral infection is a common cause of olfactory disorder.¹⁶ Prior to the COVID-19 epidemic, the prevalence of olfactory dysfunction due to upper respiratory tract infection in the general population was approximately 3%–20%.¹⁷ However, the worldwide prevalence of olfactory disorder in COVID-19 patients is 46%,¹⁸ with estimates ranging from 50% to 85%. Prevalence is particularly high in Europe and North America.¹⁴ Therefore, olfactory dysfunction is a representative finding of COVID-19 patients and is in fact typically the only clinical symptom.⁴ However, it is not yet known whether the proportion of patients with olfactory dysfunction is significantly higher than that of other viral infections.

In general, olfactory disorders caused by viruses arise due to local inflammation of the nasal cavity and olfactory nerve damage; similar

mechanisms likely explain olfactory disorders related to COVID-19 infection.¹⁹ It has been suggested that anosmia that recovers within a short time can be attributed to a transient inflammatory process in the olfactory epithelium, whereas neuronal damage is responsible for long-lasting anosmia.²⁰ When the COVID-19 pandemic spread to Europe, many patients were advised to perform olfactory training, a therapeutic method without complications promoting neuronal plasticity in the olfactory system.¹⁴ Although the prevalence of olfactory dysfunction due to COVID-19 is high compared with other upper respiratory viral infections, the proportion of patients with long-term anosmia is similar, and our analysis shows that topical corticosteroid administration can accelerate recovery from the olfactory dysfunction caused by COVID-19 infection at 2 and 4 weeks post-treatment compared with non-use of corticosteroid ($p < .0001$). These results support the hypothesis that olfactory dysfunction in COVID-19 is mainly caused by an inflammatory process

in the olfactory epithelium,²¹ where intranasal corticosteroids may have beneficial anti-inflammatory effects.^{21,22} In addition to reducing local inflammation, intranasal corticosteroids may improve olfaction by modulating the function of olfactory receptor neurons through their effects on Na-K-ATPase enzyme activity.²³

Although the analysis on this topic was conducted in the Cochrane review, additional evidence is needed as the analysis was conducted based on a single study.²⁴ We attempted to add evidence by further analysing recently reported articles.

In our study, the SMD for the measurements regarding the olfactory scoring at 2 and 4 weeks after treatment was mostly around 0.8, which meant that these effect sizes were clinically significant. While the olfactory score differed significantly between the treatment and control groups, the number of patients who showed a clinical response, defined as self-reported normosmia (Ali Rashid et al. and Ahmed Abdelalim et al.) or normosmia demonstrated by psychophysical testing (Kasiri et al. and Saussez et al.) did not. Psychophysical tests such as the University of Pennsylvania Smell Identification Test provide more reliable assessments of olfactory symptoms than self-report measures, and inconsistency in the methods used for olfactory assessment can lead to heterogeneity in the results.⁷ Interestingly, two of the studies included in our meta-analysis showed that topical steroids were either not significantly more effective or less effective than the control, although two others showed that steroids were an effective treatment. The former two studies had younger patient cohorts. It has been reported that olfaction in younger patients recovers faster than in older ones; age is an important prognostic factor with respect to recovery and regeneration of the olfactory epithelium.^{10,13} Therefore, topical steroids might be of more benefit for older individuals. Moreover, patients whose pathogenesis is neurological might remain anosmic or hyposmic.

The present meta-analysis had several limitations. First, it included studies using different methods and steroids for olfactory recovery. However, since the study procedures were similar between the intervention and control groups for the individual RCTs, any confounding effect on our analysis was likely to be small.²⁵ Second, the meta-analysis included only five prospective studies, resulting in a small overall sample size. In addition, the timing, amounts and dose measurements of the topical steroids differed among the studies. Third, in some cases, olfactory dysfunction may have occurred prior to the patient being aware of having COVID-19, which may have affected the therapeutic outcomes.¹⁴ Although topical nasal corticosteroids are known to be very safe, three studies made no mention of side effects, one study stated no side effects, and one study investigated side effects, but no side effects were mentioned in the results. Given these limitations, large-sample RCTs should be conducted to validate our findings.

Long-duration olfactory impairment not only affects patients emotionally, but also reduces their awareness of environmental hazards (e.g. fires and gas leaks). Also, when a patient visits a doctor, it is important that the doctor has treatments to offer. In addition, impaired olfactory function is typically accompanied by a decrease in taste function. For COVID-19, the incidence of both anosmia and

the accompanying dysgeusia is higher than for other viral upper respiratory tract infections.²⁶ Therefore, interventions to reduce the duration of disease are important in terms of quality of life. Based on our results, topical steroids appear beneficial for treating olfactory dysfunction in patients suffering from COVID-19. However, the effect of persistent olfactory dysfunction due to COVID-19 on the quality of life should be further studied in the future.

5 | CONCLUSION

Topical steroids improve the acute-onset olfactory dysfunction caused by COVID-19, although we found no statistically significant difference in the rate of full olfactory recovery between patients receiving and controls.

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CONFLICT OF INTEREST

The authors have declared that no competing interests exist.

AUTHOR CONTRIBUTIONS

SHH involved in conceptualisation. MK and SWK involved in data curation. SHH involved in formal analysis. DHK and SWK involved in funding acquisition. DHK and SWK involved in investigation. SHH involved in methodology. MK and SWK involved in validation. DHK involved in writing—original draft. SHK, MK, SWK and SHH and writing—review and editing.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

[Correction added on April 13, 2022, after first online publication: Peer review history is not available for this article, so the peer review history statement has been removed.]

DATA AVAILABILITY STATEMENT

This meta-analysis extracted data from previously published articles.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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