Systematic Review: Effectiveness of Corticosteroid Treatment in Anosmia Patients Post COVID-19

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Abstract

This systematic review aims to determine the effectiveness of corticosteroids in treating anosmia in COVID 19 patients. This study used a systematic review approach in gathering data, from scouring through web-based journals into sifting through unrelated studies. The sifting process are levelled with varying degrees of specificity, from the PICO (Population, Intervention, Comparison, Outcome) which were Post COVID-19 patients with anosmia, corticosteroid therapy, placebo treatment, and an outcome in clinical recovery. The papers that fit the PICO criteria then were sifter through inclusion and exclusion criterias such as : it has to be a Randomised Clinical Trial (RCT), there are uses of corticosteroid, and the subjects were post covid patients. There were first searched with keywords of anosmia, COVID-19, corticosteroid through Pubmed (n=5) Google Scholar (n=200), SCOPUS (n=175), EBSCO (n=121), ScienceDirect (n=186). After gathering those papers, it was then judged based on their abstract for inclusion criterias and exclusion criterias. The final studies that were in this systematic review consists of three studies. The end results showed that there were no effectivity of corticosteroids in treating anosmia in post covid patients.

Keywords: COVID-19, Anosmia, Corticosteroid

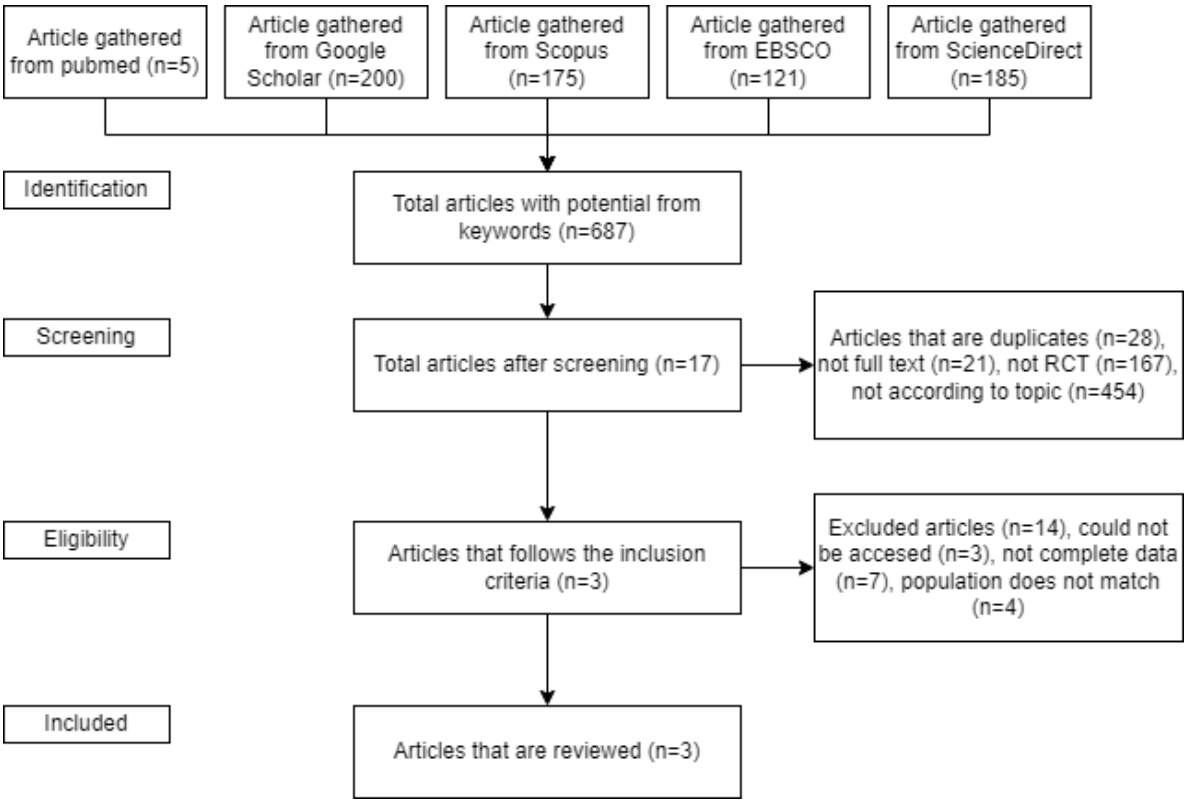
1. Introduction

Coronavirus Disease 2019 (COVID-19) that is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is still a large health issue across the whole world and has been classified as a global pandemic. The WHO has covered that there were, per 16 November 2021, more than 253 million cases of COVID-19 that had been confirmed globally with a death toll of as big as 5 million lives. Infected patients of COVID-19 especially those with symptoms of lower respiratory syndrome such as fever, cough, dyspnoea, and shortness of breath [1]. COVID-19 also causes a difference in sense of smell and taste, whether their in the acute or chronic stage of the illness. Problems in sense of smell could be drawn as Anosmia (no sense of smell), hyposmia (lowered sense of smell), parosmia (difference in sense of smell), and phantosmia (sense of smell while not having a source) [2]. These sensory changes has impact in day to day lives, such as cooking, hygiene, and social relationships [3].

2. Methods and Materials

This study uses a systematic review approach in which using other researches with a design of Randomised Clinical Trial. The systematic reviews used are from Africa, Asia, and Europe with an online study basis that ends in November 2021. This study uses a PICO (Population, Intervention, Comparison, Outcome) method and the population characteristics that were used were anosmia patients post COVID-19, with intervention of corticosteroid therapy and comparison between using the therapy and placebo, end results being the clinical recovery. The online databases that were used and the number of papers that were found consist of Pubmed (n = 5), Google Scholar (n = 200), Scopus (n = 175), Science Direct (n = 186) and EBSCO (n = 121). With