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Comparative Study between Use of Intranasal Steroids with Olfactory Training in Comparison to Olfactory Training Only in Treatment of Post-COVID Smell Dysfunction (Anosmia)

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ABSTRACT

Background: The smell sense is primarily connected to taste perception, avoidance behavior, and the reaction to warning signals from dangerous compounds. A viral upper airway infection may result in anosmia that is persistent. Nearly 20% of instances of anosmia are caused by viral infections. **Aim and objectives:** to assess the effectiveness of olfactory training alone vs topical corticosteroid nasal spray (mometasone furoate nasal spray) with olfactory training in treating anosmia in individuals who have recovered from COVID_19 infection.

Subjects and methods: This study was conducted in El-Minia Health Insurance Hospital, which was an isolation hospital for COVID-19 only, in the period between 1/1/2022 to 31/12/2022 and included 50 patients, aged 18 to 70, including 28 males and 22 females, they were divided into 2 groups each of them contained 25 patients: group (A) 25 patients received olfactory training and intranasal steroids and group (B) 25 patients were solely given olfactory training.

Results: There was no statistical substantial variation between the groups as regard patient characteristics, infection characteristics and terms of smell scores pre-treatment, at 1 week (wk), 2 wks, and 3 wks follow-up (Independent sample t test, P > .05). **Conclusion:** Mometasone furoate nasal spray had no advantages over olfactory training as a topical corticosteroid therapy for the management of post-COVID-19 anosmia. There was no superiority in this topical corticosteroid nasal spray. According to our findings, olfactory training may be recommended for anosmia in individuals who have recovered from COVID-19 infection since there is currently no strong data supporting the usage of topical corticosteroids in the management of post-COVID-19 olfactory dysfunction.

Keywords: Intranasal steroids, Olfactory training, post-COVID smell dysfunction (anosmia).

INTRODUCTION

A global pandemic called the coronavirus illness (COVID-19), which is brought on by the coronavirus 2 (SARS-CoV-2) virus, was first noted in China in December 2019. As of 25 September 2021, the World Health Organization (WHO) received reports of more than 219 million cases from 188 nations and territories, resulting in more than 4.55 million fatalities [1]. Patients with COVID-19 infection often appear with symptoms of the lower respiratory tract, including fever, cough, dyspnea, and tightness in the chest. However, some patients may also have symptoms of the upper respiratory tract, including sore throat, rhinorrhea, nasal congestion, and olfactory impairment [2]. The specific etiology of this condition is yet unknown since nasoendoscopy and a comprehensive objective smell evaluation are not available (and are thus contraindicated in the present scenario). Two options seem to be more likely: Olfactory cleft syndrome, in which the olfactory cleft is mucosal blocked and there is a "conductive" loss, or post-viral anosmia syndrome, in which the olfactory mucosa is directly infected and the olfactory sensory neurons are destroyed and there is a "neural" loss [3,4].

While there are currently no established evidence-based standards for the treatment of abrupt anosmia in a viral infection, broad principles may be inferred from them. Although empirical oral steroids may be used to treat idiopathic anosmia and reduce swelling and inflammation, doing so is not advised since steroids have a suppressive impact on the immune system [5]. In virtually every case of scent loss, it has been shown that smell training helps with smell recovery. It is easy, safe, employs readily accessible household items, and can be completed at home [6].

This research compared the effects of topical corticosteroids nasal spray (mometasone furoate nasal spray) with olfactory training in comparison to olfactory training alone in treating anosmia in individuals who had recovered from COVID-19 infection.

PATIENTS AND METHODS

This study was conducted in El-Minia Health Insurance Hospital, which was an isolation hospital for COVID-19 only, in the period between 1/1/2022 to 31/12/2022 and included 50 patients who were admitted to the hospital or isolated at home (as their general condition allowed that) and they were COVID-19 positive confirmed by PCR and then they recovered from COVID-19 by 2 consecutive negative PCR samples but still suffering from recent anosmia or hyposmia.

There were 50 patients, aged 18 to 70, including 28 males and 22 females, they were divided into 2 groups each of them contained 25 patients: group (A) 25 patients received olfactory training and intranasal steroids and group (B) 25 patients were solely given olfactory training. Both groups were followed up at baseline just after discharge/recovery, after 1, 2 and 3 weeks for assessment of their degree of anosmia.

