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ORIGINAL ARTICLE

Evaluating high power laser therapy (HPLT) as treatment for chemotherapy-induced oral mucositis in paediatric patients with oncohematological diseases

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Abstract

Background: Oral mucositis (OM) is one of the most debilitating side effects of chemotherapy. Among the current methods used in OM management, the feasibility of high power laser therapy (HPLT) has been proposed but not fully evaluated.

Aim: The aim of this study was to evaluate the efficacy of HPLT in the treatment of OM in paediatric patients.

Design: Fourteen oncohematological paediatric patients treated with chemotherapy and/or hematopoietic stem cell transplantation and affected by OM at different grades were enrolled in this study. All patients were treated with a class IV laser device in four sessions for four consecutive days, OM was evaluated with the WHO-OTS scale. The perception of pain was assessed by the visual analog scale. Photographs of and information about lesions and patient questionnaires were taken and collected, respectively. Descriptive analyses and the Wilcoxon signed-rank test (nonparametric test) were used, with a statistical significance of $\alpha = .05$.

Results: After a week into the treatment, 57% of patients were completely healed, whereas the whole cohort experienced a drastic decrease in pain, from an average value of 5.8–1.1 ($p = .0016$). The average number of injuries per patient decreased from 7.4 to 3.1 ($p = .008$).

Conclusion: High power laser therapy appears to be a safe and efficacious method for managing OM. It reduces pain and severity of oral cavity injuries. Further studies are needed to determine the optimal parameters useful in OM treatment and to evaluate the relative effectiveness of HPLT to other treatments like LLLT.

KEYWORDS

community paediatric dentistry, medically compromised/disability, oral medicine/oral surgery, pain control, sedation

1 | INTRODUCTION

Inflammation of mucosal tissues is the most common oral complication of antiblastic therapies, due to the high cell turnover in the mouth. Oral mucositis (OM) develops in approximately 40% of children treated with standard-dose chemotherapy, in 80% of patients undergoing radiation therapy for head and neck cancers, and in 75% of patients undergoing bone marrow transplantation.[1–3] Oral mucositis is characterized by ulcerations of the oro-esophageal and gastrointestinal mucosae that cause pain, dysphagia, diarrhea, and dysfunction depending on the affected tissue. Thus, OM can interfere with the patient's capability to tolerate planned therapy, leading to an increased risk of both local and systemic infections.[4,5] These injuries can be severe enough to require medical support with parenteral nutrition and opioid therapy; moreover, they contribute to the risk of local and systemic infection.[6]

Although OM cannot be completely prevented, several prevention and treatment strategies can help reduce its incidence, severity, and duration. These strategies were reported in the MASCC/ISOO International Clinical Practice Guidelines (2019)[7] and in the subanalysis of Miranda-Silva et al,[8] which revealed the preventive and therapeutic use of photobiomodulation (PBM). PBM stimulates and promotes positive tissue processes such as healing of wounds, tissue regeneration, and immune responses, and it mediates negative tissue processes such as inflammation, pain, and aberrant immune responses. Therefore, PBM has been suggested for the management of OM, despite limitations due to its many heterogeneous parameters and the lack of consensus about dosage in the literature.[7–9]

Usually, biostimulation protocols use class I, II, and III lasers that have less than 1 W power and which are conventionally defined as low-level laser therapy (LLLT). On the contrary, the intensity of class IV laser devices is greater than 1 W, and they are defined as high power laser therapy (HPLT). The MASCC/ISOO guidelines have supported a protective role of intraoral PBM with LLLT for the prevention of OM in adult patients undergoing conditioning regimens for hematopoietic stem cell transplantation (HSCT), with or without total body radiation (TBI). Similarly, this protective role was found in head and neck cancer patients who underwent radiotherapy (RT) or RT combined with chemotherapy (CT).[10–11] Based on promising data reported in the adult population, the Paediatric Oncology Group of Ontario (POGO) recommended the use of LLLT as prevention in paediatric patients receiving CT or undergoing pretransplant conditioning regimens associated with a high rate of mucositis.[11]

Why this paper is important to paediatric dentists

- Oral mucositis is one of the most debilitating side effects of chemotherapy because it can compromise one's overall and oral health status. This paper describes how HPLT can be an alternative in the treatment of patients with nonsevere grade of OM who present minor lesions.
- High power laser therapy not only reduces the complications related to OM, but is also effective in relieving pain.

