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ORIGINAL ARTICLE

Systemic corticosteroid and antiviral co-therapy in acute herpetic gingivostomatitis: an exploratory study

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Abstract:

Objective: This study compared the treatment of acute herpetic gingivostomatitis (AHGS) using antiviral therapy alone versus combined antiviral and systemic corticosteroid therapy. **Methods:** This retrospective case series included 20 consecutively selected records from a postgraduate oral medicine clinic. Patients received either acyclovir alone (200 mg, 5 days) or acyclovir plus prednisone (20 mg, 5 days). Clinical features, symptom progression, and healing time were extracted from descriptive clinical notes by a single examiner. Comparative statistics used the Mann–Whitney test, with 95% confidence intervals, and an exploratory logistic regression was performed to identify potential predictors of prolonged healing (≥7 days). **Results:** Patients receiving combined therapy showed an observed difference toward faster symptom relief and healing. Logistic regression indicated a trend toward lower odds of prolonged healing in the combination group (OR 0.01; 95%CI 0.00–1.66) and a borderline effect of age on healing duration. No adverse effects were recorded. **Conclusion:** Combined antiviral and corticosteroid therapy may be associated with an observed difference toward faster symptom resolution and healing compared with antiviral therapy alone. These findings are exploratory, and prospective studies are needed to confirm clinical benefit.

Keywords: AHGS; Corticosteroids; Antiviral therapy; HSV-1; Logistic regression.

INTRODUCTION

AHGS is a highly contagious viral infection of the oral mucosa and lips caused by herpes simplex virus type 1 (HSV-1). The clinical presentation typically includes painful oral lesions, fluid-filled vesicles, ulcerations, and gingival inflammation. Symptoms may include fever, general malaise, drooling, eating and drinking difficulties, and intense pain. Lesions often appear in clusters and may involve the tongue, palate, tonsils, and perioral skin[1]. In more severe cases, difficulty swallowing, reduced oral intake, and cervical lymphadenopathy may also be present.

Conventional management of AHGS aims to relieve symptoms and promote lesion healing[2,3]. Oral antivirals, such as Acyclovir, Valacyclovir, and Famciclovir, are commonly prescribed to reduce the duration and severity of the infection[4] by inhibiting viral replication and thereby reducing recurrence and symptom burden.

In more severe cases, systemic corticosteroids may be considered[5]. Corticosteroids are potent anti-inflammatory agents that can attenuate tissue inflammation and improve patient comfort. However, their use in herpes simplex infections requires caution because indiscriminate use, including administration without adequate antiviral coverage or in clinical scenarios associated with immunosuppressive risk, can increase susceptibility to secondary infections[6]. Appropriate clinical judgment is therefore essential when considering corticosteroid therapy in AHGS.

Because AHGS may mimic other ulcerative or vesiculobullous conditions, including HSV-associated erythema multiforme, accurate clinical differentiation is critical. In this study, diagnoses were based on

Statement of Clinical Significance
The combination of systemic corticosteroids and antivirals in AHGS treatment reduced symptom severity and lesion healing time without adverse effects, supporting its use as an effective and safe therapeutic option to improve patient outcomes in clinical dental practice.

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characteristic clinical features, lesion distribution, and overall presentation to distinguish AHGS from other conditions.

In this study, we evaluated the effects of treating AHGS with antiviral therapy alone compared with combined antiviral and systemic corticosteroid therapy.

METHODS

The current study was carried out with the approval of the Research Ethics Committee of the Araraquara School of Dentistry-UNESP, under protocol 75046423.2.0000.5416. A retrospective cohort study was conducted, with clinical data obtained from the clinical records of patients diagnosed with AHGS at the Oral Medicine Service (OMS) of the Araraquara School of Dentistry-UNESP. In this study, two treatment protocols for AHGS were compared, antiviral treatment combined with corticosteroids and exclusive antiviral therapy.