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Inclusion criteria: PCR verified COVID-19 positive patients and recovered from COVID-19 by 2 consecutive negative PCR samples but still suffering from recent anosmia or hyposmia and adult patients ranging from 18 to 70 years old, both sexes were included in this study.

Exclusion criteria: Suspected COVID-19 infection but not confirmed by PCR, Confirmed COVID-19 infection by PCR but with intact smell sensation, Patients under 18 years, Patients over 70 years, Any other cause of anosmia as ((Congenital: choanal atresia, Traumatic: trauma to cribriform plate and surgical trauma (adhesions), Inflammatory: sinusitis, Neoplastic: tumors of nose and paranasal sinuses either benign as (inverted papilloma – angiofibroma) or malignant as (olfactory neuroblastoma – carcinoma) and Others: atrophic rhinitis, deviated nasal septum, concha bullosa, hypertrophy of inferior turbinates, allergic rhinitis, allergic nasal polypi, all causes of nasal obstruction), History of anosmia before infection with COVID-19, History of any previous nasal operations, History of head and neck irradiations and Brain tumors or surgery.

Methods

Every patient was submitted to the following: Full detailed history, Examination (General examination and ENT examination: Nasal examination and Ear examination) (Figures 1-4).

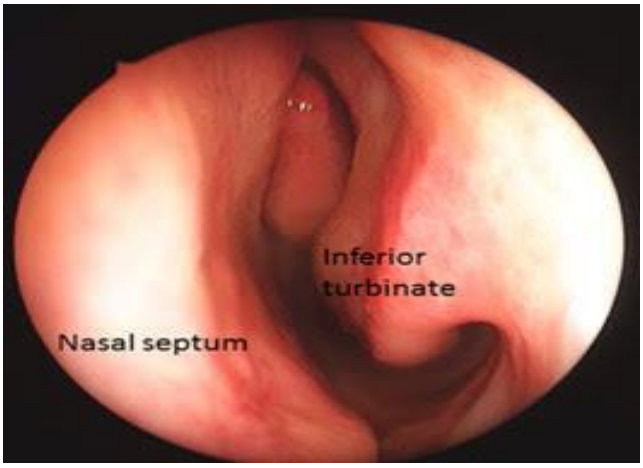

Figure (1): Sinuscopic view of normal inferior turbinate in left nasal cavity.

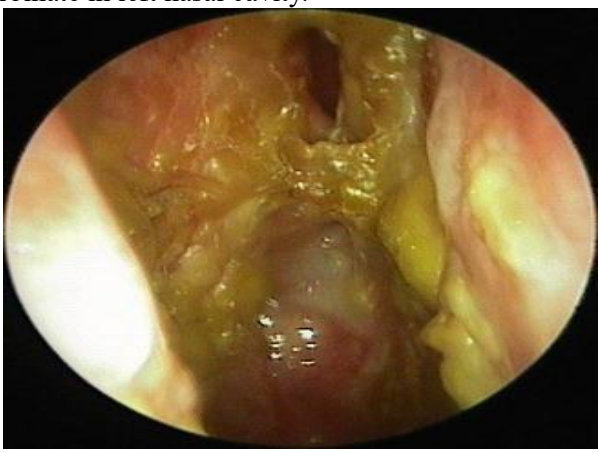

Figure (2): Sinuscopic view of nasal crustations (atrophic rhinitis)

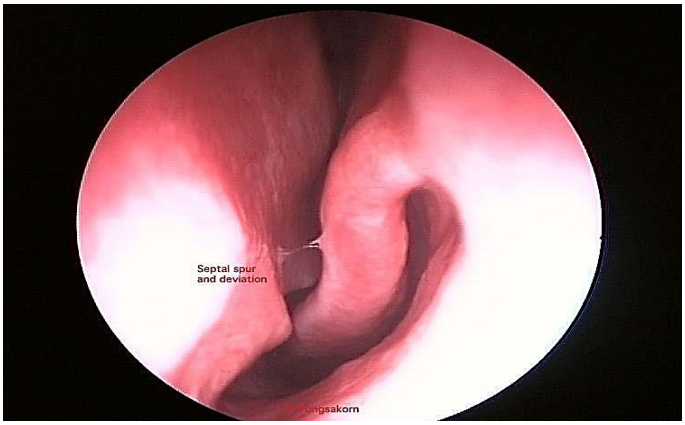

Figure (3): Sinuscopic view of deviated nasal septum.