To date, there are no guidelines about the treatment of established OM with intraoral PBM therapy, especially for the use of HPLT, both at the preventive level and at the therapeutic level.

Class IV laser protocols are associated with numerous advantages: First, because of the high power (>1 W), a substantial amount of energy can be supplied in a limited period of time, which also meets the need for the rapid treatment of paediatric patients who may not be able to comply.[12] Second, the combination of two different wavelengths (660 and 970 nm) can easily provide a biostimulating, analgesic, and anti-inflammatory effect.[13]

In both adults and children, almost all the studies compared LLLT treatment protocols with placebo. Only recently, the therapeutic efficacy of HPLT has been demonstrated, especially in populations of paediatric patients. Interestingly, no clinically significant side effects were found to be associated with HPLT treatment. Despite promising results, further investigations are needed to determine specific parameters to make HPLT an integral part of the protocols for the management of OM induced by anticancer therapies.

The aim of this study was to evaluate the efficacy of HPLT in the treatment of OM induced by chemotherapy drugs and by the pre-HSCT conditioning regimen in a population of paediatric patients with oncohaematological diseases. The goal was to understand whether HPLT reduces the OM grade, the perception of pain, and the number of lesions (ulcerative and erythematous). Furthermore, the investigation is aimed to evaluate which regions of the oral cavity are most frequently affected by ulceration and erythema. Consequently, the way in which the healing of these lesions progresses is also investigated: Setting the seventh day as cutoff starting from the first session of laser therapy, it is possible to identify the lesions and sites that show an improvement (reduction in the degree of mucositis) or a restitutio ad integrum (absence of lesions).

2 | MATERIALS AND METHODS

2.1 | Population

This prospective study was coordinated by the Dental Clinic of the Padua Hospital in collaboration with the Paediatric Hematology, Oncology and Stem Cell Transplant Division, Padua University Hospital Paediatric (via Giustiniani 2, 35128 Padua). The examined cohort was made up of 14 patients aged between 5 and 16 years recruited between December 2019 and February 2020. All patients underwent chemotherapy or pre-HSCT conditioning regimen in the 3 weeks before the enrollment, they were required to show signs of mucositis of any grade (relative to the WHO-OTS 1979 scale) on the morning of the treatment day and, with informed consent, they were asked to be available for treatment for four consecutive days and follow-up on Day 8. Individuals who received prior laser therapy for oral mucositis, who presented dysplastic lesions in the oral cavity, with reduced mouth opening (<1 cm) and undergoing radiotherapy on the head and neck area were excluded from the study. All the enrolled subjects also received topical and analgesic treatments for mucositis, according to the protocol adopted by the Paediatric Hematology, Oncology and Stem Cell Transplant Division.

2.2 | Instrumentation

Laser therapy was performed with a class IV GaAlAs diode laser device (K-Laser Cube 3, Eltech K-Laser, Via Castagnole 20/H, 31100 Treviso, Italy), owned by the Paediatric Hematology, Oncology and Stem Cell Transplant Division, according to an established "stomatitis protocol," with the following parameters: combined wavelengths 660–970 nm, total dose 810 J, average power 3.2 W (6.4 W pulsed at 50%), treatment time 231 s, frequency from 1 to 20000 Hz, spot size 1 $cm^{2,}$ and defocused mode. During the procedure, the operator, the patient, and any parent present in the room wore goggles (5X7, Univet Srl, Via Giovanni Prati 87, 25086 Rezzato, Italy) to prevent corneal damage.

2.3 | Data collection

Patient discomfort due to OM was assessed by administering a questionnaire with scores from 0 to 3 (0—not at all, 1—moderate, 2 —enough, 3—a lot), to quantify the difficulty experienced during swallowing, chewing, and speaking. The grade of pain was recorded with the aid of the visual analog scale (VAS) adapted to paediatric patients.

The objective examination of the oral cavity was carried out by dividing the area into nine sectors: upper lip, lower lip, right cheek, left cheek, right side of the tongue, left side of the tongue, oral floor, hard palate, and soft palate (Table 1).

TABLE 1 Extent and severity of ulcerations and erythema, respectively, in the different areas into which the oral cavity has been divided.

