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RESEARCH ARTICLE

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Multicenter randomized, double-blind controlled trial to evaluate the efficacy of laser therapy for the treatment of severe oral mucositis induced by chemotherapy in children: laMPO RCT

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Abstract

Objectives: To demonstrate the efficacy of laser photobiomodulation (PBM) compared to that of placebo on severe oral mucositis (OM) in pediatric oncology patients. The primary objective was

Abbreviations: AIEOP, Italian Pediatric Hematology Oncology Association; CT, chemotherapy; MASCC/ISOO, Multinational Association of Supportive Care in Cancer/International Association of Oral Oncology; OM, oral mucositis; PBM, photobiomodulation; WHO, World Health Organization

the reduction of OM grade (World Health Organization [WHO] scale) 7 days after starting PBM. Secondary objectives were reduction of pain, analgesic consumption, and incidence of side effects.

Methods: One hundred and one children with WHO grade > 2 chemotherapy-induced OM were enrolled in eight Italian hospitals. Patients were randomized to either PBM or sham treatment for four consecutive days (days +1 to +4). On days +4, +7, and +11, OM grade, pain (following a 0–10 numeric pain rating scale, NRS) and need for analgesics were evaluated by an operator blinded to treatment.

Results: Fifty-one patients were allocated to the PBM group, and 50 were allocated to the sham group. In total, 93.7% of PBM patients and 72% of sham patients had OM grade < 3 WHO on day +7 ($P = 0.01$). A significant reduction of pain was registered on day +7 in the PBM versus sham group (NRS 1 [0–3] vs. 2.5 [1–5], $P < 0.006$). Reduced use of analgesics was reported in the PBM group, although it was not statistically significant. No significant adverse events attributable to treatment were recorded.

Conclusions: PBM is a safe, feasible, and effective treatment for children affected by chemotherapy-induced OM, as it accelerates mucosal recovery and reduces pain.

KEYWORDS

clinical trial, laser, mucositis, pediatric hemato-oncology, supportive care

1 | INTRODUCTION

Oncology patients undergoing cancer treatment are prone to a series of toxicities, of which oral mucositis (OM) is one of the most frequent and debilitating. OM can occur after standard and high-dose chemotherapy[1] (CT) and is commonly encountered in patients receiving hematopoietic stem cell transplantation.[2] Children and adolescents are even more susceptible to OM due to the rapidity of cellular mitosis and to specific intensive CT regimens for pediatric cancer,[3] with incidence varying between 40% and 81% of cases.[4]

The general experience in oncology patients is that OM resolves in conjunction with the recovery of blood counts, but pain and feeding difficulties due to severe OM frequently lead to hospitalization for pain control, fluid replacement, and nutritional support.[5]

At present, no standard treatment of OM is defined, and aggressive pain management, mucosal coating agents, and local antiseptics are employed. In recent years, the role of laser therapy, which has recently been renamed photobiomodulation (PBM),[6] has been investigated and this approach is now a recommended option by Multinational Association of Supportive Care in Cancer/International Association of Oral Oncology (MASCC/ISOO) guidelines for patients receiving high-dose chemotherapy or transplants.[7,8]

Opinions regarding the mechanism of action are controversial, but recent studies have demonstrated a reduction of oxidative stress and a direct activation of intracellular chromophores following PBM, thereby triggering an increased proliferation of endothelial cells, keratinocytes, fibroblasts, osteoblasts, and pericytes, with biomodulatory and analgesic effects.[9]

One controlled randomized study on a small number of patients has been published on the use of PBM in children affected by OM,[10] which supported its effectiveness.

We conducted a preliminary investigation of laser therapy in children treated in a single institution after CT and, in some cases, total-body irradiation, where relevant improvement of pain and grade of mucositis was observed.[11] Then, we organized a multicenter randomized controlled trial to better define the role of PBM in children affected by severe OM.

The choice of the employed PBM protocol was derived from preclinical and clinical studies of PBM routinely used for the management of anticancer therapy side effects.[12–15] According to the literature, wavelengths between 600 nm and 1,000 nm exert analgesic and anti-inflammatory effects.[16–18] A wavelength of 660 nm is effective in reducing pain and in healing OM lesions while clinical and preclinical studies have demonstrated that the use of a 970 nm wavelength combined with high power and energy densities is associated with better healing and reduced inflammation. In the present study, the two combined wavelengths were used, aimed at maximizing their beneficial effects.