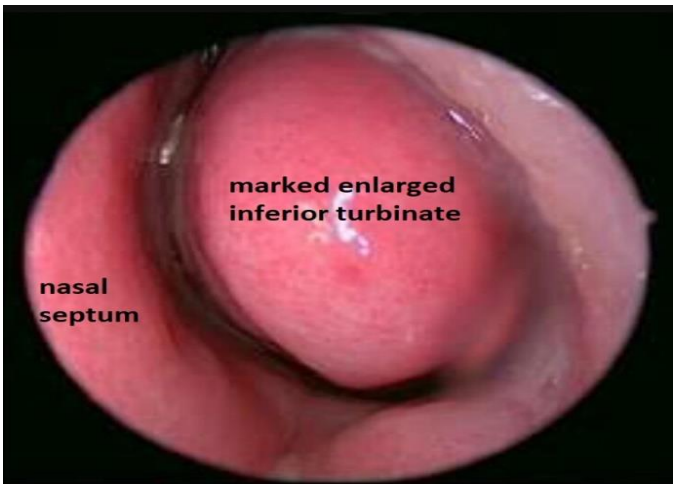

Figure (4): Sinuscopic view of grade III (marked enlarged) inferior turbinate with signs of allergic rhinitis.

Lines of treatment: Nasal steroid course: in group (A) 25 patients got topical corticosteroid nasal spray (mometasone furoate nasal spray) twice daily for three weeks in each nostril at the recommended dose of 2 puffs (100 micrograms), along with olfactory training that included sniffing specific family odors like coffee, mint, vanilla, and cinnamon for 20 seconds each.

Investigations: Complete blood count, C-reactive protein, ESR, serum ferritin, COVID-19 PCR, D-Dimer test, BT, CT, PT, PC, INR, chest X-ray, chest CT, abdominal ultrasound and CT nose and paranasal sinuses to exclude trauma and tumors, to see anatomy and any pathology (Figures 5 and 6).

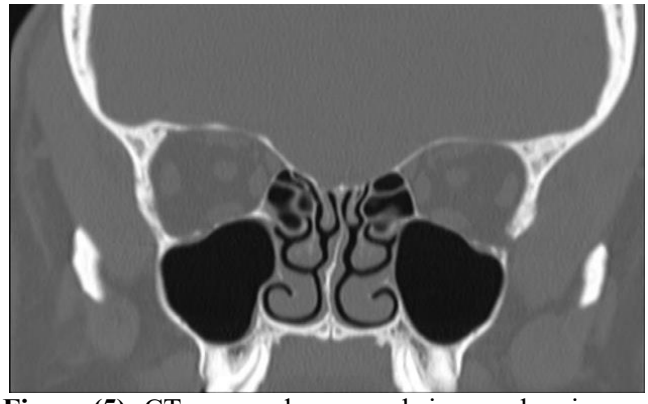

Figure (5): CT nose and paranasal sinuses showing normal anatomy.

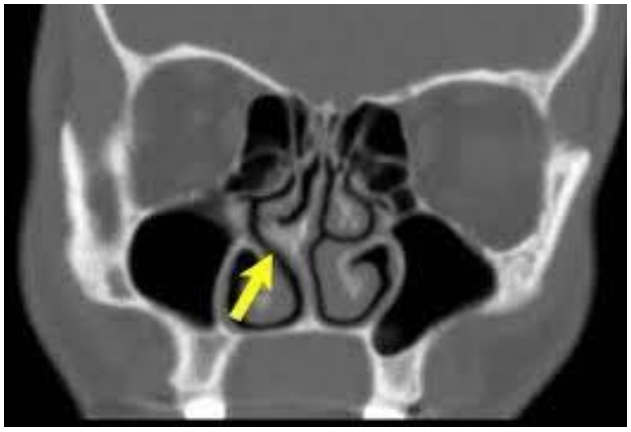

Figure (6): CT nose and paranasal sinuses showing deviated nasal septum.