Area	Ulcerations					Erythema			
Upper lip	0	1	2	3	4	0	1	2	3
Lower lip	0	1	2	3	4	0	1	2	3
Right cheek	0	1	2	3	4	0	1	2	3
Left cheek	0	1	2	3	4	0	1	2	3
Right side of tongue	0	1	2	3	4	0	1	2	3
Left side of tongue	0	1	2	3	4	0	1	2	3
Floor of the mouth	0	1	2	3	4	0	1	2	3
Hard palate	0	1	2	3	4	0	1	2	3
Soft palate	0	1	2	3	4	0	1	2	3

In each sector, the extent of the ulcerated areas and the severity of the erythema were quantified with a numerical scale from 0 to 4 (0—none, 1—diameter < 1 cm, 2—diameter 1–2 cm, 3—diameter 2–3 cm, 4—diameter < 3 cm) for the first, and from 0 to 3 (0—absent, 1—not serious, 2—serious, 3—very serious), for the second.

2.4 | Intervention and evaluations

Four therapy sessions were performed by the same operator, one per day for four consecutive days. The patient was examined 1 week after the start of therapy.

Mucositis was staged with the WHO scale on Days 1 and 4 of laser therapy and Day 8 of follow-up. In these days, the operator collected data related to discomfort during swallowing, chewing, and speaking, to pain perception, parenteral nutrition need, the use of morphine, and the number of neutrophil granulocytes to monitor the patient's state of immunosuppression. Furthermore, on the same days, an objective examination of the oral cavity was performed to evaluate the clinical manifestation of the lesions with the aid of photographic documentation.

2.5 | Statistical analysis

For statistical analyses, descriptive analyses and the Wilcoxon signed-rank test (nonparametric test) were used, with a statistical significance of $\alpha = .05$.

2.6 | Ethical board approvement and written consent

This study was approved by the local ethical board, and all the data about patients were collected after obtaining their written informed consent.

3 | RESULTS

The study cohort consisted of 14 patients: 8 female (57%) and 6 male (43%), and the average age was 12 years. Of these, nine (64%) received treatment for acute lymphoblastic leukemia, three (21%) received treatment for lymphoma, and two (14%) underwent hematopoietic stem cell transplantation (HSCT). On Day 1 of laser therapy, before the start of the treatment, seven patients had mild mucositis (group I), four (29%) had grade 1 mucositis, and three (21%) had grade 2 mucositis, whereas the other seven had severe mucositis (group II), precisely four (29%) with grade 3 and three (21%) with grade 4 on the WHO-OTS scale.

3.1 | Degree of OM

One week after the start of treatment, eight (57%) patients were completely healed: The degree of mucositis was 0, and they no longer presented any type of lesion. Of these, 62.5% belonged to group I, whereas 37.5% belonged to group II. Both groups had an approximately 60% reduction in the number of cases after laser application, meaning the number of patients who still suffered from mucositis decreased from 7 to 3 on Day 8.

3.2 | Perception of pain

Before treatment, the mean score on the VAS was 5.86, from a minimum value of 2 to a maximum value of 9. On Day 8, however, the observed values are significantly lower than those previously declared: The mean value decreased to 1.14 ($p = .0016$), with a minimum and maximum value of 0 and 5, respectively (Figure 1).

Furthermore, the number of patients using opioid analgesics decrease from nine prior to laser therapy to five after laser therapy, and there was also a decrease in the number of patients who used parenteral nutrition from five to three. Analyzing the data collected with the questionnaire concerning the discomfort caused by OM during swallowing, chewing, and speaking, a significant reduction in the score attributed to the extent of discomfort was noted. Before the treatment, nine patients reported pain when swallowing, 13 patients when chewing, and 11 when speaking. After laser therapy, these numbers decreased to 4, 2, and 2 patients respectively.

In addition, the average score attributed to discomfort decreased from 1.14 to 0.43 for swallowing, from 1.9 to 0.29 for chewing, and from 1.29 to 0.29 for speaking.

3.3 | Number of lesions (ulcerations and erythema)

Through the recording of lesions located in the nine selected areas, performed on Days 1 and 8, it was possible to measure the reduction in the number of patients presenting ulcerative lesions (of any size) and erythema (of any entity). The number of lesions corresponds to the number of patients who have developed ulceration or erythema in a specific region of the oral cavity. For ulcerative lesions, the most affected areas were the right cheek (43%), the left cheek (43%), and the oral floor (43%) (Figure 2).