For the study, 20 clinical records of patients with AHGS were selected, consecutively, divided into 2 groups according to the treatment protocol used as follow: 10 patients treated with antiviral combined with corticosteroid (Acyclovir 200 mg 1 tablet every 4 hours for 5 days + Prednisone 20 mg for 5 days) and 10 patients treated exclusively with antiviral (Acyclovir 200 mg 1 tablet every 4 hours for 5 days). Clinical records were excluded from the study in which the diagnoses were inconclusive or when the patients underwent head and neck chemotherapy and/or radiotherapy or presented with an immunomediated disease with oral manifestations.

Data on the main complaint, oral and systemic health, medication use, associated comorbidities, history of oral diseases associated with HSV infection, previous episodes of AHGS were collected from the OMS records. The photographic documentation archived in the clinical records was evaluated, as well as notes in those records to evaluate the evolution of the proposed treatment. All data were extracted by a single examiner to minimize extraction-related bias.

The diagnosis of AHGS was based on characteristic clinical features. Cases presenting target-like skin lesions were classified as HSV-associated erythema multiforme, based on lesion distribution and morphology.

Statistical analysis was carried out with the Epi Info 7 program (Centers for Disease Control and Prevention https://www.cdc.gov/epiinfo/index.html). To compare the different proposed treatments, the normality test was performed using the Shapiro-Wilk test, and as the sample presented a non-normal distribution, the Mann-Whitney test was performed. The results were considered statistically significant when $p<0.05$.

A logistic regression model was constructed to identify independent predictors of prolonged healing (≥7 days). Variables included age, sex, palpable lymph nodes, and therapeutic regimen. Odds ratios (ORs) and 95% confidence intervals (95%CI) were estimated using maximum likelihood. Model quality was assessed using pseudo R^2 and the likelihood ratio test (LRT). This analysis was performed in JASP (version 0.18) and interpreted cautiously due to the small sample size and the exploratory nature of the study.

RESULTS

The clinicopathological features of the patients investigated are described in Table 1. In the sample of 20 clinical files, the average age of patients treated with antiviral and corticosteroid was 30.5 years, with 90% being male and 10% female. In the group of patients treated with antiviral alone, the average age was 18.1 years, with 80% of patients being female and 20% male (Table 2).

Regarding the symptoms and functional changes observed, both treatment groups exhibited a similar pattern of symptoms, with pain, fever, and prostration being the most prevalent. The functional changes observed in both groups were primarily related to swallowing and feeding.

The analysis of the location of the lesions revealed a prevalence in both the group of patients treated with antiviral and corticosteroid and the group of patients treated with antiviral alone in the lower lip, tongue, and gingiva region.

According to clinical records, it was been observed that patients who were administered a combination of corticosteroids and antivirals for a duration of 5 days experienced no adverse effects. Additionally, their symptoms showed a more rapid decrease in intensity compared to those who were treated with antiviral alone. Furthermore, the healing of oral lesions was also observed to be more rapid when corticosteroid treatment was combined with antivirals, although this difference did not reach statistical significance (Table 2).

Figure 1 illustrates an exemplary response in a patient treated with a combination of corticosteroid and antiviral, resulting in the complete resolution of all oral lesions and symptomatology within seven and two days, respectively.

Table 1. Clinicopathological findings of the 20 cases of acute herpetic gingivostomatitis investigated.

Patient	Sex	Age (years)	Palpable lymph nodes	Symptomatology	Skin lesions	Lesions location	Functional change	Treatment	Oral lesions healing (days)	Remission of symptoms (days)
1	Male	36	Yes	Yes	Yes	Upper and lower lip, tongue, buccal mucosa, oral floor and gingiva	Yes	Corticosteroid and antiviral	7	2
2	Male	42	No	Yes	Yes	Upper and lower lip, tongue, buccal mucosa, alveolar ridge, palate and gingiva	Yes	Corticosteroid and antiviral	9	4
3	Male	27	Yes	Yes	No	Tongue, buccal mucosa and gingiva	No	Corticosteroid and antiviral	6	6
4	Male	22	No	Yes	No	Upper and lower lip, tongue, buccal mucosa, oral floor, palate and gingiva	Yes	Corticosteroid and antiviral	7	3
5	Male	34	Yes	Yes	Yes	Upper and lower lip, tongue and buccal mucosa	Yes	Corticosteroid and antiviral	3	2
6	Male	40	Yes	Yes	No	Upper and lower lip and tongue	No	Corticosteroid and antiviral	10	5
7	Male	28	No	Yes	No	Upper and lower lip, buccal mucosa, and gingiva	No	Corticosteroid and antiviral	6	6
8	Female	21	No	Yes	No	Upper and lower lip and gingiva	No	Corticosteroid and antiviral	5	2
9	Male	10	No	Yes	No	Upper and lower lip, tongue, buccal mucosa, oral floor and gingiva	Yes	Corticosteroid and antiviral	3	3

Continue...