Ethical approval:

An approval of Al-Azhar Assuit Faculty of Medicine Ethical Committee [Approval No.: MSc/AZ.AST./ENT030/9/220/6/2023] and approval of El-Minia Health Insurance Hospital were obtained before the start of this study. Before collecting data, each participant in the research was given a brief explanation of its purpose.

Verbal and written agreement was sought from those who agreed to participate in the research, and data privacy was guaranteed. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

Utilizing SPSS 20.0 (SPSS Inc., Chicago, IL, USA), the data were examined. Clinical and demographic information was presented as mean ±standard deviation or frequency and percentage (%). To compare the two research groups, the unpaired t test and Pearson's correlation coefficient were utilized. For post hoc analysis, Bonferroni correction was utilized. P = 0.05 was utilized as the alpha threshold.

RESULTS

Table 1 compares the baseline demographic data of enrolled patients, including age, gender, place of isolation, and associated comorbidities. Regarding patient characteristics, no statistically substantial variation between groups was found **[Table 1]**.

Table (1): Patient Characteristics (n = 50)

	Group A (n = 25)	Group B (n = 25)	P value
Age (years)*	38.8 ± 12.3	41.2 ± 12.3	0.454[a]
Less than 30**	6 (24)	6 (24)	0.762[b]
30 – 50**	15 (60)	13 (52)	
More than 50**	4 (16)	6 (24)	
Gender**			0.569[b]
Females	10 (40)	12 (48)	
Males	15 (60)	13 (52)	
Isolation Place**			0.564[b]
Home	14 (56)	16 (64)	
Hospital	11 (44)	9 (36)	
Diabetes Miletus**	7 (28)	6 (24)	0.747[b]
Hypertension**	6 (24)	5 (20)	0.733[b]

* Data are shown as mean ± standard deviation

** Data are shown as frequency (percentage)

[a] Independent sample t test; [b] Chi-square test.

Table 2 compares the baseline infection data of enrolled patients, including duration of COVID infection, severity of COVID infection, and duration of anosmia/hyposmia before recovery of infection. No statistically substantial variation was detected between groups regarding infection characteristics **[Table 2]**.

Table (2): Infection Characteristics (n = 50)

	Group A (n = 25)	Group B (n = 25)	P value
COVID Duration (days)*	15.8 ± 2.9	14.2 ± 3.3	0.061[a]
COVID Severity**			0.792[b]
Mild	14 (56)	16 (64)	
Moderate	7 (28)	5 (20)	
Severe	4 (16)	4 (16)	
Anosmia/Hyposmia Duration Before Recovery (days)*	10.3 ± 2.5	9.2 ± 2.7	0.152[b]

* Data are shown as mean ± standard deviation

** Data are shown as frequency (percentage)

[a] Independent sample t test; [b] Chi-square test.

As demonstrated in table 3, both groups showed a statistically substantial increase in smell scores at different follow-up intervals. By running a post-hoc test for pairwise comparisons within each group, a statistically substantial variation was found between pre-treatment, at 1 wk, 2 wks, and 3 wks smell scores.

Table (3): Comparing Smell Scores Within Groups (n = 50)

	Pre-Treatment	1 wk.	2 wk.	3 wk.
Group A	3.1 ± 1.3	4.7 ± 1.3	6.9 ± 1.2	9.0 ± 1.2
P value		<0.001[a]	<0.001[b]	<0.001[c]
P value			<0.001[d]	<0.001[e]
P value				<0.001[f]
Group B	2.7 ± 1.4	5.1 ± 1.5	7.1 1± .5	9.3 ± 1.1
P value		<0.001[a]	<0.001[b]	<0.001[c]
P value			<0.001[d]	<0.001[e]
P value				0.001[f]

[a] Pre vs 1 wk; [b] pre vs 2 wk; [c] pre vs 3wk; [d] 1 wk vs 2 wk; [e] 1 wk vs 3 wk; [f] 2 wk vs 3wk.
Repeated measure ANOVA and Bonferroni post-hoc tests were used.

As demonstrated in table 4, no substantial variation was found between groups in terms of smell scores pre-treatment, at 1 wk, 2 wks, and 3 wks follow-up.