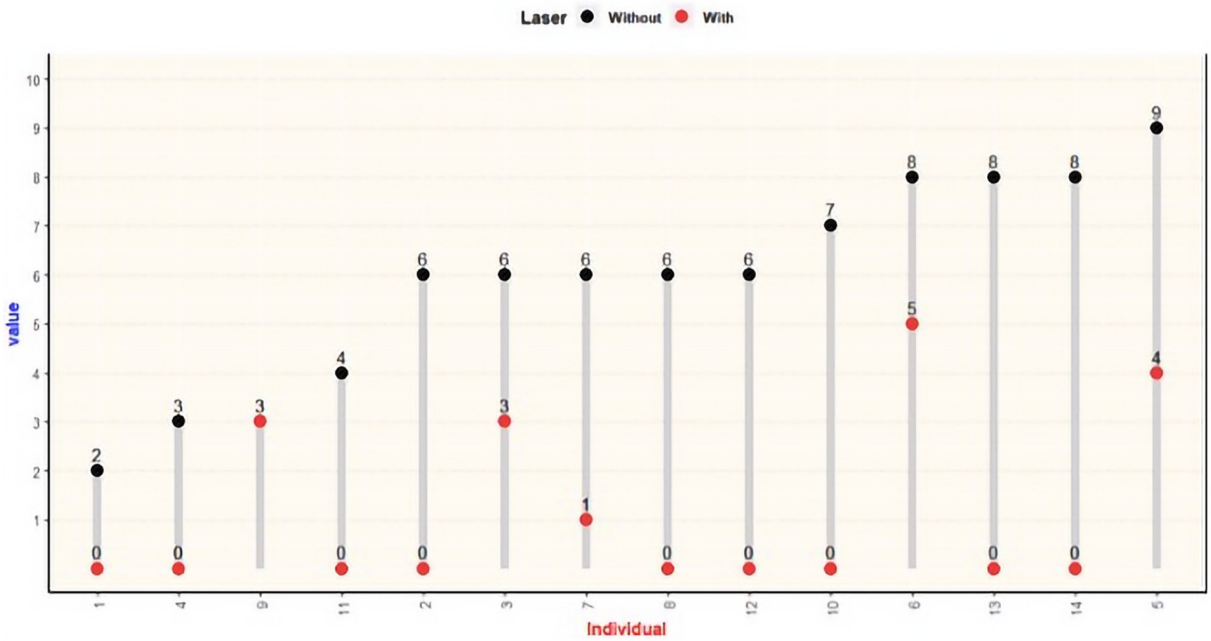

FIGURE 1 Perception of pain before and after laser therapy.

The right side of the tongue (71%), the right cheek (79%), and the left cheek (79%) were the regions found to be the most affected by erythema (Figure 3) and Figure 4.

To understand whether there was an effective decrease in the number of injuries per patient, the ulcerative and erythematous lesions for each individual, regardless of their degree, were combined. It was found that the average number of lesions per patient decreased from 7.4 to 3.1.

4 | DISCUSSION

This prospective study was conducted to evaluate the efficacy of HPLT with a class IV device in the treatment of OM lesions in paediatric oncohematological patients. In this study, 14 patients were recruited: seven with mild mucositis (grades 1 and 2, group I) and seven with severe mucositis (OM grades 3 and 4, group II); all underwent four laser therapy sessions, carried out in four consecutive days. The progression of healing was assessed using the WHO-OTS scale, before and after laser treatment. At the end of the observation (Day 8), 57% (8) of patients had no lesions (OM grade = 0). Of the eight patients who recovered, 62.5% belonged to group I and 37.5% to group II. This result was attributable to the fact that group II patients presented with lesions of greater entity and severity, compared with group I, and consequently required a longer time for complete healing. The main innovation of this work is the enrollment of paediatric patients with grade 1 and grade 2 mucositis, whereas other studies recruited only patients with severe grade of mucositis to test the therapeutic efficacy of HPLT.[12–14] The fact that half of the completely recovered patients belong to group I may support the idea that HPLT can be simultaneously used for preventive and therapeutic purposesthan the previous and better known LLLT,[15] the POGO-recommended approach for paediatric patients.[11] This hypothesis is supported by the fact that no patient, in particular in group I, experienced any side effect due to an "earlier" therapy. Photobiomodulation was widely tolerated by all patients, who were perfectly cooperative and did not report any kind of discomfort, as already found in the studies by Eduardo et al.[16] and Gobbo et al.[13] The safe use of this type of treatment has been demonstrated previously. In a retrospective study, Zecha et al.[17] concluded that it seems unlikely that PBM has carcinogenic effects on normal cells as the nonionizing wavelengths of the red and NIR spectrum used in PBM are far longer than the safety limit of 320 nm for DNA damage. Moreover, in our study, no short-term side effect was observed, and this is in accordance with many studies in the literature.[18,19]

