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ORIGINAL ARTICLE

# Low-level laser therapy for treatment of chemotherapy-induced oral mucositis in childhood: a randomized double-blind controlled study

**Francesca Amadori[1] · Elena Bardellini[1] · Giulio Conti[2] · Nicola Pedrini[1] · Richard Fabian Schumacher[3] · Alessandra Majorana[1]**

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**Abstract** The aim of this study was to verify if low-level laser therapy could be useful to reduce chemotherapy-related oral mucositis grading and pain in childhood undergoing chemotherapy. A randomized double-blind clinical trial was carried out. Patients from 3 to 18 years of age undergoing cancer therapy and presenting OM grade 2 or more were eligible for this study. Patients were randomly divided in two groups: group A received laser therapy from the day of OM diagnosis and other 3 consecutive days (830 nm wavelength, power 150 mW, spot size 1 $cm^2$, 30 s per $cm^2$, energy density 4.5 $J/cm^2$); group B received sham therapy (placebo) with the same timing. Two blind clinicians performed OM scoring and pain evaluation at day 1 (immediately before the beginning of laser treatment—T0), day 4 (after finishing laser therapy cycle—T1) and at day 7 (T2) as follow-up. A total of 123 patients were included in the study. Group A was composed of 62 children while group B is 61; in both groups, there was a progressive reduction in grade of OM, and at day 7, not every mucosal lesion disappeared. The difference in the decline of OM grading between the two groups resulted not statistically significant ($p = 0.07$). A statistically significant difference in pain reduction between two groups both at T1 and at T2 ($p < 0.005$) was observed. This study demonstrated the efficacy of LLLT in reducing pain due to chemotherapy-induced oral mucositis in children, while no significant benefit was noted in reducing OM grade.

**Keywords** LLLT · Children · Cancer · Mucositis

✉ Francesca Amadori
francesca.amadori@unibs.it

[1] Department of Medical and Surgical Specialities, Radiological Sciences and Public Health, Dental School, University of Brescia, P.le Spedali Civili 1, 25125 Brescia, Italy

[2] Department of Oral Surgery, University of Milan, IRCCS Ca' Granda, Ospedale Maggiore, Milan, Italy

[3] Pediatric Clinic-Department of Transplantation, AO Spedali Civili di Brescia-Italy, Brescia, Italy

## Introduction

Although the effectiveness of anti-cancer treatment in children has continued to improve over the past decades, collateral damage to the head and neck structures are frequently reported [1].

Oral mucositis (OM) is a common side effect of chemotherapy, especially in the case of haematopoietic stem cell transplantation (HSCT) due to the high dose of myeloablative chemotherapy used for conditioning regimens with an incidence in the paediatric cancer population of 50 to 80 % [2, 3].

OM reduces the ability to consume adequate nutrients and limits food intake, due to pain and discomfort when patients swallow or chew. Therefore, it increases the risk of malnutrition and impairs the quality of life.

In addition, ulcers in immunocompromised children can be the gateway for microorganisms, which can cause local and systemic infections [4].

Current management of OM might comprise growth factors and cytokines, anti-inflammatory agents, anaesthetics, analgesics, antimicrobial and coating agents, cryotherapy and mucosal protectants, such as zinc [5, 6]. In addition, oral care protocols are suggested to be used to prevent oral mucositis in all age groups and across all cancer treatment modalities. Among the current topical therapies, 2 % morphine mouthwash and 0.5 % doxepin mouthwash may be effective to treat pain due to OM, while sucralfate mouthwash and chlorexidine mouthwash are not recommended to treat chemotherapy-