criterias for inclusion and exclusion being the languages having to be in Indonesian or English, outcome has to be the effectivity of corticosteroids in Anosmia patients post COVID-19, study design has to be RCT, and study duration has to be in 2021. The technique used were using electronic database with keywords such as ("Anosmia: OR "Olfactory disorder" OR "Smell") AND ("Corticosteroid" OR "Steroid")) AND ("Covid" OR "Covid-19"). With these results being processed with the inclusion and exclusion criteria from the abstract.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)



3. Results

From the search conducted, there were 687 literatures available. During the process there were 28 duplicates, thus leaving with 659 literatures. After the first screening, there were 21 literatures that were not full text, 167 literatures without the RCT method. And 454 not consisting of the compatible research topic, leaving with 17 literatures. During the final screening process, there were 3 inaccessible literatures, 7 without complete data, and 4 with population not fitting with what were searched for, leaving with 3 final literatures.

Table 1. Quality of Literature

Author	Selection Bias	Study Design	Cofounders	Binding	Data Collection Method	Withdrawals and Dropouts	Rating
Abdelalim et al	1	1	1	2	1	3	Strong
Kasiri et al	1	1	1	2	1	1	Strong
Vaira et al	1	1	1	2	1	1	Strong

Table 2. Characteristics of the Systematic Review

No	Title	Authors & Year	Study Design	Location and time	Database	DOI	Result		Conclusion
							Outcome	Value	
1	Corticosteroid nasal spray for recovery of smell sensation in COVID-19 patients: A randomized controlled trial	Abdelalim et al., 2021	RCT	Egypt	Science Direct	10.1016/j.amjoto.2020.102884	By comparing smell scores between both groups after 1 week, 2 weeks, and 3 weeks of treatment, there were no statistically significant differences between both groups. In group I, (62%) of patients completely	P = 0.31	The results suggested that using mometasone furoate nasal spray as a topical corticosteroid in the treatment of post COVID-19 anosmia offers no superiority benefits over the olfactory training, regarding smell scores, duration of anosmia, and recovery rates.

							recovered their sense of smell after 3 weeks of treatment, compared to (52%) of patients in group II.		
2	Mometasone furoate nasal spray in the treatment of patients with COVID-19 olfactory dysfunction: A randomized, double blind clinical trial	Kasiri et al., 2021	RCT	Iran	Science Direct	10.1016/j.intimp.2021.107871	The olfactory scores (VAS) at one week, two weeks, three weeks, and four weeks of the treatment were compared, showing a significant difference between the groups.	P: 0.318, <0.001, <0.001, <0.001, respectively	The findings of our study, especially SIT results, showed that the combination of mometasone furoate nasal spray and olfactory training for COVID-19–induced olfactory dysfunction could increase the recovery rate more than olfactory training alone. Moreover, the therapeutic regimen was tolerable without any alarming signal.
							There was no significant difference between the groups according to the olfactory scores on Iran-SIT tests and the observed changes at the study endpoint .	P = 0.239, 0.91	

