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ORIGINAL RESEARCH

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Photodynamic therapy by curcumin *vs.* photo-bio-modulation therapy of oral mucositis in paedology patient undergoing anti-cancer non-invasive treatment

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Abstract

Background: The main objective of this study was to assess the impact of non-invasive photodynamic therapy by Curcumin and photo-bio-modulation low level (LL) laser treatment in managing oral mucositis induced by chemotherapy in pediatric patients. **Methods**: A cliinical trial was conducted involving 90 patients aged between 3 years and 15 years. The trial was open, controlled and blind. Patients were divided into two groups; Group A received photodynamic therapy, using Curcumin and a red laser at a wavelength of 450 nm, at 142 J/cm^2, 100 mW. Group B received LL laser at a wavelength of 660 nm, delivering 1 joule of energy per point at 100 mW power output for 10 seconds. The results were assessed using both the World Health Organization (WHO) and Children's International Mucositis Evaluation Scale (ChIMES). Statistical analysis included the Chi-square, Exact Fisher, Student's *t* test and Mann-Whitney tests, as well as a mixed linear regression model for group comparisons, with a maximum allowable error of 5%. **Results**: There was no distinction observed between the groups in terms of the number of sessions required to achieve clinical resolution of oral lesions ($p \geq 0.05$) or the reported reduction in patient pain ($p \geq 0.05$). Nevertheless, within each group, a notable reduction in pain was evident ($p \geq 0.05$). **Conclusions**: Photodynamic (PD)- and low level (LL) laser-therapy are viable options for managing oral mucositis (OM) in children and young patients. Both treatments were well-received and demonstrated positive outcomes in alleviating the pain associated with the condition. **Clinical Trial Registration**: A randomized clinical trial was register on ClinicalTrials.gov, ID NCT06044142. https://clinicaltrials.gov/study/NCT06044142.

Keywords

Curcumin; Photodynamic therapy; Paedology; Photo-bio-modulation; Oral mucositis

1. Introduction

Anti-neoplastic treatments chemo- and radio-therapies are widely used non-invasive techniques. These have led to significant improvement of subsistence for pedo-oncological patients [1–3]. However, these therapies have adverse effects on the oral mucosal lining, such as oral mucositis (OM), increasing the mortality of approximately forty percent of severely affected individuals [3–5].

There are many scales to evaluate the severity of OM, but the most commonly used scale till date is the one proposed by the World Health Organization (WHO) in 1979 [6]. OM is an inflammatory, painful, and incapacitating condition commonly affecting the oral mucosa of the patients on anti-neoplastic therapies. It leads to multiple erythematous, ulcerative, and oedematous oro-pharyngeal lesions, which make it difficult to speak, eat and swallow the food [7]. The prevalence of OM is dependent on various factors: (i) type and location of neoplasm; (ii) treatment plan; (iii) dosage and frequency of anti-neoplastic therapies; (iv) erythrocyte count; and (v) oral hygiene status [7, 8]. In severe conditions, it can lead to hospitalisation in order to change the mode of nutrition to par-enteral/enteral; however, in some scenarios, the anti-neoplastic treatment plan is altered, which in turn adversely affects the disease prognosis [1, 4, 9, 10].

In general, 20–40% of the individuals undergoing chemo-therapy suffer from OM, but paediatric patients treated with myelo-bative therapies are most commonly affected (90–100%) [1]. The paediatric patients are most frequently affected by haematological neoplastic diseases in comparison to any particular organ or tissue [11, 12].

For preventing/minimising the modalities of OM, various therapies, particularly for adults, have been suggested till date, as displayed in Fig. 1 [2, 3, 7, 10–18]. But till date there is no

consensus on the best therapeutic option for the OM [7, 9, 10, 12, 17, 19, 20].