Knowledge of long-term side effects of HPLT is sparse due to the limited number of studies. Although PBM might improve survival of head and neck cancer patients treated with chemoradiotherapy,[20] whether PBM might enhance or potentially interfere with cancer therapy remains to be investigated.[21,22]

In addition, the laser device was used in defocused mode: It enables the irradiation of areas first affected by lesions and then of areas with symptoms that are not yet clearly obvious clinically. The treatment by HPLT should mitigate the pathogenetic processes of these initial injuries, and it should allow early clinical remission. The patient off HPLT therapy presents a high risk of lesion progression, with a generalized worsening of OM clinical features, which was also found in the observational study by Ribeiro *et al*[23]: In a cohort of 105 patients, the number of patients with severe OM increased and peaked at the second and eighth week after starting chemotherapy.

Various factors may have contributed to the healing and improvement of oral functional abilities, including correct oral hygiene, absence of other systemic diseases,[24–27] supportive care with Mycostatin® (an antifungal drug) and Vea Oris® (a complex of vitamin E acetate), and psychological support from the family and medical staff.

The decrease in pain perception can be attributed to the characteristics of the laser technology, which specifically inhibits the nociceptive signal from the peripheral nerves, blocking the painful stimulus.[28,29] That pain perception could be a contributing factor to a faster recovery due to a decrease in the levels of stress cannot be excluded. Also of note is that the VAS is purely subjective and the analgesic effect of laser therapy might be underestimated: When the patient began to report a decrease in pain, the medical staff proceeded to decrease the dose of opioid drugs. There may not be a noticeable difference between the VAS before and after the HPLT as the operator who recorded the VAS score adhered to the child's reporting verbatim. This event can have two interrelated explanations: The perception of pain at the beginning of the therapy could be underestimated thanks to the administration of morphine which made bearable the discomfort caused by OM; similarly, its reduction or suspension could cause the child to continue to feel the pain caused by OM, regardless of the laser treatment.

In the majority of patients, the painful symptom before HPLT was most frequently triggered by chewing (93%) followed by speaking (79%) and swallowing (64%), indicating the location of the most painful ulcerative lesions. During the act of chewing, cheeks and lateral sides of the tongue are the areas most subjected to compression and friction.

Concerning healing induced by HPLT, in the present study all areas of the oral cavity presented with ulcerations and/or erythema. The most affected areas were the right cheek, the left cheek, and the oral floor, which are nonkeratinized areas. Here, afterlaser therapy, the