							However, there was a significant between-group difference concerning the severity of loss of smell. After four weeks, 19 patients in the intervention group regained their normal sense of smell, while the number amounted to 8 in the control group	P < 0.00.1	
3	Efficacy of corticosteroid therapy in the treatment of long-lasting olfactory disorders in COVID-19 patients	Vaira et al., 2021	RCT	Italy	Rhinology	10.4193/Rhin20.515	Patients in the treatment group reported significantly higher improvements of the olfactory scores than the controls at both the 20-day and 40-day evaluations	[40 (IQR 45) versus 10 (IQR 15); p = 0.011] [60 (IQR 40) versus 30 (IQR 25); p = 0.024]	Based on the results of this study, the mix of drugs including steroids could represent a useful specific therapy to reduce the prevalence of this long-term morbidity.

Table 3. Effectiveness in corticosteroids within Two Variables f intervention and Control

Research	Abdelalim et al			Kasiri et al			Vaira et al		
Score	Smell Score			VAS Score			CRCC SCore		
Population	Intervention n = 50	Control n = 50	P value	Intervention n = 39	Control n = 38	P value	Intervention n = 9	Control n = 9	P value
Week 1	5.0	2.0	0,10	2.1	2.4	0,444	-	-	-
Week 2	7.0	5.0	0,08	4	4.4	0,402	51.1	24.4	**0,013**
Week 3	10.0	10.0	0,16	4.8	5.3	0,267	-	-	-
Week 4	-	-	-	5.2	5.7	0,329	-	-	-
Week 5	-	-	-	-	-	-	75.5	48.8	**0,009**

Table 4. Evaluation in Anosmia Conditions in Two Variables of Intervention and Control

Research	Abdelalim et al			Kasiri et al			Vaira et al		
Population	Intervention n = 50	Control n = 50	P value	Intervention n = 39	Control n = 38	P value	Intervention n = 9	Control n = 9	P value
Before Intervention	50	50	0,081	39	38	0,841	9	9	0,586
Week 2	-	-	-	-	-	-	4/9	8/9	**0,011**
Week 3	19/50	24/50	0,31	-	-	-	-	-	-
Week 4	-	-	-	20/39	30/38	**<0,001**	-	-	-
Week 5	-	-	-	-	-	-	0/9	3/9	**0,024**

4. Discussion

Anosmia is defined as the absence of the sense of smell and can be caused by a number of causes. These causes can be divided into conductive and central defectiveness, or sensorineural [4], [5]. Anosmia hinders the ability of a person to smell by blockade or destruction of nerve pathways for smelling from olfactory bulb to piriform cortex, entorhinal, amygdala, and hippocampus in the brain [6]. The presence of Anosmia symptoms in COVID-19 patients signifies mild to medium COVID-19 severity level. Anosmia can plague the victims this way by the infection of nose epithelial tissue by SARS COV-2 virus, inducting type 1 cell inflammation, inducing cell degeneration and apoptosis as a protective mechanism of central nervous system [7]. The increasing number of COVID-19 cases affects the prevalence of people with Anosmia, as a main symptom of COVID-19 or post COVID-19 complication. This condition can affect the psychology and life quality of the victims. Post COVID-19 therapy has not shown definitive results on curing Anosmia, but patients can be given oral corticosteroids by topical or olfactory training [3], [8]. Administration of corticosteroids can result in good prognosis, because of the presence of enzyme receptor converted from angiotensin type 2 that is targeted by SARS CoV-2 [9].

In this research, we have found that nasal corticosteroids administered by nasal spray does not have a significant impact in curing anosmia post COVID-19. Effects of corticosteroid towards post COVID-19 Anosmia condition is insignificant with p-value monitoring of the first, second-, and third-week showing $p>0.05$, while one of three studies noted p value of 0.009 on week five. Anosmia condition evaluation one the three studies show a significant difference in number of cured patients on week four and week five (two out of three studies) with a p-value of 0.001 and 0.024 between treated group and control group, while from week one to week three the number of patients returning to normal olfactory functions are higher on the treated group

compared to the control group, however they are statistically insignificant. Further evaluation is needed on the two groups for viewing the therapy results.