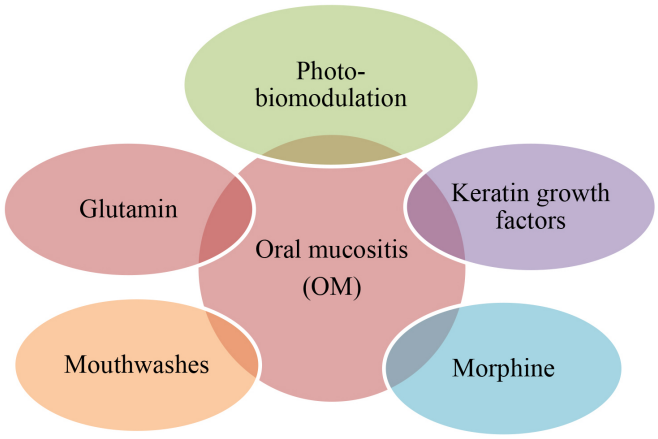

FIGURE 1. Treatment options for oral mucositis.

In the recent era, photo-bio-modulation (PBM), a low-intensity therapy by light-emitting laser/light/infrared spectrum, has evolved as an effective modality for reducing and preventing the symptoms associated with OM [21, 22]. The non-thermal PBM therapy has evolved as a treatment enhancing microcirculation and tissue regeneration while reducing the inflammatory response [17, 23–25]. The PBM therapy activates the chromophores (endogens) leading to the production of reactive oxygen species. It stimulated the proliferation of mucosal epithelial cells, promoting tissue healing [26]. In order to treat OM, lasers of 600–900 nm wavelengths have the potential to reduce the severity and intensity of pain [21]. However, individuals under anti-neoplastic therapies tend to have a suppressed immune system, as the oral cavity is inhabitant of diverse microbial content, thus the patients are prone to bacterial, viral and fungal infections. In particular, in individuals with severe OM, the microbes can hinder the process of tissue healing, leading to local or systemic infectious diseases [19].

Therefore, photo-dynamic (PD) therapy has evolved as a promising treatment of choice for infectious diseases of the oral cavity [22, 27, 28]. PD therapy is a photo-physical and photo-chemical technique producing a biological response against selective microbes and cells by combining the use of light-emitting diodes and photosensitising agents [27]. It is an affordable, safe and easy-to-use technique with minimal discomfort to the individual. It can be performed on the patients undergoing anti-neoplastic treatments in the tertiary care hospitals [29]. There are few studies reporting the potential use of PD therapy for the treatment of OM [22, 30].

Thus, in view of the available literature, the chief aim of the study was to evaluate and compare the effectiveness of low-intensity laser PBM therapy and PD therapy with curcumin photosensitiser in paediatric patients undergoing anti-neoplastic therapies.

2. Materials and methods

The study was registered on Clinical Trials (ClinicalTrials.gov ID: NCT06044142) and designed based on the Consolidated Standards of Reporting Trials (CONSORT) and conducted on approval from the Ethics Committee of the University with registration number FRP/2023/519 [31]. The study timeline is as follows: it actually started on 15 March 2023, with primary completion on 30 December 2023, and study completion on 30 January 2024. It was a randomised controlled trial conducted among 90 paediatric patients in the 3–15 year age group. The inclusion criteria for the study were (i) patients in the age group of 3 years to 15 years and (ii) mucositis (categorised >1) based on the guidelines of the WHO Toxicity Criteria. Paediatric patients having a malignant type of neoplasm and/or clinically evident oral microbial disease (dental caries and periodontal diseases) and/or with serious medical issues (coeliac diseases, autism spectrum disorder, diabetes mellitus and cleft lip/palate) were excluded from the study.

The oral mucositis was diagnosed by a dentist available at the site of a tertiary care hospital for chemotherapy. The potential participant was referred to the research group for inclusion in the study based on the defined inclusion criteria. The procedure of research was explained to the guardians of the participants. On acceptance, the guardians were requested to sign the informed consent form.

The patients were considered a new case for intervention on the commencement of each chemo-therapy cycle. The patients were again added to a new randomised controlled trial if encountered an episode of oral mucositis.