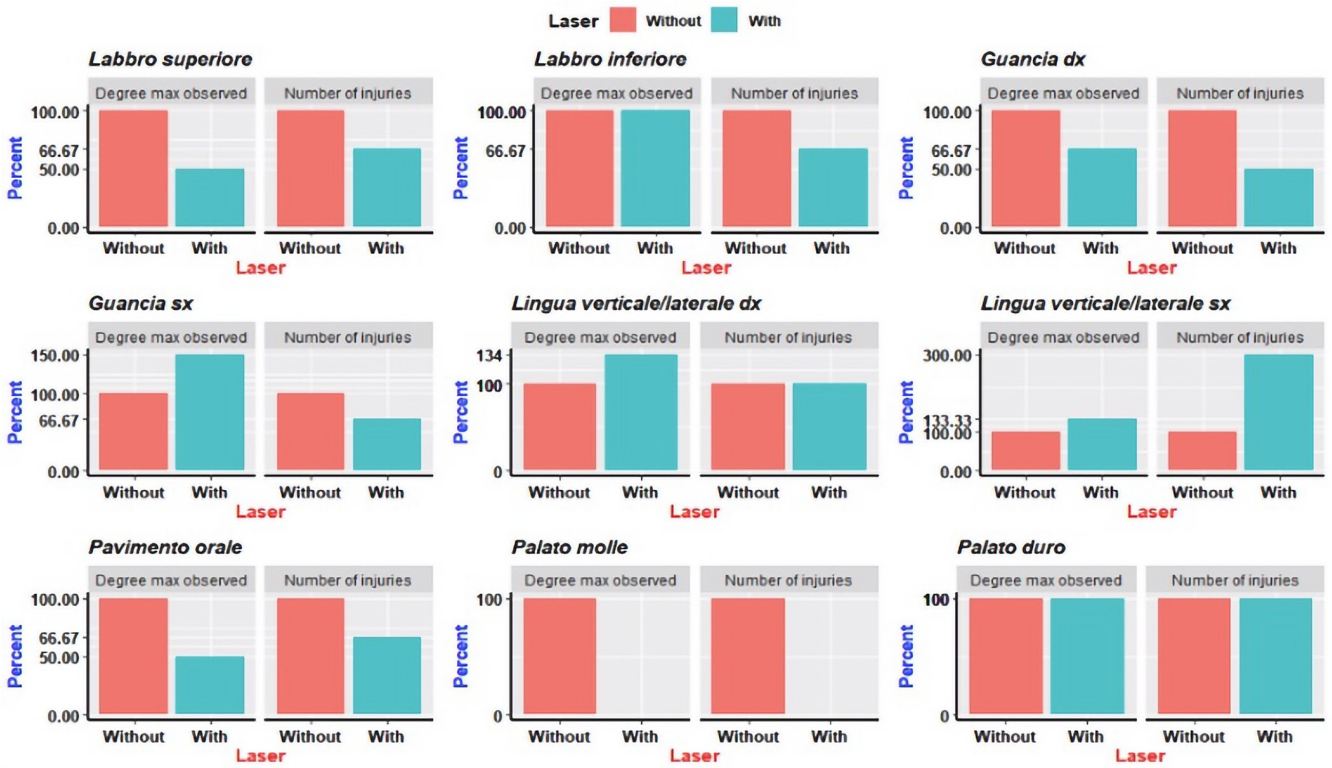

FIGURE 2 Percentage of the maximum degree observed and percentage of the number of ulcerations before (without) and after (with) laser therapy.

number of lesions and the maximum degree of ulceration clearly decreased. On the left cheek, despite the reduction in the number of lesions, the maximum degree of ulceration, however, increased, similar to that on both sides of the tongue. This may be because some patients presented with more severe immunosuppression which results in slower wound healing. The sides of the tongue are especially more prone to trauma and rubbing against the teeth, leading to progressive worsening of unhealed lesions. Furthermore, the difference in the severity of these areas might be attributed to the small sample size. Similarly, the severity of the erythema also reduced, although slightly less evident and not in all areas. The overall number of injuries per patient after treatment decreased by around 60%, falling from an average number of seven lesions to three ($p = .008$). Therefore, it can be affirmed that HPLT played an active role in the healing process of OM, as described in previous studies,[12,13] since it accelerates the normal physiological time of 2–3 weeks.[30] In the multicenter RCT conducted by Gobbo et al.,[13] patients off laser therapy presented more severe OM than patients on laser therapy (28% vs 6.1%).

There were additional benefits associated with HPLT. The need for parenteral nutrition and opioid drugs also decreased. As ulcerative lesions heal, the child is able to eat independently again, thereby boosting appetite and consequently improving one's nutritional and immune status and general psychophysical well-being.[31] The analgesic effect of the laser reduces the need for morphine to relieve OM pain. This observation could be subject to bias, because the administration of opioid drugs is standard for patients who have undergone HSCT,[32] since the pain is caused more by the extremely aggressive cytotoxic effects due to the pre-HSCT conditioning regimen than by OM. HPLT also results in a consistent analgesic effect, supported by the observed reduction in VAS values after treatment. Elting et al.[33] found that patients treated with radiation therapy or chemotherapy and that presented OM led to a cost increase in the range of 3700–30 000 US dollars. Another study by Elting et al.[34] found the cost of hospitalization increasing up to 6000 US dollars. As OM is one of the most common side effects of chemotherapy and radiation therapy used to treat head and neck malignancies, HPLT may also be helpful in decreasing the costs of hospitalization in both the public and private health care sectors.