Table 1. Continuation.

Patient	Sex	Age (years)	Palpable lymph nodes	Symptomatology	Skin lesions	Lesions location	Functional change	Treatment	Oral lesions healing (days)	Remission of symptoms (days)
10	Male	45	No	Yes	Yes	Upper and lower lip, tongue, buccal mucosa, oral floor, alveolar ridge and gingiva	No	Corticosteroid and antiviral	7	2
11	Female	26	Yes	Yes	No	Alveolar ridge and gingiva	Yes	Antiviral alone	10	10
12	Female	16	No	Yes	No	Alveolar ridge and gingiva	No	Antiviral alone	7	7
13	Female	20	Yes	Yes	No	Lower lip and buccal mucosa	No	Antiviral alone	7	7
14	Female	30	No	Yes	No	Tongue and alveolar ridge	No	Antiviral alone	18	5
15	Female	6	No	Yes	No	Upper and lower lip, tongue, buccal mucosa	No	Antiviral alone	8	8
16	Female	19	Yes	Yes	No	Tongue, oral floor, alveolar ridge, palate and gingiva	Yes	Antiviral alone	6	6
17	Male	24	Yes	Yes	No	Lower lip, tongue, alveolar ridge and gingiva	Yes	Antiviral alone	7	7
18	Male	12	Yes	Yes	No	Lower lip, tongue, buccal mucosa, alveolar ridge and gingiva	No	Antiviral alone	6	6
19	Female	13	No	Yes	No	Lower lip and tongue	Yes	Antiviral alone	11	4
20	Female	15	No	Yes	No	Lower lip, tongue, oral floor and gingiva	Yes	Antiviral alone	4	4

Table 2. Patients with acute herpetic gingivostomatitis (n=20) according to the treatment protocol.

	Corticosteroid and antiviral (n=10) Mean (SD)	Antiviral alone (n=10) Mean (SD)	p-value
Age (years)	30.5 (10.9)	18.1 (7.2)	0.008*
Female (%)	1 (10)	8 (80)	
Male (%)	9 (90)	2 (20)	
Oral lesions healing (days)	6.3 (2.3)	8.4 (4)	
No symptomatology (days)	3.5 (1.7)	6.4 (1.8)	0.004†
Recurrences	1.3 (1.9)	0.1 (0.3)	

*t-student test; †Mann-Whitney test

Figure 2 depicts another patient with an excellent response treated with a combination of corticosteroid and antiviral, resulting in the complete resolution of all oral lesions and symptomatology within nine and four days, respectively.

In Figure 3, an excellent response is observed in another patient treated with a combination of corticosteroid and antiviral, resulting in the cure of all oral lesions and symptomatology within seven and three days respectively.

In addition to the descriptive analysis, an exploratory logistic regression model was performed to identify potential independent predictors of prolonged healing (≥ 7 days). Variables included age, sex, palpable lymph nodes, and treatment regimen (Figure 4).