Table (4): Comparing Smell Scores between Groups (n = 50)

	Group A (n = 25)			Group B (n = 25)			P-value
	Mean	SD	Range	Mean	SD	Range	
Pre-Treatment	3.1	1.3	1 – 5	2.7	1.4	1 – 5	0.360
1-wk Follow-up	4.7	1.3	3 – 7	5.1	1.5	3 – 7	0.432
2-wk Follow-up	6.9	1.2	5 – 9	7.1	1.5	5 – 9	0.483
3-wk Follow-up	9.0	1.2	7 – 10	9.3	1.1	7 – 10	0.404

Independent sample t test was used.

As shown in table 5, gender and COVID severity did not demonstrate a substantial connection to duration of anosmia, whereas age, DM, and duration of COVID demonstrated a substantial positive connection to the duration of anosmia. Diabetes substantially affected the duration of anosmia/hyposmia till complete recovery, the mean time for recovery of the sense of smell was 33.7 days ± 3.5 in diabetic patients compared to 26.9 days ± 0.9 in non-diabetic ones (Independent sample t test, P <0.001).

Table (5): Correlation Analysis (n = 50)

	Correlation Coefficient	P value
Age	0.365	0.009*
Gender	-0.196	0.172**
DM	0.741	<0.001**
Duration of COVID	0.883	<0.001*
Severity of COVID	-0.056	0.698**

* Pearson correlation; ** Spearman correlation.

DISCUSSION

Wuhan, China, was the first place where the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was discovered. The WHO proclaimed SARS-CoV-2 a pandemic in January 2020 after it had infected more than 334 million individuals globally and killed more than 5,596,000 people [7].

The main results of this study were as following:

As regard the baseline demographic data of enrolled patients, including age, gender, place of isolation, and associated comorbidities, patient characteristics across the groups did not vary statistically significantly. We included 50 patients who were treated from COVID-19 infection but still had olfactory impairment in our research. To the extent that we are aware, there is only one previous comparative study **Abdelalim *et al.*** [8] to assess the effectiveness of olfactory training against topical corticosteroids nasal spray in treating anosmia in individuals who were treated from COVID-19 infections.

Our findings were consistent with research of **Abdelalim *et al.*** [8], which revealed that 50 patients in group I got topical corticosteroid nasal spray (mometasone furoate nasal spray) along with olfactory training as part of this research's randomization process. 50 more patients who were placed in group II simply got olfactory training. 100 adult patients were included in the analysis, of whom 46 (46%) were males and 54 (54%) were females. The median age of the patients, who varied in age from 18 to 61, was 29.0 years (IQR 21.75-38.0). While 69 patients (or 69%) were kept in isolation at home, 31 patients (or 31%) were handled in hospitals. In the research, there were 16 diabetes individuals (16%) and 14 hypertension patients (14%). Age and sex, isolated location, and related comorbidities were matched between the two groups without statistically significant variations.

The present study showed no statistically substantial variations between groups as regard infection characteristics {Regarding duration of COVID infection, the mean duration was 15.8 days ± 2.9 in group A, and 14.2 days ± 3.3 in group B. Regarding duration of anosmia/hyposmia before recovery, the mean duration was 10.3 days ± 2.5 in group A, and 9.2 days ± 2.7 in group B. Regarding severity of COVID infection, group A included 14 mild cases (45%), 7

moderate cases (28%), and 4 severe cases (16%). Group B included 16 mild cases (64%), 5 moderate cases (20%), and 4 severs cases (16%)} ($P > 0.05$).

In accordance with our findings, study of **Abdelalim *et al.*** [8] revealed that according to COVID-19 illness severity, there was no statistically substantial variations between the two groups; 70 patients (70%) had mild sickness, 24 patients (24%) had moderate illness, and 6 patients (6%) had severe disease. Regarding the length of the COVID-19 sickness and the time spent in anosmia or hyposmia prior to recovery or discharge, there were no statistically substantial variations between groups I and II ($P > 0.05$).

It is still unclear if corticosteroids should be used for COVID-19 olfactory malfunction. As for the course of therapy, specialists and early reports point to recovery of anosmia, but there is still a dearth of information. It's still debatable whether post-COVID-19 anosmia patients should get topical nasal corticosteroids [9].