2 | MATERIALS AND METHODS

This study was a randomized, prospective, multicenter, double-blind trial investigating the effectiveness of laser therapy (PBM) against placebo (sham therapy).

The study was supported by the Italian pediatric hemato-oncology association (AIEOP) supportive care working group and designed and coordinated by the pediatric hemato-oncology unit of the Institute for Maternal and Child Health IRCCS Burlo Garofolo, Trieste, together with the Oral Medicine and Pathology Group (Dental Clinic, University of Trieste). The study involved eight Italian pediatric hemato-oncology centers affiliated with AIEOP (Trieste, Brescia, Bologna, Cagliari, Padova, Parma, Pavia, Torino) and was performed in

collaboration with stomatologists of each center. The study protocol obtained ethical approval by the Independent Bioethics Committee of the coordinating center on December 3, 2012 (Approval Number: CE/V 151) and, subsequently, by the ethics committees of each participating center. Written informed consent was obtained from each child's parent or legal surrogate.

The trial was registered at Clinicaltrials.gov (NCT02762019).

2.1 | Population

Children of Caucasian origin were included in the study if they met the following inclusion criteria: age 3–18 years; severe OM of World Health Organization (WHO) scale[19] grade 3 or 4; antiblastic CT in the previous three weeks; willingness to undergo treatment for 4 consecutive days and to return for evaluation 7 and 11 days after enrolment.

Exclusion criteria were the following: previous treatment with PBM for OM; presence of dysplastic oral lesions; reduction of mouth opening (< 1 cm); localized head and/or neck radiation treatment in the previous four weeks; use of keratinocyte growth factor; previous enrollment in the study.

The recruitment of potential participants who met the inclusion criteria was performed during routine or urgent outpatient evaluation or among inpatients admitted for any reason.

2.2 | Procedures

Randomization was centralized and coordinated by the Clinical Epidemiology Unit of the coordinating center using a computer-based method. The randomization list was blocked and stratified by grade of OM (grade 3 and grade 4) and by center. The allocation concealment was guaranteed through the use of two sets of closed, opaque envelopes (one for grade 3 and one for grade 4 OM), consecutively numbered. Based on the expected recruitment capacity, a certain number of closed envelopes were sent to each center. As described below, in each center, the enrolling stomatologist opened the envelope of the corresponding OM grade with the lowest number available and started the treatment indicated.

Operators who performed the treatment were not blinded to the allocation group. The blindness of enrolled subjects was guaranteed by the sham treatment, which was indistinguishable from PBM. Outcome evaluators were also blinded to the study group.

The procedure was performed as follows: On day +1, an initial stomatologist evaluated and enrolled the children in the study after collecting clinical and laboratory data, filling out a validated questionnaire to evaluate OM grade, and opening the envelope of the corresponding OM grade with the lowest number available. The treatment was then started as indicated in the envelope and continued by the same stomatologist on day +2, +3 and +4. Starting from day +4, and subsequently, On days +7 and +11, another stomatologist or a trained onco-hematologic pediatrician, blinded to the patient's allocation, evaluated the outcomes. The questionnaire filled out by the first stomatologist, containing the information on the group allocation, was stored in a closed envelope and was not accessible to the outcome evaluators. Consequently, both enrolled subjects and outcome evaluators were blinded to the treatment performed.

The severity of OM was evaluated according to the WHO scale,[19] graded 0–4, where grade 3 indicates an inability to consume solids and grade 4 corresponds to complete absence of solid or liquid intake by mouth.[5]

Clinical and laboratory data, including blood counts, were collected on days +1, +4, +7, and +11. Admittance due to isolated OM was registered. Buccal swabs for microbiological culture were performed following clinical suspicion for bacterial infection, candidiasis, and herpes simplex virus infection.

2.3 | Treatment

All subjects who met the inclusion/exclusion criteria were randomized to one of the two study arms.