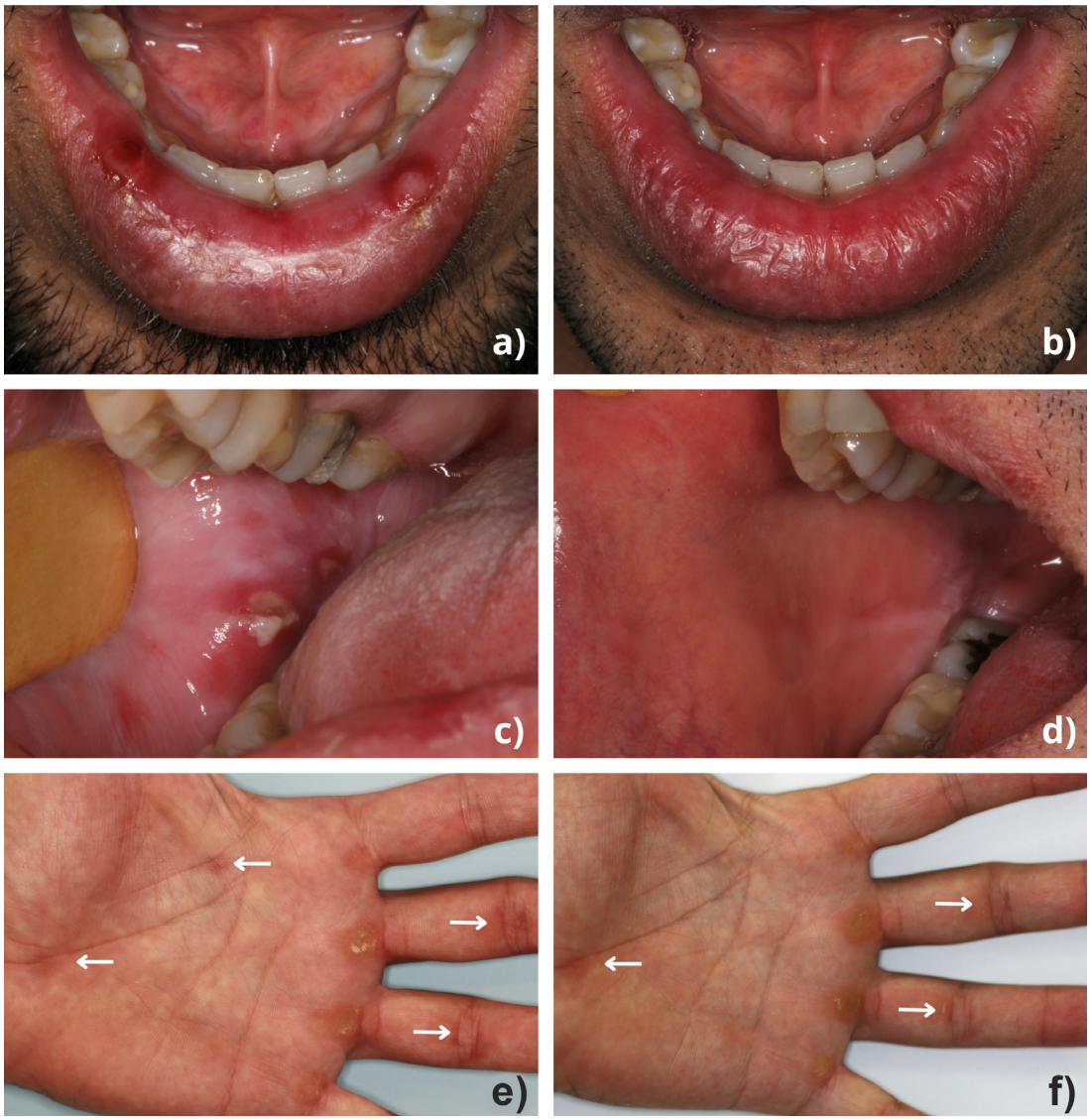

Figure 1. Oral lesions on the lip (**A**), buccal mucosa (**C**), and target lesions on the palm of the hand (**E**) (white arrows). After seven days of treatment with corticosteroids combined with antiviral medication, the lesions were completely healed (**B**), (**D**), (**F**).

