RESEARCH ARTICLE

Effect of corticosteroid and immune-suppressive drugs on oral manifestations in hospitalized COVID-19 patients

Ahmed Mohamed Al Elgendy, Enas Ahmed Elgendy, Marwa Sabry, Mohamed Kamal Salama, Tamer Aboshady

Abstract

Objective: To explore if the oral lesions in coronavirus disease-2019 patients are caused by the drugs used in the treatment or by the virus itself.

Method: The cross-sectional study was conducted from September 2020 to September 2021 at the Kafrelsheikh University Hospital, Egypt, and comprised coronavirus disease-2019 patients of either gender aged 20-60 years having severe pneumonia and breathing difficulties who had no comorbidities. Based on the level of interleukin-6 and procalcitonin, the patients were classified into high group I receiving tocilizumab and methylprednisolone, medium group II receiving methylprednisolone alone, and low group III receiving antiviral drugs. The oral manifestations were recorded at the time of admission before treatment and at 2 weeks after the respective treatment. Data was analysed using SPSS 20.

Results: Of the 90 patients, 30(33.3%) were in group I; 16(%) males and 14(%) females with mean age 44.82±6.10 years. Group II had 27(%) patients; 14(%) males and 13(%) females with mean age 43.74±4.87 years. Group III had 33(%) patients; 9(%) males and 14(%) females with mean age 42.66±2.51 years ($p>0.05$). There was no significant difference among the groups at baseline and after 2 weeks of treatment regarding oral manifestations. Intragroup comparison demonstrated a significant difference in the two values in all the three groups ($p<0.05$).

Conclusion: Oral lesions in coronavirus disease-2019 patients were caused by the virus itself rather than the drugs used in its treatment.

Keywords: Tocilizumab, Dentists, Methylprednisolone, COVID-19. **DOI: 10.47391/JPMA.EGY-S4-38**

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-sense, single-stranded ribonucleic acid (RNA) virus, and 80% of patients have moderate symptoms, 20% may have a serious illness, and 5% may have pneumonia or acute respiratory distress syndrome (ARDS), which would necessitate hospitalisation in an intensive care unit (ICU) and mechanical ventilation.[1]

About 15% of patients require oxygen administration, which is the cornerstone of supportive care. In contrast, severe patients may require invasive mechanical breathing in up to 7% of instances.[2] In coronavirus disease-2019 (COVID-19) patients, interleukin-6 (IL-6) levels are significantly elevated and are associated with suboptimal clinical results. Treatment for COVID-19 patients, who have dysregulated host responses may depend on IL-6 inhibition as a novel target.[3] In fact, several real-world experiences with COVID-19 patients suggest that anti-inflammatory medications might be helpful. Corticosteroids have potent anti-inflammatory effects by reducing the generation of proinflammatory cytokines and chemokines together with lowering the activation of T cells, monocytes and macrophages.[4] In fact, among 201 ARDS patients, short-term steroid therapy was linked to decreased mortality.[5]

Additionally, tocilizumab (TZM) (Actemra®), the first marketed IL-60blocking antibody, has proven to be safe and effective in treating COVID-19 after data on the emergence of an inflammatory cytokine storm in extreme cases. It does this by targeting IL-6 receptors. Because the monoclonal antibody binds to the IL-6 receptor and inhibits the IL-6-mediated inflammatory response, it is acceptable in the treatment of COVID-19-induced inflammation.[6]

According to recent studies, people with COVID-19 exhibit many clinical characteristics along with oral symptoms. The most frequently documented clinical oral symptoms in patients with COVID-19 include ulcers, blisters, necrotising gingivitis, opportunistic co-infections, salivary gland changes, white and erythematous plaques, and gustatory dysfunction. The loss of taste and smell usually coincides with the lesions.[7,8]

However, the exact relationship between many of these oral lesions and pathological processes of SARS-CoV-2 infection is still a subject of investigation.

Oral and Dental Medicine, Kafrelsheikh University, Egypt

Corrospondience: Enas Ahmed Elgendy

email: enaselgendy2005@gmail.com

The current study was planned to explore if the oral lesions in COVID-19 pneumonia patients are caused by the drugs used in the treatment or by the virus itself.

Patients and Methods

The cross-sectional study was conducted from September 2020 to September 2021 at the Kafrelsheikh University Hospital, Egypt. After approval from the institutional ethics review committee, the sample size was calculated using EpiInfo calculator 2002 version[9] with 95% confidence limit and 84% power. The sample was raised using non-probability convenience sampling technique. Those included were COVID-19 patients of either gender aged 20-60 years having severe pneumonia, breathing difficulties (30 breaths per minute [bpm]), oxygen saturation 93% at rest, or partial pressure of oxygen (PaO2) or fraction of inspired oxygen (FiO2) 300mmHg and who were without any associated medical comorbidity. Those excluded were COVID-19 patients who were smokers, alcohol abusers or pregnant. Also patients with any autoimmune or other systemic illnesses, like diabetes, and patients who had used any antibiotics, anti-inflammatory medications, immune suppressor drugs or corticosteroids during the preceding month were excluded.