PBM (experimental arm): Patients were treated with a diode laser device (class IV, K-Laser Cube series, Eltech K-Laser, Via Castagnole 20/H, Treviso, Italy) over 4 consecutive days, with the following protocol: 660 and 970 nm-combined wavelengths, 3.2 W peak power, 320 mW/cm^2 irradiance, 36.8 J/cm^2 fluence, and 50% frequency. Laser application was performed over the entire oral cavity, both in ulcerated and erythematous areas and in areas free of clinical signs. The tissue was irradiated through a rotatory motion over the entire oral cavity (defocused, non-contact modality). The spot size was 1 cm^2. Nine areas in the oral cavity were irradiated maintaining the tip orthogonally concerning the tissue: upper lip, lower lip, right side of the tongue, left side of the tongue, right cheek, left cheek, hard palate, soft palate, and floor of the mouth. Each of the nine areas received 8 J over 25 sec (total session time: 3 min, 45 sec); the protocol was performed twice consecutively with 2–3 min intervals between the two sessions (whole treatment time: 7 min, 30 sec) for 4 consecutive days.

Sham treatment: Patients received the exact repetition of the treatment modality but without any laser emission: although switched off, the laser devices emitted the same sound and showed the same screen parameters when working in the effective PBM modality.

Patients, operators, and other people present in the room during the protocol application wore protective goggles. Regardless of the allocation group, patients enrolled in the study received the standard topical/analgesic treatments for OM used in the enrolling hospital, except for keratinocyte growth factors (exclusion criteria).

2.4 | Outcomes

The primary study outcome was the evaluation of OM grade on day +7, as evaluated with the WHO scale.

The secondary outcomes were OM grade on day +4 and day +11, reduction of pain evaluated with the validated 0–10 NRS scale (Tomlinson et al. 2007), reduction in the use of analgesics, and presence of adverse events.

2.5 | Sample size

The study was designed as a superiority trial. Given the results of the previously published RCT in children,[10] we estimated a priori that the enrolment of 100 subjects (50 in each group) would provide us a power of 80% to detect a between-group difference of 30% in the primary study outcome (i.e., a 70% success rate in the laser treatment group vs. 40% in the sham treatment group) with a two-sided type I error of 0.05.

2.6 | Statistical analysis

Continuous variables are reported as median and interquartile range (IQR) and categorical variables as proportions and percentages. For categorical outcomes, between group differences were evaluated using the chi-squared test or Fisher exact test when appropriate and for continuous outcomes using the non-parametric Mann–Whitney U test, as the data were not normally distributed. Analyses were performed with SPSS software (version 21.0) according to the intention-to-treat principle. Statistically significant differences were determined by a *P*-value lower than 0.05.

3 | RESULTS

3.1 | Population

Participants were recruited between September 2013 and October 2015. A total of 102 children with severe OM were admitted at the eight pediatric hematology oncology units during the study period, of whom 101 were eligible and were then randomized (in one case, the parents declined to participate). The two groups were thus 51 in the laser treatment group and 50 in the sham group. There were no deviations from the random allocation. In the PBM group, one child died before day +7, one did not return for the scheduled follow up visits on days +7 and +11 and one did not return for the follow up visit on day +11. The evaluation of the primary study outcome was performed in 49 and 50 children in the PBM and control group (Fig. 1).

The baseline socio-demographic and clinical characteristics of the two groups were similar (Table 1): The basic oncological diseases were equally represented in the two groups, and white blood cells (WBC) and neutrophil counts were not different in the groups on days +1, +4, +7, and +11. The buccal swab was performed in 43.8 and 49% of the patients in the treatment and control groups, with non-significantly different low positivity rates for candida (2%) and HSV (2 and 4%) in both groups. The admittance rate due to isolated OM was not different in the two groups.

The study results are shown in Table 2.

3.2 | Outcomes

3.2.1 | Primary outcome

A statistically significant difference in OM grade was observed between the study groups on day +7.