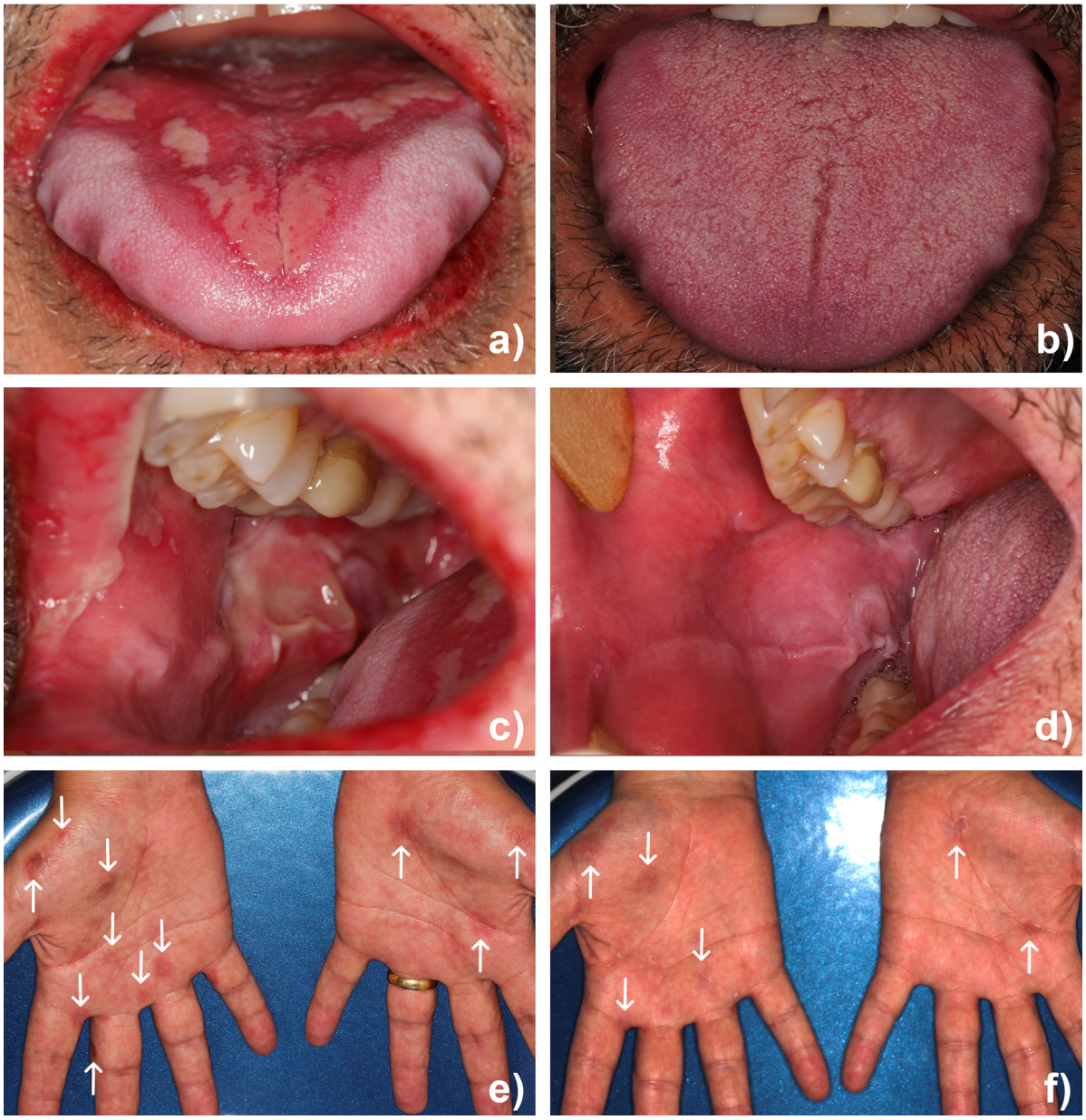

Figure 2. Oral lesions on the lips and tongue (**A**), buccal mucosa (**C**), and target lesions on the palm of the hands (**E**) (white arrows). After nine days of treatment with corticosteroids combined with antiviral medication, the lesions were completely healed (**B**), (**D**), (**F**).

The analysis showed that combined therapy presented a strong trend toward reduced odds of prolonged healing (OR 0.01; 95%CI 0.00–1.66; p=0.077). Age demonstrated a borderline association with prolonged healing (OR 1.26; 95%CI 0.99–1.61; p=0.064). Sex and palpable lymph nodes were not significant predictors.