2.1 Intervention for photodynamic and laser therapy

Prior to the intervention of laser and photodynamic therapy, the patients were educated and instructed to maintain oral hygiene during cancer treatments. The instructions included brushing teeth with an adequate amount of toothpaste and recording it on a follow-up chart. Later on inspection by the research team, if a patient was diagnosed with any carious lesion, retained root or gingival infection associated with dental plaque were categorised as excluded from study. The procedure performed beside the patients admitted to the hospital, whereas outpatients were seated on dental chairs in outpatient clinics.

An open-controlled and blind, randomised clinical trial was conducted with 45 patients, from 3 years to 15 years old, who were divided into two groups. Group A was submitted to photodynamic therapy (curcumin and red laser, λ450 nm) (Glentham Life Sciences Ltd., Corsham, United Kingdom) with 142 J/cm^2, 100 mW. The number of points was calculated based on the size of the lesion (1 laser shot per cm^2 of lesion). The intervention was repeated daily until cure of the oral mucositis was attained. The clinical cure was categorised by a dentist restoring the normal physiological functions such as chewing, swallowing and phonation without any symptoms of pain; additionally, signs of tissue regeneration were evident.

Group B (control group) was submitted to low-level (LL) laser therapy (λ660 nm) (Prototype, Finep/Gnatus LED Edixeon, Edison Opto Corporation, New Taipei, Taiwan) with 1 J energy per point at 100 mW power output for 10 seconds on a daily basis until the lesion was clinically cured. The light was applied perpendicular to the lesion in a continuous mode. The number of points was calculated similarly as mentioned

for patients included in Group A (Fig. 2).

2.2 Oral mucositis evaluation

After an inter-examiner reliability test (95%), the patients were evaluated by the research group. The scale proposed and accepted by the World Health Organisation (WHO) was used to categorise the changes in oral mucositis condition evaluated over time in four different categories: (i) Category 0 = absence of change in condition; (ii) Category I = persistence of erythematous condition with dietary intake of solid food; (iii) Category II = persistence of erythematous condition with solid dietary food intake; (iv) Category III: presence of painful erythematous lesion with liquids as a dietary intake; and Category IV: patient with special mode for dietary intake (parenteral or enteral).

For evaluating the intensity of pain and variation in function, the ChIME scale was used [32]. The data was recorded on specially designed forms. The patients were divided randomly and later treated with lasers and photodynamic therapy. The summary of the study design is displayed in Fig. 3.

2.3 Statistical analysis

The data was evaluated and expressed in absolute and relative values. Statistically, the data was evaluated using the Chi-square, Exact Fisher, Student's *t* and Mann-Whitney tests. Additionally, a mixed linear regression model was used to compare between the groups, with a maximum error of 5%. All the data was analysed by the SPSS software (version 19, IBM, Chicago, NY, USA). The level of significance of the *p* value was set at ≤ 0.05.

3. Results

The number of patients recruited in the study was 90 based on the defined criteria. One patient in Group A (2.22%) and two patients in Group B (4.44%) discontinued and did not complete the follow-up, totalling up to 86 patients of paedology data included in the results. The Figs. 4,5 displayed the demographic and clinical characteristics of the participants recruited in the study.

The patients recruited in group A mostly belonged to an age group of 7–12 years of age 23 (51.11%), whereas most of the participants in group B were ≥12 years of age 30 (66.66%). Male paediatric patients were recruited in predominance for both groups: group A with 23 (51.11%) and group B with