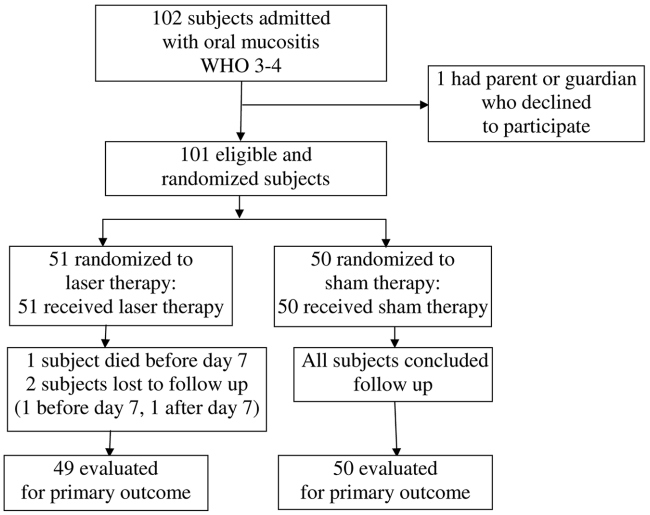

FIGURE 1 Study flow chart

In the PBM group, one subject (2.0%) had severe OM of grade 4 and two subjects (4.1%) had grade 3 versus eight (16.0%) and six subjects (12.0%) in the sham group ($P < 0.02$). Consequently, 6.1% of subjects in the PBM group versus 28% in sham group had an OM grade of 3 or 4 on day +7 ($P < 0.007$).

3.2.2 | Secondary outcomes

No statistically significant differences in OM grade and self-reported pain were observed on day +4 while on day +7, a reduction in the self-reported pain score was statistically significant in the PBM group ($P < 0.007$), although the use of analgesics did not vary significantly.

A statistically significant difference between the two groups concerning OM grade and self-reported pain persisted through day +11: There were no subjects with grade 4 OM and one subject with grade 3 (2.1%) in the PBM group versus five (10%) and five (10%), respectively, in the sham group ($P < 0.03$). Therefore, 2.1 and 20% of subjects, respectively, in the PBM and sham group had an OM grade 3 or 4 on day +11 ($P < 0.009$). Correspondingly, the self-reported pain score was also significantly reduced in the PBM group ($P < 0.02$).

None of the participants reported clinically evident side effects. Figure 2 shows the percentage of subjects with severe OM on days 1, 4, 7, and 11 in both groups.

4 | DISCUSSION

The primary aim of the study evaluated the reduction of OM at 7 days from the beginning of PBM. The timing was chosen to allow for comparisons with previous findings from the literature[10] and as a reasonable time to consider and evaluate the clinical benefit from treatment, as OM is expected to heal in 2–3 weeks.[17] In both groups, OM tended to resolve in most patients, but a consistent difference between study groups was evident on day +7 and persisted until day +11, with a non-negligible portion of patients still suffering from severe OM in the control arm. On day +7, only approximately 6% of patients in the PBM

TABLE 1 Baseline socio-demographic and clinical characteristics of the two study groups

	Laser therapy n = 51	Sham therapy, n = 50	*P*
Age, median (IQR)	11.9 (7.0–14.7)	11.7 (8.0–14.8)	0.67
Male sex, number (%)	24 (47%)	30 (60%)	0.19
Grade of mucositis, number (%)			
Grade 3	30 (59%)	27 (54%)	0.63
Grade 4	21 (41%)	23 (46%)	
Type of oncologic disease, number (%)			
Acute lymphoblastic leukemia	20 (39%)	21 (42%)	
Bone marrow transplantation	13 (26%)	13 (26%)	
Lymphoma	14 (28%)	9 (18%)	0.52
Acute myeloid leukemia	2 (3.9%)	2 (4.0%)	
Other solid tumors	2 (3.9%)	5 (10%)	
Total body irradiation, number (%)	5 (9.8%)	8 (16%)	0.06
Neutrophil count, median (IQR)	40.0 (0.0–201.0)	67.5 (0.0–300.0)	0.65
Buccal swab, number (%)			
Carried out	21 (44%)	24 (49%)	
Positive for candida	1 (1.9%)	1 (2%)	0.61
Positive for HSV	2 (3.9%)	1 (2%)	
Presence of mouth or throat symptoms, number (%)	51 (100%)	50 (100%)	-
Relevance of mouth or throat symptoms, number (%)			
None	0	0	
Moderate	5 (9.8%)	5 (10%)	0.61
Severe	20 (39%)	15 (30%)	
Very severe	26 (51%)	30 (60%)	
Pain score, median (IQR)	8.0 (7.0–8.5)	8.0 (7.0–9.0)	0.47
Presence of pain (pain score > 4), number (%)	48 (94%)	45 (90%)	0.44
Duration of pain in days before enrollment, median (IQR)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.36
Ongoing treatments, number (%)			
Topical mucosal protectants	30 (59%)	34 (68%)	0.34
Topical analgesics	11 (22%)	9 (18%)	0.65
Systemic antimycotics	33 (65%)	38 (76%)	0.21
Systemic antibiotics	39 (77%)	37 (74%)	0.77
Systemic antivirals	31 (61%)	26 (52%)	0.37
Oral analgesics	12 (24%)	11 (22%)	0.86
Parenteral analgesics	33 (65%)	38 (76%)	0.21
Parenteral nutrition	26 (51%)	28 (56%)	0.61