Model quality assessment indicated a pseudo R^2 of 0.32, and the likelihood ratio test (LRT) showed a trend toward significance (χ^2=7.19; p=0.126), consistent with the exploratory nature of this analysis. The full results of the logistic regression are presented in Table 3.

The corresponding forest plot (Figure 4) displays the odds ratios and 95% confidence intervals on a logarithmic scale, illustrating the relative contribution of each predictor.

DISCUSSION

Several studies that have demonstrated the efficacy of the combination of antivirals and corticosteroids in the treatment of recurrent cold sores, but mainly when administered topically[7-9]. This study represents the first

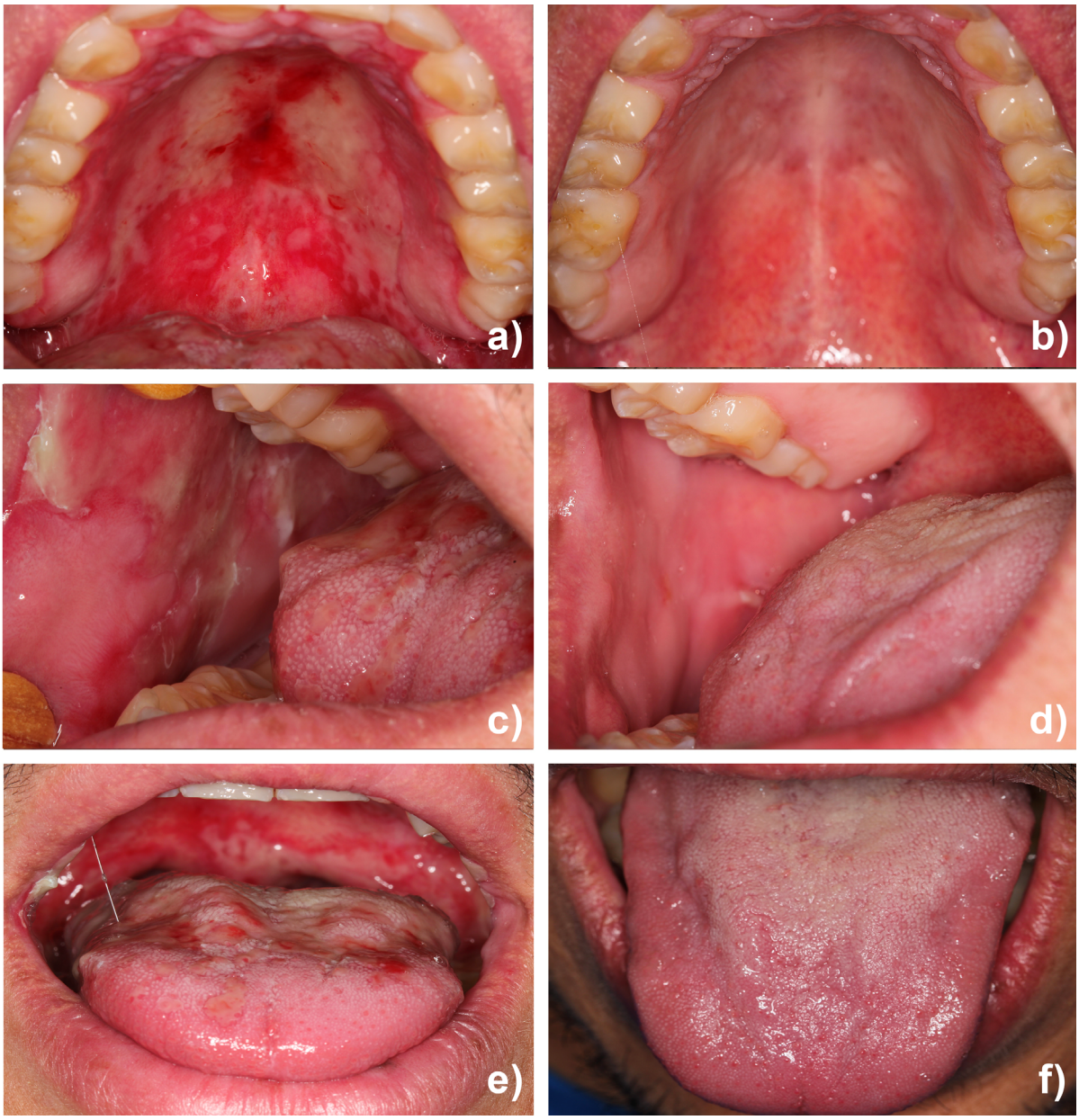

Figure 3. Oral lesions on the palate (**A**), buccal mucosa (**C**), and tongue (**E**). After seven days of treatment with corticosteroids combined with antiviral medication, the lesions were completely healed (**B**), (**D**), (**F**).