Finally, especially in children, another important point in favor of laser treatment is its easy compliance when compared to rinsing. It is not always easy to convince very young patients on the proper use of an oral rinse, particularly if they need to keep it in the mouth for 1 min or more. Our study agrees with the literature not finding any sort of compliance issue when applying laser therapy to young patients.[35,36]

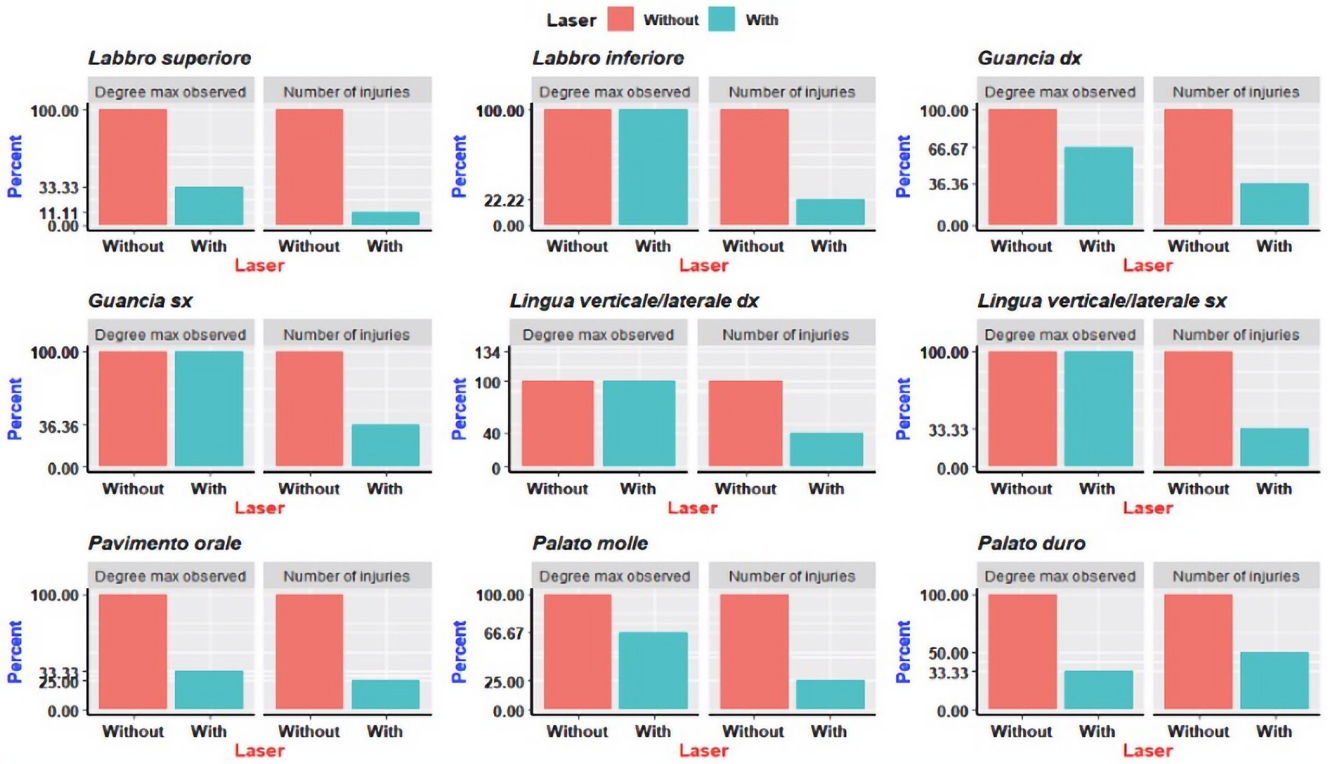

FIGURE 3 Percentage of the maximum degree observed and percentage of the number of erythematous lesions before (without) and after (with) laser therapy.

FIGURE 4 Evolution of OM in a grade 2 patient (Days 1, 4, and 8).

This, together with its proven results, makes it a safe and easy-to-administer treatment.

Further studies are needed, especially RCT and with a larger cohort of patients, to verify the potential preventive effect and to establish standard parameters, in order to obtain the maximum result in terms of prevention and treatment. Furthermore, it would be interesting to compare HPLT with LLLT and to evaluate which of the two is the most effective methodology, since there is only one study in the literature carried out on an animal model that proves the greater efficacy of HPLT compared with LLLT.[37]

AUTHOR CONTRIBUTIONS

Ludovichetti FS: Conceptualization, methodology, writing final version of the manusctipt and formal analysis. Costa G: Methodology and original draft preparation and investigation. Signoriello AG: Methodology and original draft preparation. Stellini E: Supervision and conceptualization, validation. Zerman N: Visualization. Biffi A:

Conceptualization, Supervision. Mazzoleni S: Supervision, validation.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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