Research done by Abdelalim et al., 2021 with the title "Corticosteroid Nasal Spray for Recovery of Smell Sensation in COVID-19 Patients: A Randomized Control Trial" uses the randomized controlled trial prospective model on 100 participants aged 18 and over in Egypt from August to November 2020 with participants required to show proof for being tested positive with COVID-19 by real time reverse transcription-polymerase chain reaction (rRT-PCR) nasopharynx swab, and has recovered in two examinations with anosmia or hyposmia complaint without ageusia or the loss of sense of taste. Exclusion criteria in this research is if the patient already received intranasal and oral corticosteroids treatment, chronic disorder on the nasal area, patient with anosmia history and has recovered on the previous check-up or unable to report the development of the illness. Participants are randomly distributed into two groups with an equal number of people in each group. All member of group one (50 people) which is the treated group are given topical corticosteroid nasal spray (mometasone furoate) with dosage of two puffs (100 ug) every day on both of the nostrils for three weeks, with olfactory training by smelling rose flowers, lemons, and cloves for twenty seconds every day. All members of group two are not given topical corticosteroid therapy, but are still given olfactory training. Research results are measured using the smell score, periodically. The results show that there are no significant statistical differences between the control group and the treated group on the first, second and third week with p values of 0.10, 0.08, and 0.16 respectively. The number of patients experiencing anosmia in the treated group decreased more than the control group, with 24 out of 50 people in the treated group and 19 out of 50 people in the control group, with a p-value of 0.31. It is concluded that from the study, there are no significant effects on using mometasone furoate spray as anosmia remedy post COVID-19 infection. These researches indicate that there are no significant changes of post COVID-19 anosmia patients' condition by administering corticosteroid. The research also shows relation between gender, how long the patient was infected with COVID-19, and age with how long anosmia or hyposmia will affect the corresponding patients. Ultimately, anosmia or hyposmia that affects patients is dependent on how the COVID-19 was affecting the patient, and quite different from the presumption on prognosis only dependent on fever as the deciding factor for olfactory related diseases for COVID-19 patients [3].

Kasiri et al., research in 2021 with the title "Mometasone Furoate Nasal Spray in the Treatment of Patients with COVID-19 Olfactory Dysfunction" while using the method "a prospective double-blind randomized clinical trial" for 90 adult patients aged 18 and over that was diagnosed with COVID-19 based on clinical finding and RT-PCR or lungs CT scan, and the aforementioned patient has a dysfunction in the olfactory system for two weeks because of COVID-19, but not hospitalized, including individuals with severe anosmia or microsemia (according to UPSIT). Participants in this research are randomly assigned to two groups based on block permutations. In the treated group, 40 patients received two topical corticosteroid nasal spray (nasal spray 0.05% mometasone furoate) with a dose of 100 Aˆµg twice daily in both nostrils for four weeks with smell training. The other 40 patients act as a control group, receiving two topical saline spray puffs in every nostril twice a day together with smell training. During five months of research, two participants from the control group and one participant from the treated group are omitted, so there are only 38 and 39 participants respectively [10].The increase in normosmia number is higher on the endpoint from the treated group, recorded at 19/39, while patients in the control group recorded 8/38 with p-value of 0.001. However, from evaluation and analysis, we can get p-value VAS score changes from baseline of both groups on the first, second, third, and fourth weeks with p-values of 0.444, 0.402, 0.267, 0.329 respectively. From the study it can be concluded that there are no significant effects of using mometasone furoate spray as treatment post COVID-19. Mometasone furoate spray can be useful in speeding up recovery time for the olfactory that was hindered by COVID-19 infection without significant side effects. Even though both groups show improvement according to VAS. Newest histopathology study that was aimed for understanding olfactory dysfunction pathogenesis has reported neuropathy inflammation with high leukocyte infiltration in lamina propria, olfactory atrophy focal mucosa and digestive system in neural fibers in acute phase infections and chronic inflammation, and extensive

olfactory epithelial dysfunction on patients with long term anosmia. Evidence supporting steroid role as therapeutic in preventing and treating long term olfactory problem on COVID-19 patients [11].