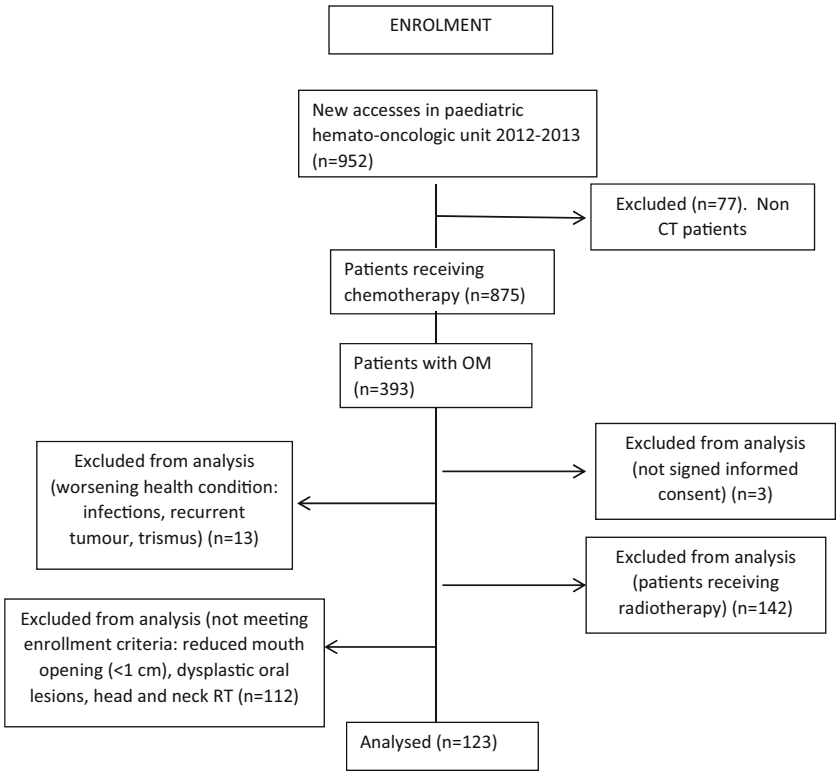


**Fig. 1** Diagram demonstrating the flow of participants during enrolment stage

induced OM [5]. In children, apart from oral care protocols, only weak recommendations are available to prevent and to reduce the severity of cancer related OM; in particular, the literature suggests cryotherapy, keratinocyte growth factor (KGF) and low-level light therapy to treat oral mucositis [7].

The last update of the guidelines for the management of mucositis secondary to cancer therapy recommends the use of low-level laser therapy (LLLT) for the prevention of OM in patients receiving HSCT conditioning high-dose chemotherapy, to reduce OM severity and pain [5]. In addition, recent studies recommend including photo medicine using LLLT as a possible way of prophylactic and therapeutic intervention in the management protocol of OM in adult cancer patients, in order to prevent and reduce duration and severity of OM and associated pain [8]. Guidelines for photobiomodulation (PBM) are still not possible in cancer children, but a recent study ruled on a children population undergoing chemotherapy states that laser therapy, even if conducted through daily section, was fast, well tolerated, feasible and affordable [9, 10]. In addition, all the papers focusing on LLLT in cancer children reported a positive feedback from patients and caregivers [4, 11]. On the other hand, since LLLT should be executed with full oral care protocols and incorporated into the routines of the children, it requests an intense participation of patients' caregivers and a multidisciplinary staff including dentists and oral hygienists [12].

LLLT seems to have three main effects: analgesic, anti-inflammatory and wound-healing properties [13, 14].

The mechanism through which the laser interacts with biological tissues seems to modulate various metabolic processes, by conversion of the laser light energy input into energy useful to cells [15]. Visible laser is absorbed by primary

**Table 1** Demographic characteristics of the patients

| | Group A ($n = 62$) | Group B ($n = 61$) | $p$ value |
|---|---|---|---|
| Male–female | 43.5 % ($n = 27$) | 47.5 % ($n = 29$) | 0.65 |
| Age | 9.8 ± 3.25 | 9.27 ± 3.85 | 0.41 |
| Disease | | | |
| Leukemia and lymphoma | 38 | 34 | |
| Solid tumours | 6 | 7 | |
| HSCT | 18 | 20 | |