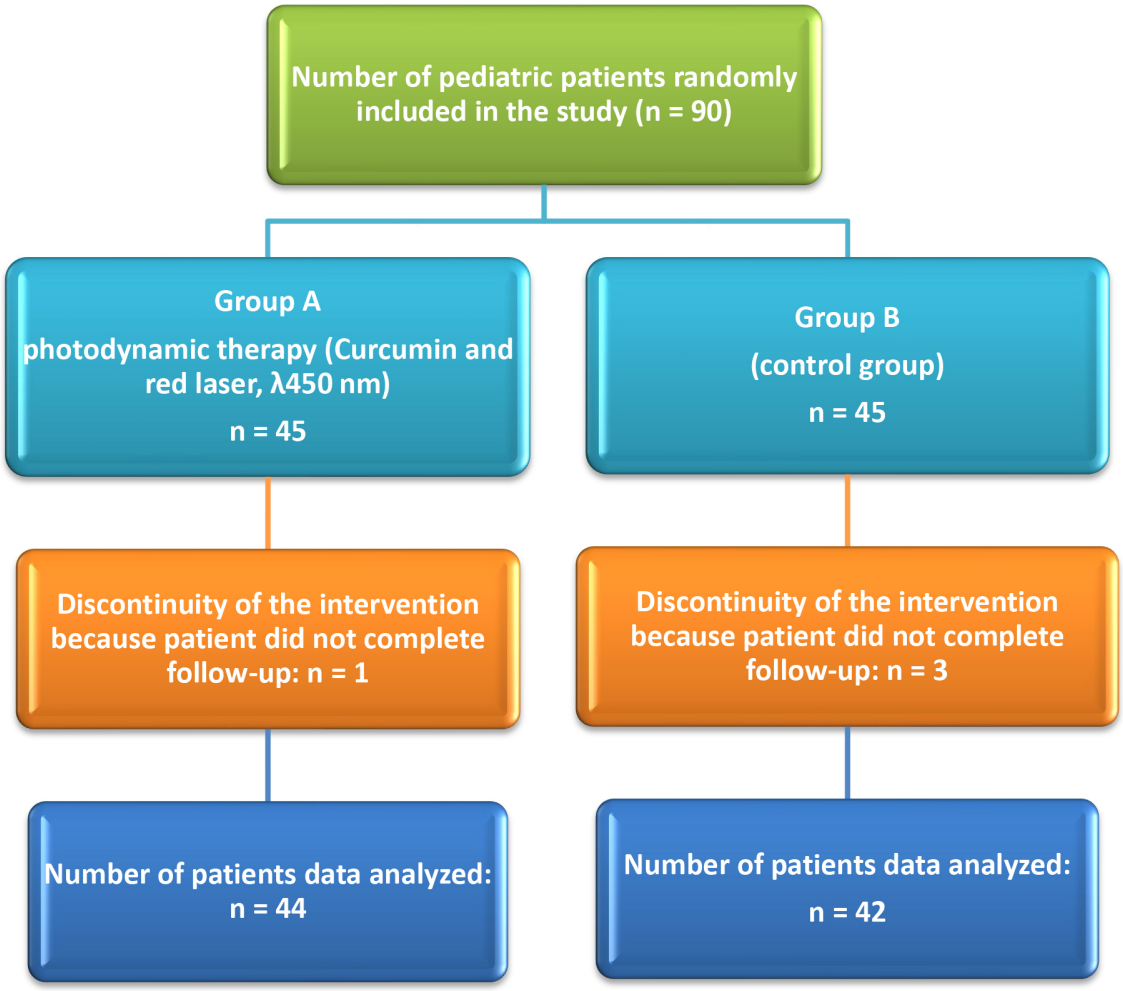

FIGURE 2. Patient study flowchart included for the research.