Table 3. Logistic regression analysis for predictors of prolonged healing (≥7 days).

Predictor	OR	95%CI	p-value
Age (years)	1.26	0.99–1.61	0.064
Sex (Male)	1.86	0.06–0.58	0.727
Lymph nodes (present)	0.09	0.00–2.85	0.170
Therapeutic regimen			
Antiviral therapy alone (reference)	1.00	-	-
Corticosteroid+antiviral	0.01	0.00–1.66	0.077

Pseudo R^2=0.32; p = 0.126.
OR: odds ratio; CI: confidence interval.

evaluation of the correlation between the use of antivirals and systemic corticosteroids for the treatment of HSV lesions in dental practice.

In this study, patients treated with combined corticosteroid and antiviral therapy showed an observed difference in symptom reduction, compared to those treated with antiviral alone[5]. The use of combined therapy also demonstrated an observed difference over antiviral therapy alone in terms of time to oral lesion healing. However, these findings must be interpreted with caution due to the non-randomized design and baseline differences in age and sex between groups,

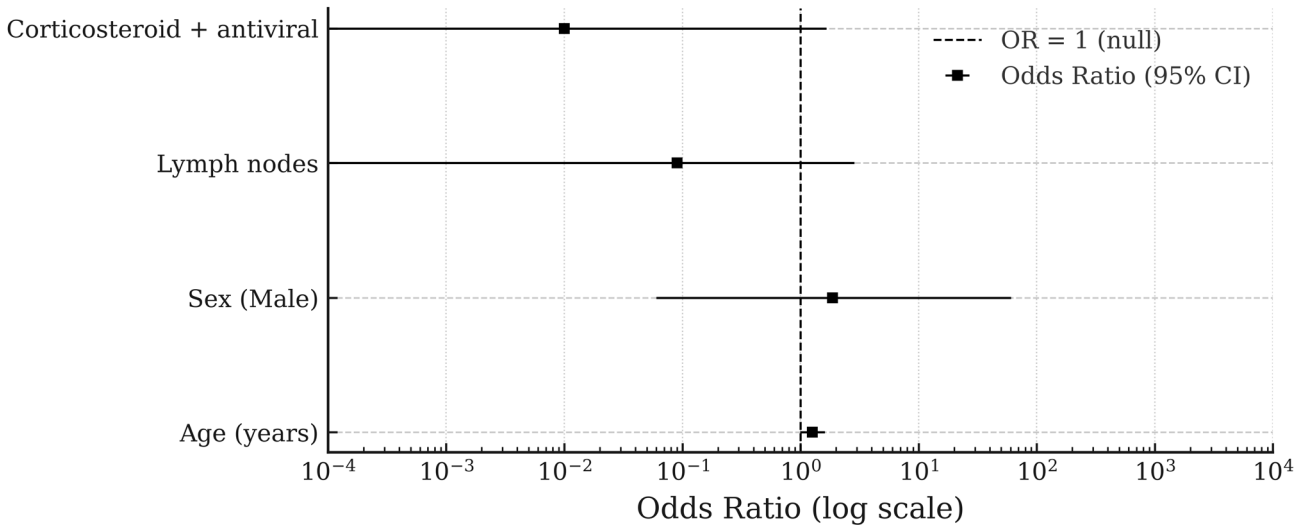

Figure 4. Forest plot presenting adjusted odds ratios and 95% confidence intervals for predictors of prolonged healing (≥7 days). The dashed vertical line represents the null value (OR=1). The x-axis uses a logarithmic scale from 10^{-4} to 10^{4}.

which may have influenced both treatment selection and clinical outcomes.