group experienced severe OM versus 28% in the sham group and a 27% increase in patients with OM grade < 3 was observed in the PBM group. On day 11, only 2.1% of patients in the PBM group had grade 3 mucositis (and no patient had grade 4), whereas 20% of patients in the sham group still had grade 3 (10%) or 4 (10%) mucositis.

Self-reported pain was significantly reduced in our study: Eliminating pain is of major interest when treating severe OM and is even more relevant in children for whom pain is usually managed with analgesics and narcotics that have side effects; of note, Damani and colleagues reported that codeine and high doses of NSAIDs are among the most commonly prescribed drugs in cancer pediatrics.[20] Although widely employed, opioid analgesics cannot always adequately palliate severe OM pain and may lead to adjunctive problems, such as dry mouth, constipation, and impaired conscience. Treatment with PBM has high tolerability and compliance, which[21] was confirmed in our study. There were no difficulties in administering PBM to children and young adolescents, nor any side effects or adverse reactions documented in any patient. Most likely, the acceptance of treatment in young children was eased by dividing the procedure into two shorter sessions.

The reduction of analgesic consumption was not statistically significant in our study though the intake of analgesics was not thoroughly investigated regarding substances, doses, length, or modality of administration, as the sample size did not allow for adding statistically significant elements to the subject. Khun and colleagues[10] evaluated the

TABLE 2 Study results

	Laser therapy (n = 51)	Sham therapy (n = 50)	*P*
OM grade at day +4, number (%)			
Grade 4 Grade 3 Grade < 3	7 (14%) 16 (31%) 28 (55%)	12 (24%) 19 (38%) 19 (38%)	0.19
OM grade at day +7, number (%)	(n = 49)		
Grade 4 Grade 3 Grade < 3	1 (2.0%) 2 (4.1%) 46 (94%)	8 (16%) 6 (12%) 36 (72%)	0.01
OM grade at day +11, number (%)	(n = 49)		
Grade 4 Grade 3 Grade < 3	0 1 (2.1%) 47 (98%)	5 (10%) 5 (10%) 40 (80%)	0.02
Self-reported pain score at day +4, median (IQR)	4 (2–6)	5 (3–7)	0.07
Self-reported pain score at day +7, median (IQR)	1 (0–3)	2.5 (1–5)	0.006
Self-reported pain score at day +11, median (IQR)	0 (0–1)	1 (0–3)	0.01
Analgesic use at day +7, number (%)			
Parenteral Oral Topical Combined No use	15 (31%) 5 (10%) 0 4 (8.2%) 25 (51%)	18 (36%) 8 (16%) 0 5 (10%) 19 (38%)	0.60
Neutrophil count at day +4, median (IQR)	100 (0–800)	104 (0–580)	0.98
Neutrophil count at day +7, median (IQR)	770 (100–1938)	917 (50–2100)	0.79
Neutrophil count at day +11, median (IQR)	1456 (503–4158)	1380 (275–2875)	0.32
Admission due to isolated OM	(n = 48) 6 / 48 (13%)	8 / 50 (16%)	0.62