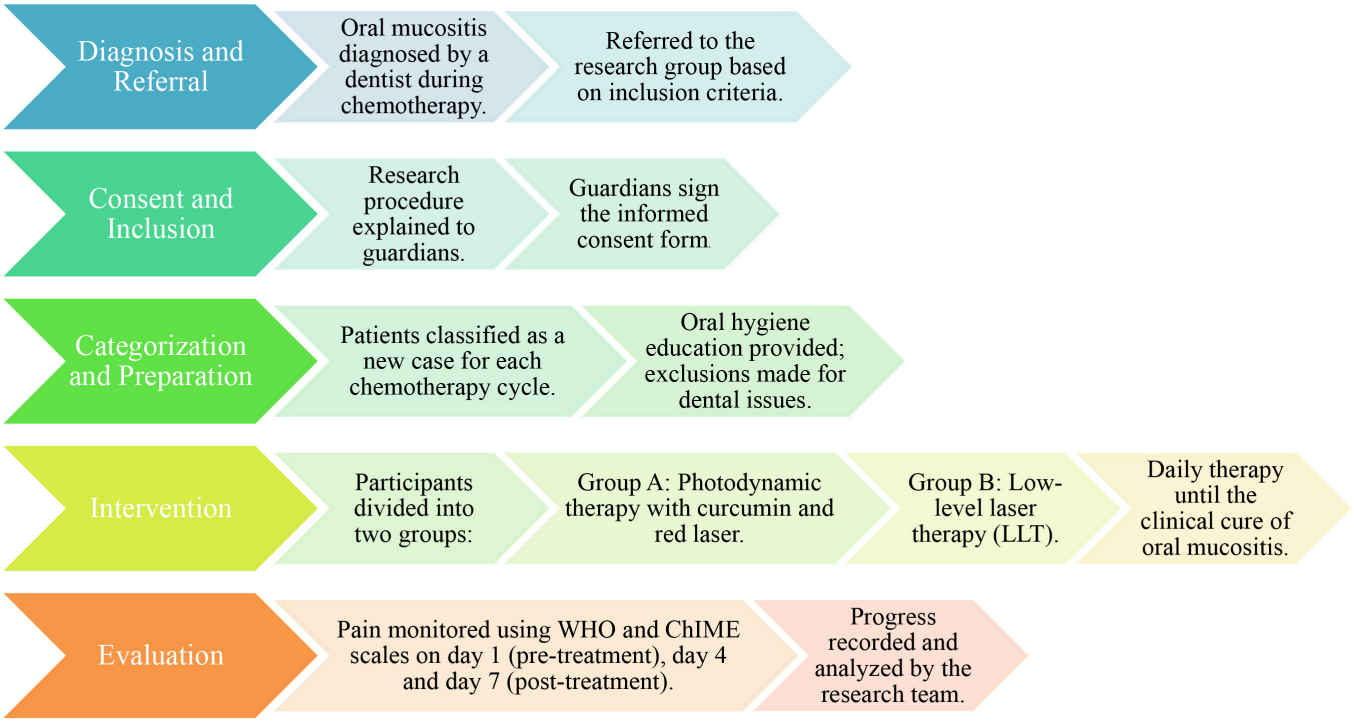

FIGURE 3. Summary showing study design. WHO: World Health Organisation; ChIME: Children's International Mucositis Evaluation.