Vaira research in 2021 with the title "Efficacy of Corticosteroid Therapy in the Treatment of Long-Lasting Olfactory Disorders in COVID-19 Patients" using randomized controlled trial on 18 patients with severe anosmia or hyposmia complaints 30 days after COVID-19 clinical onset in Italy. All participants in this research are COVID-19 patients with mild to medium symptoms that do not require hospitalization, not one patient receives corticosteroid therapy during the infection. Patients are randomized and split into two groups of 9 patients. Both groups do not show any significant difference on gender (p=0.629), age (p=0.894) and a score of basic smell capabilities (p=0.586) from patients. The criteria of inclusion in this research is adult patients aged 18 and above, have been infected with SARS-CoV-2 that is confirmed by nasopharynx swab, recovered from the confirmed infection and clarified by two negative nasopharynx swab, Connecticut Chemosensory Clinical Research Center (CCCRC) test score of ≤ 40 (e.g. severe anosmia or hyposmia) 30 days after clinical onset. Excluded patients are those with olfactory dysfunction before COVID-19 infection, trauma, surgery or radiotherapy in mouth and nose cavities, rhinitis, allergies, or rhinosinusitis, psychiatric or neurological disorders, and contraindication towards corticosteroid therapy. Participants are split into a treated group who are given corticosteroid treatment and a control group which are given nothing. All patients from the treated group are given systemic cortisone therapy with prednisone, starting from 1mg/kg/day and then the dose is lowered for 15 days and the nose is irrigated with betamethasone, ambroxol, mucolytic and decongestant for 15 days. Olfactory function from all the patients in both groups are evaluated with CCCRC test on the 20th day and 40th day after the first check-up. In the control group, the average olfactory score on the first check-up is 20 (IQR 30), consisting of four anosmia patients and five severe hyposmia patients. After evaluation on the 20th day, CCRC results do not show any significant improvement on olfactory function (p = 0.053). On the 40th day, olfactory function improvement becomes more significant if compared to the starting score [60 (IQR 60) versus 20 (IQR 30); p = 0.009]. At the end of the observation period, there are no patients with normal olfactory function: mild and medium hyposmia on three patients, residual anosmia on one patient, and severe hyposmia on two patients. In the treated group, average olfactory score is 10 (IQR 15) consists of six anosmia patients and three severe hyposmia patients on the first check-up. On the 20th day evaluation, there are significant improvement on the olfactory score if compared to the starting score [70 (IQR 40) versus 10 (IQR 15); p = 0.013). Olfactory function improves more on the 40th day [average score of 90 (IQR 50); p = 0.009). At the end of the observation period, there are five patients that has completely recovered on the olfactory function, there are no patients with severe hyposmia or anosmia, and there are no patients with side effects tied to the therapy [12]. From Vaira et al (2021) it is shown that patients in treated group have a significant olfactory function recovery compared to the control group on the 20th day [40 (IQR 45) versus 10 (IQR 15); p = 0.011] and the 40th day [60 (IQR 40) versus 30 (IQR 25); p = 0.024]. Thus, it can be concluded that regimental therapy that involves corticosteroid is useful for reducing prevalence of long-term olfactory disorder post COVID-19 infection. On the patients with olfactory dysfunction that is persistent for over three months, there will be extensive de-epithelization with mild chronic inflammation on the olfactory epithelial [12] This damage can be caused and maintained by inflammation phenomena especially those seen at the early stage of infection [13]. Corticosteroid can reduce local inflammation that allows olfactory epithelial to regenerate, while continued local inflammation can reduce olfactory epithelial regenerative capacity that causes the disappearance of stem cells and other progenitor cells. However, optimal corticosteroid treatment duration on olfactory disorder post COVID-19 infection still needs to be evaluated further [12].

5. Conclusion

Based on the systematic review conducted in this research, there was not any significant effectiveness between the use of corticosteroids and recovery from anosmia in post COVID-19 patients.

6. Recommendations

The researcher realizes that writing a report on the results of this research still has many shortcomings and limitations. More research with longer monitoring is still needed regarding the effectiveness of corticosteroids in post-Covid-19 anosmia conditions.

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