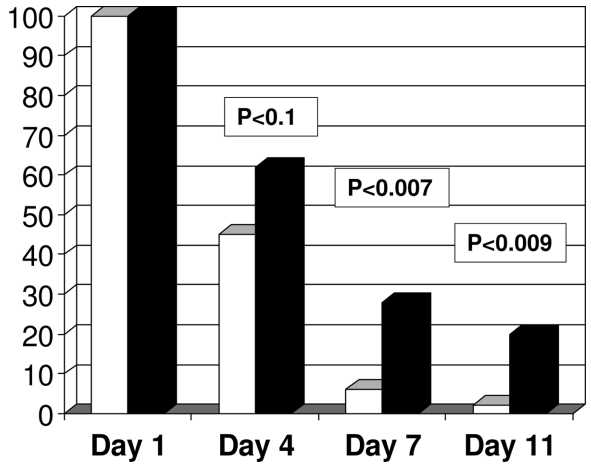

FIGURE 2 Percentage of patients with OM grade 3–4 in the PBM group (white columns) and sham group (black columns) on days +1, +4, +7, and +11

efficacy of laser therapy in a population of children with cancer including 21 patients, with no stratification between OM grades, with promising results. The present study investigated the use of PBM in a similar pediatric population but in a multicenter setting and a broader sample population. The study was designed to select only severe cases of OM (grades 3–4) to stress the clinical efficacy of PBM regarding the restoration of feeding capacity, as grade 2 is generally associated with a maintained nutritional condition and appropriate food intake. In this perspective, the reduction of OM grade due to PBM may result in concrete clinical and quality of life improvement as the restoration of feeding capacity is perceived as a strong indicator of patient well-being, and malnutrition increases the risk of toxicities and infections but also decreases response and compliance to treatment of patients with cancer.[22]

There are some points to note: First, the remarkably high rate of participation (101 of 102 eligible patients), which might be explained by the fact that, in spite of the presence of highly debilitating and worrisome symptoms perceived by patients and families, no effective treatments are available yet for OM. Moreover, laser treatment is appealing due to its non-invasive nature, the absence of expected side effects, and previous knowledge of the use of modern technology to support health.

In the samples examined, we registered some dropouts, specifically two on day +7 and one on day +11. One drop out occurred due to death of the patient caused by worsening of the neoplastic condition while the two others were due to logistical reasons: The patients lived far from the hospital and decided not to return for follow up on day +11, and the OM had already healed.

The WBC and neutrophil counts were monitored over time as previous studies have demonstrated that blood counts, especially absolute

neutrophil count, are associated with OM onset and severity.[23] In our study, the efficacy of PBM was not influenced or mediated by alterations in neutrophil counts, as these did not differ in the two groups.

Some limitations are evident in the present study. The majority of subjects enrolled (data not registered) were hospitalized due to complications secondary to chemotherapy, mainly febrile neutropenia, as shown by the high rate of administration of parenteral analgesics, parenteral nutrition and systemic antibiotics (Table 1 . Specific admittance due to OM was registered in 12.5 and 16% of patients in the PBM and sham group, and the difference was not statistically significant ($P < 0.63$); in such cases, admittance was generally deemed necessary at the onset of severe symptoms, which indicated recruitment to the study. In general, the study was not adequately designed to demonstrate a possible role for PBM in preventing admittance or shortening admittance duration.

We have not included the evaluation of oral health status in our study design. At present, many studies report that the maintenance of good oral health status reduces the severity of OM but also helps its healing.[24] Other studies have reported that a low decayed, missed, filled teeth index, plaque index, and bleeding on probing index are associated with less severe OM.[25] The MASCC/ISOO guidelines recommend the use of a standardized oral care protocol, including brushing with a soft toothbrush, flossing, and the use of non-medicated rinses (e.g., saline or sodium bicarbonate rinses).[26]

Finally, the possible role of PBM in the prevention of OM has not been investigated in the present study. Some literature has reported an effective role of laser therapy in reducing the incidence and severity of OM when performed before the onset of symptoms but no multicenter setting has been investigated.[27] This aspect should be studied in the future.

At present, our study confirms that PBM is safe, feasible, and effective and should be introduced as the standard therapy for pediatric patients affected by OM.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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