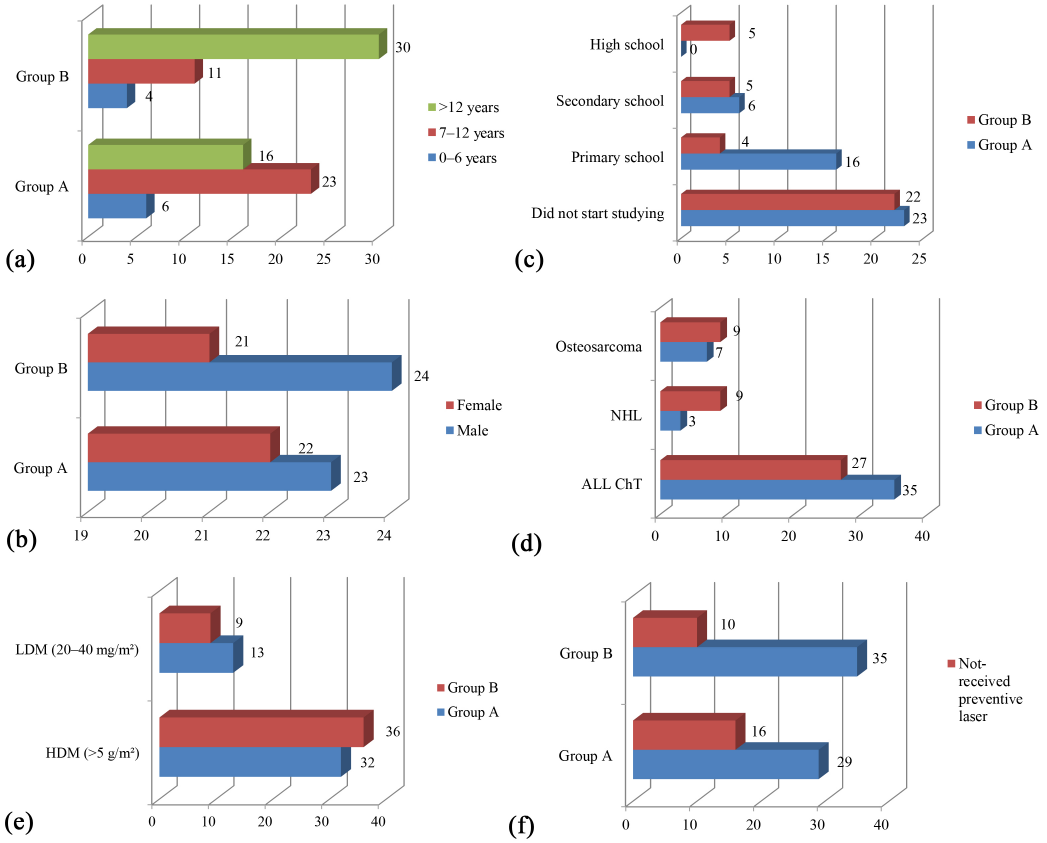

FIGURE 4. Demographic and clinical characteristics of the participants recruited in the study. (a) age group of the participants recruited in the study; (b) gender of the participants in respective groups; (c) level of education of the participants in the respective groups; (d) type of malignancy observed in the patients recruited in the respective groups; (e) amount of metotrexate administered; (f) participants received preventive laser. ALL ChT: Acute lymphoblastic leukemia; NHL: Non-Hodgkin Lymphoma; HDM: High dose of Metotrexate; LDM: Low dose of Metotrexate.

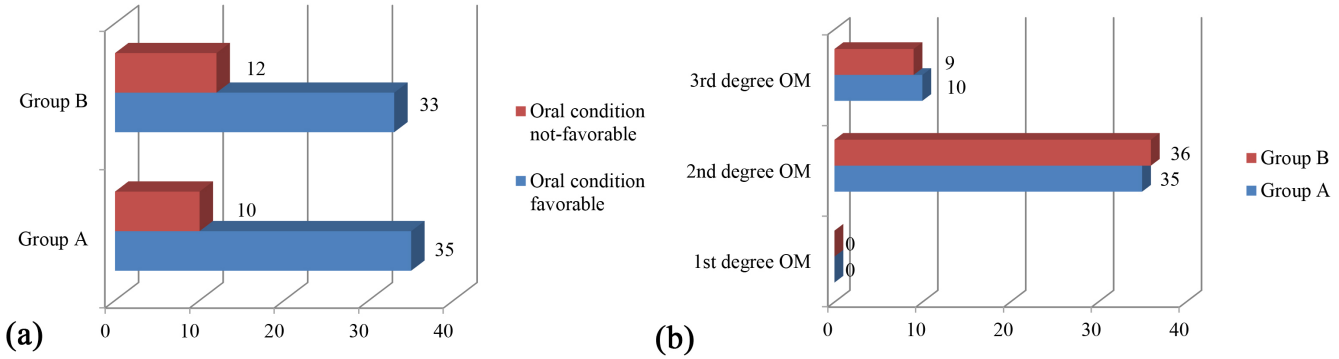

FIGURE 5. Summary of the patients condition and degree of oral mucositis. (a) Number of participants with favorable/unfavorable condition for oral mucositis (OM) treatement; (b) degree of OM observed in the participants recruited in the study.