Mean ± SD; test: $t$ Student, $p$ value < 0.05

*HSCT* hemopoietic stem cell transplantation

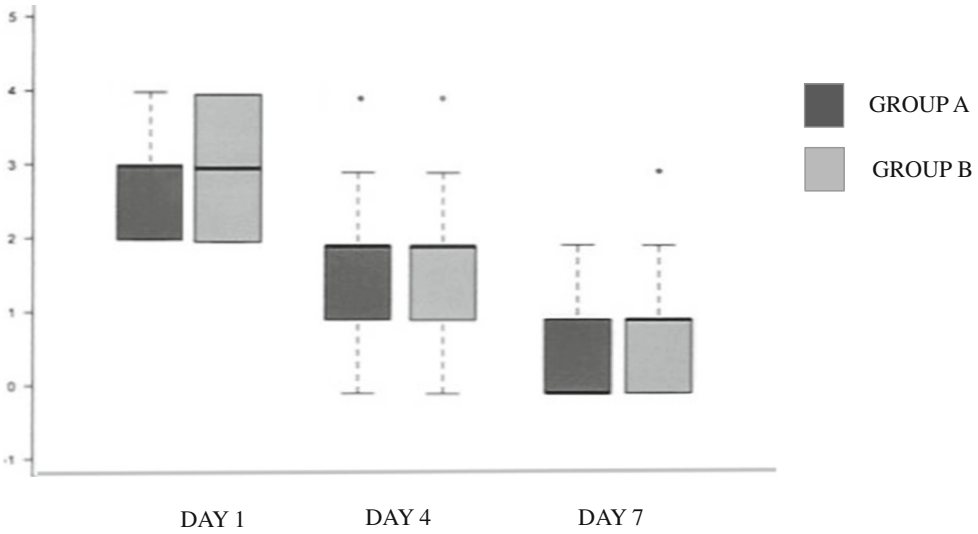


**Fig. 2** Assessment of OM grade on day 1 (T0), day 4 (T1) and day 7 (T2) in group A and group B

photoacceptors (chromophores) in the mitochondria respiratory chain with an increase in ATP production, cellular proliferation and protein synthesis, aiding tissue repair, through an increased vascularity and re-epithelialization. In addition, the anti-inflammatory and analgesic effect can be linked to the peripheral endogenous opioid production, a decrease in pro-inflammatory cytokines, a decrease in free oxygen radicals and to the alterations in nerve impulse conduction [16–18].

Although in recent years, several papers have focused attention on the use of LLLT for chemotherapy-induced OM prevention and treatment in adults, at the best of our knowledge, there are very few papers examining the efficacy of this methodology in children undergoing chemotherapy, with contradictory results. Cruz et al. 2007 [4] found no evidence of benefit from the prophylactic use of LLLT in children undergoing chemotherapy with optimal dental care; on the contrary, Kuhn et al. 2009 [11] encouraged the use of laser treatment in children with chemotherapy-induced OM, as did Moraes et al. 2009 [19], who experimented OM healing through extra oral application of LLLT in children.

The aim of this study is to verify the efficacy of LLLT in reducing the severity and pain of chemotherapy-induced oral mucositis in childhood.

**Table 2** Results for decline in VAS at T0, T1 and T2

| | Group A (Laser treatment) | Group B (Sham therapy) | W (Wilcoxon test) | *p* value |
|---|---|---|---|---|
| T0 | 4 | 4 | 3805.5 | 0.90 |
| T1 | 1 | 2 | 3252 | 0.002 |
| T2 | 0 | 1 | 3160.5 | 0.0005 |

Medians, Wilcoxon rank sum test and *p* value. Test: Wilcoxon rank sum test, $p$ value $< 0.05$

## Methods

### Sample selection

This study was carried out from January 2012 to December 2013 at the Paediatric Dentistry Department and at the Paediatric Oncology Unit of Spedali Civili of Brescia (Italy). All children between 3 and 18 years of age receiving chemotherapy for haematological malignancies, solid tumours or HSCT and presenting OM grade 2 or greater were eligible for this study. Patients with reduced mouth opening <1 $cm^2$ not allowing the laser irradiation of soft tissues or with dysplastic oral lesions or undergoing head and neck radiation therapy in the previous 4 weeks were excluded from the study.

Patients were randomized into two groups by a computer code: group A was made up of children receiving laser therapy and group B of patients receiving sham therapy (placebo), i.e. the device was turned on but the hand piece did not work.