Similar results were observed in the systematic review showing advantages in the use of corticosteroid combined with topical antiviral to treat recurrent herpes labialis[7].

Monotherapy with corticosteroids in lesions caused by HSV infection can worsen the clinical condition, as corticosteroids can suppress the inflammatory response that is important in combating the infection. This emphasizes the importance of combining corticosteroids with appropriate antiviral therapy when indicated.

Although the use of corticosteroids is controversial and often contraindicated by some authors for the treatment of active infections[10], the present study demonstrated that corticosteroids, when combined with antiviral therapy, may provide an observed benefit in cases of AHGS. This combination may improve patient comfort and prevent worsening of the clinical condition or progression to other diseases such as erythema multiform or Steven-Johnson syndrome. In this study, cases presenting target-like cutaneous lesions were classified as HSV-associated erythema multiforme rather than isolated AHGS, which highlights the importance of accurate differential diagnosis.

There have been few studies[11-14] on the association between corticosteroid and antiviral for treating HSV infections such as recurrent herpes labialis, but all of them have demonstrated that the combination is more effective than the use of antiviral alone. However, these prior studies also share limitations in sample size and methodological heterogeneity, which parallel the limitations of the present report.

The exploratory logistic regression performed in this study provided additional insight into potential independent predictors of prolonged healing (≥7 days). While the model did not reach formal statistical significance, it showed a strong trend toward a protective effect of the combination therapy (OR 0.01; 95%CI 0.00–1.66) and a borderline association between age and longer healing time (OR 1.26; 95%CI 0.99–1.61). These findings support the descriptive results but remain exploratory and should not be interpreted as definitive evidence of efficacy.

This study has several strengths. It is, to our knowledge, the first to evaluate the use of systemic corticosteroids in combination with antivirals for the treatment of AHGS in a dental care setting. All patients were managed within the same institutional protocol, reducing variability in treatment administration. Clinical outcomes were assessed through photographic documentation and detailed chart analysis, ensuring a consistent evaluation of lesion progression and symptom resolution. Furthermore, the study provides relevant insights into the feasibility and safety of short-term corticosteroid use in HSV-1 infections, with no adverse effects reported.

However, this study also has limitations. Due to its retrospective design, several clinical records lacked comprehensive documentation, especially regarding follow-up visits and symptom progression beyond the initial treatment period. Notably, complementary

diagnostic tests, particularly serologic assays for HSV, were not consistently performed or reported in the records. Serologic testing plays a crucial role in confirming infection and monitoring disease progression. In future studies, the routine inclusion of complementary exams could enhance diagnostic accuracy and support the correlation between clinical response and laboratory confirmation. Additionally, the small sample size limits the statistical power of the findings, and the non-randomized allocation introduces potential selection bias that may have contributed to the observed differences between groups. Further prospective studies with larger cohorts are necessary to validate these preliminary observations.

CONCLUSION

Based on the results of the present study, the authors consider that the combination of corticosteroids and antiviral medication may be associated with an observed difference toward reduced symptom duration and faster healing in cases AHGS. Given the retrospective design and small sample size, these findings should be interpreted as exploratory and not as definitive evidence of efficacy. Nevertheless, the combined regimen appeared to improve patient comfort and may have the potential to enhance overall quality of life during the acute phase of the condition. Prospective controlled studies are necessary to confirm these preliminary observations and to establish clear clinical guidelines for the use of systemic corticosteroids in AHGS.

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AUTHORS' CONTRIBUTIONS

HSC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. AB: Methodology, Validation, Writing – review & editing. EMSM: Validation, Writing – review & editing. DDSO: Data curation, Visualization, Writing – review & editing. CMN: Conceptualization, Methodology, Supervision, Validation, Writing – review & editing.

CONFLICT OF INTEREST STATEMENT

Funding: This study was supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001.

Competing interests: The authors have no competing interests to declare that are relevant to the content of this article.

Ethics approval: The current study was carried out with the approval of the Research Ethics Committee of the Araraquara School of Dentistry-UNESP, under protocol 75046423.2.0000.5416.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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