24 (53.33%). A higher number of paedeology patients did not start studying (Group A: 51.11%; Group B: 48.88%), as shown in Fig. 4c. Most of the patients recruited were suffering from acute lymphoid leukaemia, 35 (77.77%) trailed by osteosarcoma, 7 (15.55%) in group A, whereas 27 (60%) with acute lymphoid leukaemia and 9 (20%), respectively, were suffering from non-hodgkin lymphoma and osteosarcoma in Group B (Fig. 4d). As displayed in Fig. 4e, majority of the patients in group A were 32 (71.11%) and 36 (80%) in group B were treated with a high dose of metotrexate ($\geq$5 g/m^2) trailed by 13 (28.89%) individuals in group A and 9 (20%) in group B treated with a low dose of metotrexate (20–40 mg/m^2). Paediatric patients in groups A and B mostly received the preventive laser treatment, trailed by the individuals not taking preventive laser treatment. As shown in Fig. 4f, 29 patients (64.44%) in group A and 35 (77.77%) in group B received preventive laser therapy.

Fig. 5a displays the number of paediatric patients having a favourable/unfavourable (carious lesions, bleeding from gingival tissue, retained roots, gingival/bony recession) condition for OM treatment. The 35 (77.77%) participants inducted in group A, whereas 33 (73.33%) of group B had favourable conditions for the treatment of OM. There was no association observed between OM and unfavourable condition for therapy for both group A (p value = 0.171) and group B (p value = 0.234) participants.

A total of 71 (78.88%) patients from 90 presented with 2nd degree of OM; 35 patients were in group A, whereas 36 were in group B (Fig. 5b). Patients with 3rd degree of OM were 10 in group A, but 9 patients in group B. Three patients in group A, whereas one patient in group B initially presented as 2nd degree due to aggravation, converted to 3rd degree of OM. The signs of lesion appeared at an average of 5.83 $\pm$ 2.63 standard deviation (SD) days of chemotherapy. The sites of the oral cavity most commonly involved were the upper/lower lips, gingival tissue, sides and inferior region of the tongues mucosal surface with the base of the oral cavity.

Twenty-nine patients in Group A (64.44%) and thirty-five (77.77%) participants in group B underwent preventive laser therapy. But no statistically significant difference (p = 1.00) in the degree of OM was observed pre- and post-treatment laser therapy, as shown in Fig. 6, between group A and group B on day 1 (baseline).

The mean number of clinical sessions received by paediatric patients for photodynamic therapy was 6.18 $\pm$ 2.96, whereas those exposed to low laser therapy required a mean of 6.26 $\pm$ 3.61 sessions for a complete clinical cure of the lesion. On statistically analysing the data between the patients treated with PD therapy and low laser therapy, no significant difference was observed for the number of required clinical sessions for healing of oral ulcers (p = 0.981), as shown in Fig. 6.

On evaluating the degree of pain on days 1, 4 and 7 of treatment, a significant reduction in the pain perception was observed for both groups. However, the group subjected to PD therapy displayed a higher level of effectiveness. On statistical analysis using the Mann-Whitney test, no significant difference in pain reduction was observed between two groups on pre- and post-treatment (day 4 and day 7) ($p \geq 0.05$), as displayed in Fig. 6.

The improvement in treatment with photodynamic (Fig. 7a) and LL laser therapy (Fig. 7b) can be observed in the images displayed in Fig. 7. The images were taken on days 1, 4 and the 7 respectively.

4. Discussion

The data for malignancies is recorded in the national register of the Kingdom known as the Saudi Arabia National Cancer Registry. Based on the previous data collected during 2005–2009 for the paediatric patients aged between 0 and 14 years of age, leukaemia was the most prevalent among the 1370 registered cases, making up to 35.26% in comparison to other cancerous conditions. The most common types of leukaemia observed included acute lymphoid and myeloid leukaemia.

Various potential therapeutic approaches have been proposed to prevent and treat oral mucositis, a common condition in people undergoing cancer treatment. However, most of these options lack the rigorous scientific evidence necessary for their recommendations, and their effectiveness in different types of cancer remains a matter of debate [1, 5, 12, 13, 32, 33].