Laser therapy started on day 1 of the diagnosis of OM and continued for another 3 consecutive days (4 days in total). Laser therapy was dispensed during hospitalization; discharged patients continued laser therapy as outpatients, but no patient with OM >2 was discharged.

### Laser equipment

The laser instrument used for this trial was a portable and easy to handle diode laser (DioBeam 830, CMS Dental, Copenhagen, Denmark). The laser was applied by a trained dentist and irradiated in the sites of OM (buccal mucosa, lip mucosa, tongue, floor of mouth and soft palate), with 830 nm wavelength, power 150 mW, spot size 1 $cm^2$, 30 s per $cm^2$, energy density 4.5 $J/cm^2$.

Dentist, patients and caregivers wore appropriate protective eyewear, following international safety procedures.

### OM scoring

Oral mucositis scoring was carried out by the same two paediatric dentists blind to the randomized allocation, according to the Common Toxicity Criteria Scale of the WHO. Lesions were classified as grade 0 = none; grade 1 = soreness and erythema; grade 2 = erythema and ulcers without difficulties in swallowing solid food; grade 3 = ulcers requiring only a liquid diet and grade 4 = introduction of parental nutrition.

Oral examination and OM scoring were performed on day 1 (immediately before the beginning of laser treatment) (T0), day 4 (after finishing laser therapy cycle) (T1) and on day 7 (T2) as follow-up.

Dentists who applied the laser did not participate in the scoring of OM.

### Pain scoring

Pain was evaluated through the visual analogue scale (VAS) at the same time as OM scoring. In this system, 1 indicates no pain and 10 indicates severe pain; patients were asked to select a number from 1 to 10 on a ruler with drawn faces to express the intensity of their pain. Request of additional analgesia, that means the number of times that children required pharmacological support in addition to laser therapy, was also reported in the clinical charts.

### Statistical analysis

Statistical analysis was descriptive, including mean, standard deviation and percentiles for variables such as sex, age and localization.

To compare the two groups, we analysed the data on gender and disease as frequencies and percentages. Concordance or differences in the frequency distribution between the two groups were tested using the Student *t* test. A level of significance of 5 % was used and data were analysed using Stata® software for Mac. The differences in decline of OM and VAS score were analysed using the Wilcoxon rank sum test.

Estimating that there is a success percentage of 70 % on day 7 for the group treated by laser and 40 % for the control group, the minimum number of patients for the study, assuming alpha 0.05 and beta 0.20 (study power = 80 %), was calculated to be 100 (at least 50 per group).

### Ethical considerations

The study was approved by the Ethical Committee of the Spedali Civili of Brescia (IP =1532), and all patients and their caregivers were informed about the research and signed an informed consent.

## Results

A total of 123 patients were included in the study according to the enrolment criteria (Fig. 1). Group A (laser treatment) was composed of 62 children while group B (sham therapy) of 61. Demographic characteristics are resumed in Table 1.

### OM grading

Oral mucositis appeared at a mean of 5.9 days after the beginning of chemotherapy (range 4 to 8 days).

At T0, the median of OM grading was 3 for group A and 3 for group B ($p = 0.80$). On the 4th day (T1), OM grading median was 2 for group A and 2 for group B ($p = 0.65$); after 7 days (T2), OM grading median resulted 0 in group A and 1 in group B ($p = 0.07$). In both groups, there was a progressive reduction in the grade of OM, even if on day 7, not all mucosal lesions had disappeared. The difference in the decline of OM grading between the two groups at each interval resulted not statistically significant (Fig. 2).

### Pain evaluation

The medians of VAS at the three intervals and *p* values obtained by the Wilcoxon rank sum test are displayed in Table 2. VAS values at T1 and T2 were lower in the group A respect of group B in a statistically significant way ($p < 0.05$). During the study period, children treated with laser therapy required less additional analgesia (paracetamol, tramadol or morphine) with respect to those belonging to the sham protocol ($p < 0.05$).

## Discussion

With the advancement of technology, the use of laser has been considered in various areas of medicine and dentistry. Nowadays, the price of laser devices has considerably decreased, making the technology easily available [12].