After the diagnosis was confirmed, the patients were examined for oral manifestations by ICU physician. Informed consent was obtained and, based on the level of IL-6 and procalcitonin, the patients were classified into high group I, medium group II and low group III.

Patients in group I received TZM (Actimra®, Roche Egypt, Festival City, Cairo Governorate) 8mg/kg intravenously (IV); 400mg every 12 hours for one day (not exceeding 800mg/dose) and methylprednisolone (Solu-Medrol® Pfizer, Egypt, El Zagazig, Ash-Sharqia Governorate) 1-2mg/kg, 100-200mg daily for 2 weeks. Group II patients received methylprednisolone only (Solu-Medrol®), while group III patients received antiviral drug Remdesivir, 2 amp on the first day, and 1 amp daily for 5 days.

The oral manifestations were recorded at the time of hospital admission before treatment, and at 2 weeks after respective treatment.

Data was analysed using SPSS 20. Categorical data was compared among the groups using chi-square test, whereas categorical variables were compared in terms of baseline and post-intervention values using McNemar tests. P<0.05 was considered statistically significant.

Results

Of the 90 patients, 30(33.3%) were in group I; 16(53%) males and 14(47%) females with mean age 44.82±6.10 years. Group II had 27(30%) patients; 14(52%) males and 13(48%) females with mean age 43.74±4.87 years. Group III had 33(34%) patients; 9(27%) males and 14(73%) females with mean age 42.66±2.51 years (p>0.05) (Table 1).

Various types of oral lesions were found, including loss of taste or smell, xerostomia, erosion, vesicle, coated and atrophic tongue, haemorrhagic crust, ulcer and erythema, and patients presented even with multiple oral manifestations (Figure 1, Table 2).

Baseline, oral manifestations were detected in 14(47%) cases in group I, 10(37%) in group II, and 12(36.4%) in group III. After treatment, oral manifestations decreased in all groups; 5(17%) cases in group I, 4(15%) in group II, and 3(9%) in group III.

There was no significant difference among the groups at baseline and after 2 weeks of treatment regarding oral

Table-1: Demographic characteristics.

	Group 1 (n = 30)	Group 2 (n = 27)	Group 3 (n = 33)	*p-value*
Gender	16 male/14 female	14 male/13 female	19 male/14 female	0.863
Age	44.82± 6.10	43.74 ± 4.87	42.66 ± 2.51	0.586

Table-2: Oral manifestations.

Oral manifestation	Group 1 Actimra + Cortisone (n = 30)	Group 2 Cortisone (n = 27)	Group 3 Antivirus (n = 33)
Loss of taste or smell	5 (16.6%)	4 (14.8%)	6 (18.2%)
Xerostomia	4 (13.3 %)	3 (11.2)	3 (9%)
Erythema or erosion	1 (3.3%)	1 (3.7)	2 (6%)
Candidiasis	6 (20%)	4 (14.8%)	4 (12.1%)
Coated and atrophic tongue	4 (13.4%)	3 (11.2)	3 (9.1%)
Haemorrhagic crust	0 (0%)	0 (0%)	1 (3%)
Vesicle or Ulcer	3 (10 %)	2 (7.4%)	2 (6.2%)
No Oral manifestation	16 (53.3%)	17(62.9%)	21(63.6%)

Table-3: Baseline and post-intervention intergroup comparison.

Oral manifestation	Group 1 Actimra + Cortisone (n = 30) n (%)	Group 2 Cortisone (n = 27) n (%)	Group 3 Antivirus (n = 33) n (%)	$\chi 2$	*p-value*
Before					
Negative	16 (53.3)	17(62.96)	21 (63.63)	2.010	0.366
Positive	14 (46.7)	10 (37.03)	12 (36.37)		
After					
Negative	25 (83.3)	23 (85.18)	30 (90.90)	1.482	0.616
Positive	5 (16.7)	4 (14.82)	3 (9.10)		
McN (p)	0.004*	0.031*	0.016*		

$\chi 2$: Chi square test
McN: McNemar test for comparing between before and after in each group
*: Statistically significant at P ≤ 0.05