This study showed that both groups showed a statistically significant improvement in smell scores at different follow-up intervals. By running a post-hoc test for pairwise comparisons within each group, a statistically substantial variation was found between pre-treatment, 1 wk, 2 wks, and 3 wks smell scores inside each group. No substantial variation was found between groups in terms of smell scores pre-treatment, at 1 wk, 2 wks, and 3 wks follow-up when comparing the two groups to each other. 15 patients in group A reported complete restoration of olfactory function. 16 individuals in group B reported complete restoration of olfactory function. No statistically substantial variation was found between groups in terms of recovery. In group A, the mean duration of anosmia/hyposmia till recovery was 29.1 days ± 3.9 ranging from 20 to 35 days. In group B, the mean duration was 28.2 days ± 4.6, ranging from 20 to 34 days. No statistically substantial variation was found between groups regarding the mean duration of olfactory dysfunction.

Our results were supported by study of **Abdelalim *et al.*** [8], which revealed that there was no statistical substantial variation between the two groups in terms of scent ratings at recovery/discharge at the first evaluation; the median score was 2 in both groups ($P = 0.47$). There were no statistically substantial variations between the two groups when the scent scores of the two groups were compared after 1 week, 2 weeks, and 3 weeks of therapy; the corresponding P-values were (0.10, 0.08, and 0.16). The average time (Mean ±SD) for full recovery of smell in group I was 26.41 days± 7.99, and it was 26.15 days ±5.07 in group II ($P = 0.88$), indicating no statistically substantial variations between the two groups in this respect. By the conclusion of the third week, 31 out of 50 patients (62%) in group I and 26 out of 50 patients (52%) in group II had fully regained their sense of smell, respectively ($P = 0.31$). Total mean time for full recovery of scent was 26.29 days ± 6.76 days, and at the end of the third week, recovery rate was 57%. Over the course of the trial, considerable gains were made. By the conclusion of the third week, the median smell score in group I had increased from 2.0 to 10.0 ($P< 0.001$). The mean smell score in group II started out at 2.0 and increased to 10.0 at the conclusion of the third week ($P< 0.001$), this was comparable with the research's results.

In the study of **Scangas and Bleier** [10], treatment with topical steroids has been shown to hasten the recovery of individuals with post-infectious olfactory impairment. Also, **Heilmann *et al.*** [11] used mometasone nasal spray locally to treat olfactory impairment brought on by upper respiratory tract infections, and results showed an improvement in olfactory function. However, the viral infection that caused the anosmia in those two earlier investigations wasn't the novel coronavirus, about whose pathophysiology we know very little.

Our results showed that connection analysis was carried out to determine the association between duration of anosmia/hyposmia as dependent variable, and old age, gender, DM, and duration of COVID as independent variables. Gender and COVID severity did not demonstrate a significant correlation to duration of anosmia, whereas old age, DM, and duration of COVID demonstrated a considerable positive connection to the duration of anosmia.

Our results were in line with study of **Abdelalim *et al.*** [8] as they revealed that age, diabetes and the duration of COVID-19 illness can affect the duration of anosmia/hyposmia as there was a statistically significant positive correlation between age and the duration of anosmia/hyposmia ($P = 0.004$), the average time for recovery of the sense of smell was 35.0 days ± 2.31 in diabetic patients compared to 25.64 days ± 6.53 in non-diabetic ones ($P = 0.006$). There was a statistically significant positive correlation between the duration of COVID-19 illness and the duration of anosmia ($P < 0.001$).

Our findings on the prognostic variables diverge from **Lovato *et al.*** [3] revealed that as they evaluated the prognostic markers throughout the course of COVID-19 disease, not after recovery, the lack of fever was the sole indicator of permanent olfactory/taste impairment in COVID-19 patients.

CONCLUSION

Mometasone furoate nasal spray had no advantages over olfactory training as a topical corticosteroid therapy for the treatment of post-COVID-19 anosmia. There was no superiority in this topical corticosteroid nasal spray. According to our findings, olfactory training may be recommended for anosmia in individuals who have recovered from COVID-19 infection since there is currently no strong data supporting the usage of topical corticosteroids in the management of post-COVID-19 olfactory malfunction.

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- **Consent for publication:** Not applicable.
- **Competing interests:** No competing interests.

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