In the last decade, many papers about the use of LLLT in the prevention and treatment of cancer therapy-induced mucositis have been published, even if there is a lack of exclusive paediatric studies. The results reported in previous studies are often discordant [20, 21]. Cruz et al. 2007 [4], in a paper focused on a paediatric population receiving chemotherapy or HSCT, found no benefit in the prevention or reduction of OM from the prophylactic use of LLLT when optimal dental care was provided. Similarly, Simoes et al. 2009 [16] did not find enough information to conclude that LLLT is beneficial for OM reduction. On the other hand, several papers regarding children or mixed population demonstrated that LLLT can be useful in cancer therapy-OM reduction and in the decreasing of OM related pain [11, 19, 22–25].

The results of the present trial in childhood partially confirm the findings of previous studies, both in adults and in children [22, 26–31]; the duration and the grading of OM was not actually significantly different in the group treated by laser vs sham therapy, but a statistically significant difference in pain reduction between the two groups was observed, both from VAS scale results and from request of additional analgesia. A decrease in pain should be attributed to the properties of the laser technology itself, which selectively inhibits the nociceptive signal arising from peripheral nerves, blocking the pain gate [32, 33].

The discrepancy between our findings and others reported in literature could be explained by the possibility of OM spontaneous healing in many cases without complications, especially if children undergoing cancer therapy are educated to strictly follow oral hygiene protocols, just as it was for patients of the present study. In addition, the negative result on the healing of mucositis could by be a consequence of the laser protocol chosen in this study; maybe a longer laser treatment would be more effective [4, 22].

The laser energy level used for this trial was based on several previous studies, as Migliorati et al. 2013; Bensadoun and Nair 2012 [8, 34] defined the energy density for laser therapeutic use at least 4 J/cm$^2$.

However, in literature, it is still not clear what specific extent in wavelength is meaningful in terms of light-tissue interaction, even if it is now demonstrated that wavelengths between 632 and 830 nm can be beneficial for preventing and treating OM [34]. In a previous report, Schubert et al. 2007 [28] found that wavelength of 650 nm produced better results than 780 nm in the prevention of oral mucositis.

This study reported that there was no difference in the reduction of oral mucositis between the two groups, but only in the pain amelioration. The slight contrast with other studies [37] may be partially explained by the wavelengths used. In fact, we chose a high wavelength (830 nm) in order to verify if, exploiting the spectra absorption of cytochrome c oxidase, which is about 825 nm, and increasing the cellular metabolism and the oral mucosa healing process [35, 36], this type of wavelengths could be an alternative to 632–660 nm laser lights.

It is known that oral mucositis derive from complex mechanisms in both mucosal epithelial tissues and subepithelial tissues; then, different wavelengths act on different targets at different levels. In particular, 632 to 660 nm light works on superficial layers and on epithelial tissues, and 780 to 901 nm penetrates much deeper in the subepithelial tissues. Schubert et al. 2007 demonstrated in a study [28] that shorter wavelengths would be more effective in preventing mucositis in patients undergoing haematopoietic cell transplantation, because 632–660-nm laser releases most of its energy in the superficial layers. On the contrary, Cauwels et al. 2011 [31] obtained positive results in oral mucositis healing with a 830-nm wavelength.

Although the ideal laser wavelength has not been yet well defined, the results of this and other papers seem to lead to the conclusion that it is advisable to prefer lower wavelengths (632–660 nm) to obtain oral mucositis healing, in addition to pain relief.

Neutrophil serological levels and different chemotherapy protocols are possible confounders that could affect laser therapy outcome; not having discussed them in this trial could represent a weak point of this study.

On the contrary, a strong point of this research is the double-blind randomized design, focused on an exclusive paediatric population and carried out by trained staff; the number of patients in the two groups is representative and larger than other previous reports.

This study has demonstrated the efficacy of LLLT in reducing pain due to chemotherapy-induced oral mucositis. The lack of a unique, standardized protocol for using laser therapy in treatment of OM and relief pain is to be noted; however, further randomized controlled trials with different laser application schedules in children are still needed.

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no competing interests.

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