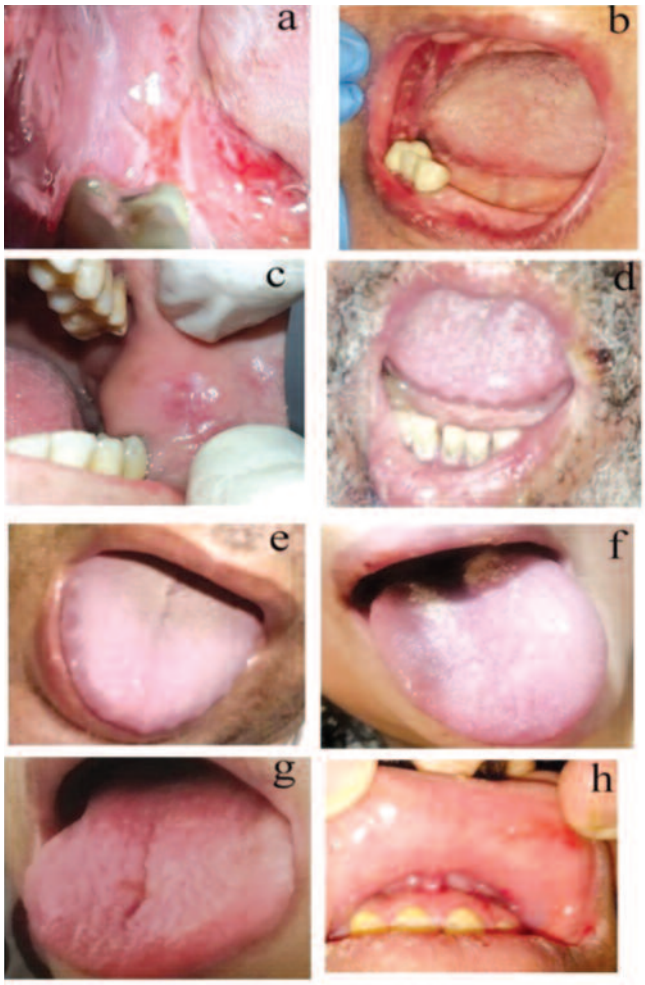

Figure: Oral manifestations in coronavirus disease-2019 (COVID-19) patients. a-b: Non-specific inflammation in buccal mucosa and tongue; c: Vesicle in buccal mucosa; d: Crusted upper lip; e-g: Coated and atrophic tongue; h: Ulcer in the upper lip.

manifestations. Intragroup comparison demonstrated a significant difference in the two values in all the three groups ($p<0.05$) (Table 3).

Discussion

Patients with COVID-19 develop oral lesions. According to studies, oral tissues may become infected with SARS-CoV-2 initially, and, theoretically, mouth lesions may present as the first symptoms of COVID-19. If this theory is correct, dental professionals will play a crucial role in the early diagnosis of the illness and may refer suspects of SARS-CoV-2 for testing and treatment.[10]

However, the exact relationship between these oral lesions and pathological processes of the infection is still unclear. Different hypotheses have been formulated to detect the aetiology of these lesions. One suggests that the virus itself is the primary cause of these lesions, while others claim that the drugs administered for the treatment, or the compromise and deterioration of the immune system, enables opportunistic infections to flourish.[11]

The finding that COVID-19-associated respiratory failure can be caused by a cytokine storm rather than viral development is the basis for utilising anti-inflammatory drugs, such as TZM.[12, 13] The first studies on TZM in COVID-19 showed a therapeutic advantage in retrospective cohorts of 21 and 15 patients with mild to critical COVID-19 pneumonia who also received steroids.[14] These treatments were subsequently supported by the Chinese Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia versions 6-7, and experience from larger cohorts in Europe has also been recorded.[15] Another anti-inflammatory drug used is cortisone, which inhibits the generation and harmful effects of cytokines, and also prevents B cells from producing antibodies, and T cells from performing their protective function.[16]

The current study reported the impact of TZM and/or steroids on the appearance of oral manifestations in hospitalised COVID-19 patients. The findings suggest that the oral manifestations were due to COVID-19 itself rather than the treatment provided for it. These results are in agreement with Marino Sanchez et al., who reported that the loss of taste or smell occurred due to viral interference with cranial nerves I, VII, IX and X as well as the inflammatory exudate that affects the neural transmission.[17]

Xu et al.[18] suggested that salivary glands may be involved in patients with COVID-19 infections. Angiotensin converting enzyme-2 (ACE-2), a key receptor for COVID-19, is broadly distributed in cells of the mouth and nose. The minor salivary glands exhibit higher levels of ACE-2 expression than the lungs, making them a potential target for the COVID-19 virus. Dry mouth in COVID-19 patients can result from viral invasion of salivary glands.[18] From a different angle, xerostomia may also be caused by the patients' psychological health, poor oral hygiene and negative pharmacological side effects.[11]

An overt immune response may be elicited by a synergistic interaction between SARS-CoV-2 and the local oral bacteria, which could worsen oral inflammation. Inflammatory mediators, such as cytokines, prostaglandins and histamines, may have pleiotropic effects on local cells, making it easier for innate and adaptive immune cells to infiltrate the body, thereby boosting the immune response.[19]

The tongue is the organ that COVID-19 targets the most, as the infection and the dysfunction it generates may include the tongue's epithelial cells. The finding is based on a recent

discovery of ACE-2 receptors there. Additionally, after the oral keratinocytes/glandular tissues become infected, the cell membrane permeability to external pathogens increases and viral replication in the cells lining the oral mucosa can cause ulcers and necrosis in the affected areas.[8]

The current results corroborated earlier observations that the healing process of the oral lesions occurred simultaneously with the eradication of the COVID-19 infection.[20]

Conclusion

Oral lesions in COVID-19 patients were caused by the virus itself rather than the drugs used in its treatment because adjunctive treatments with methylprednisolone alone or in combination with TMZ had no effect on the oral manifestations.

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Conflict of Interest: None.

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