Studies specifically targeting children are limited, probably due to the relatively low incidence of cancer in children compared to adults and the lack of a universally accepted method for evaluating oral mucositis in young patients [11, 34]. The

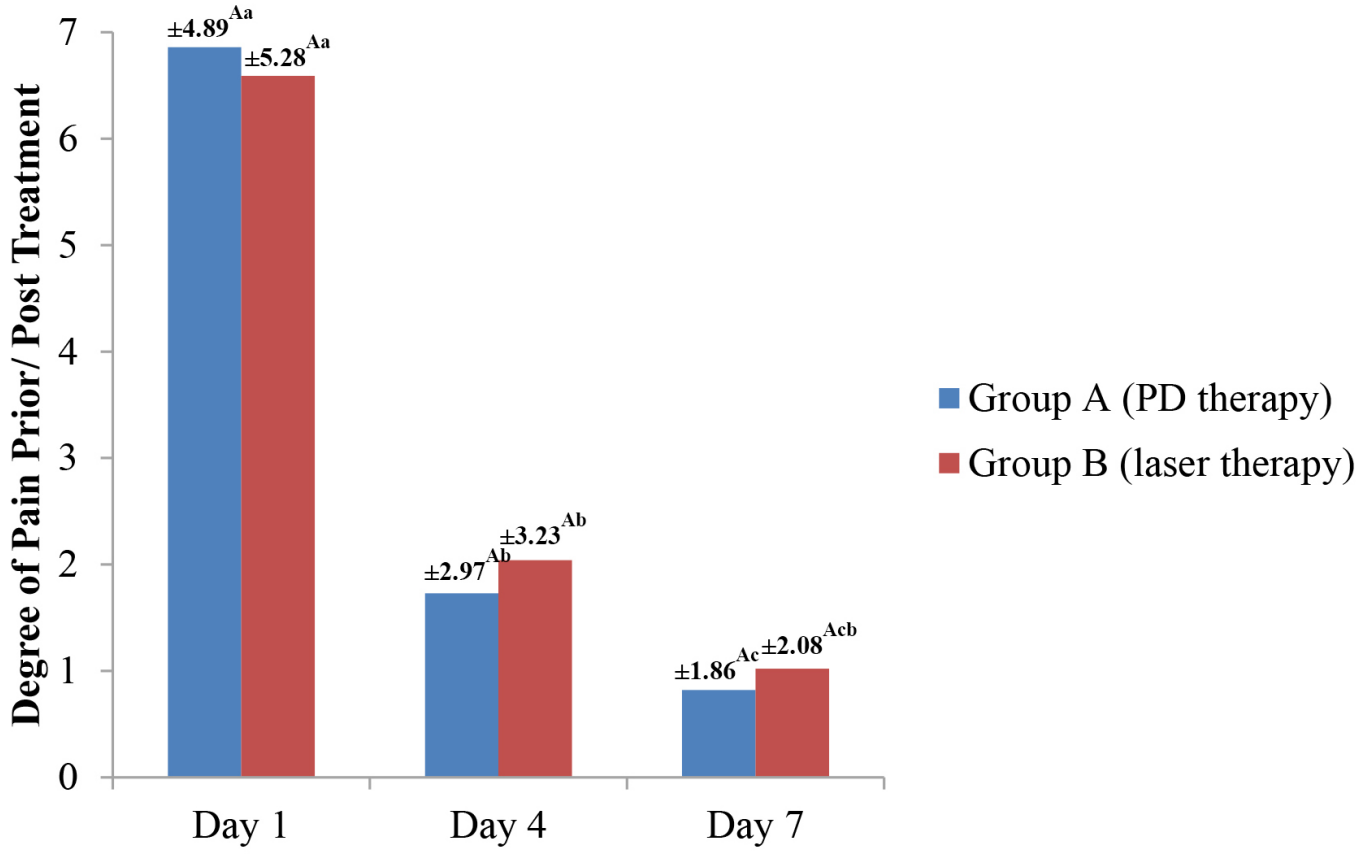

FIGURE 6. Level of Pain comparative analysis at baseline, 4th and 7th day. ^{A,B}capital super script displays the level of significance between group A and B for pre-treatment (day 1), post-treatment on day 4 and day 7 respectively ($p \leq 0.05$). $^{a-c}$small super script displays the level of significance within group A/group B in the degree of pain on pre-treatment and post-treatment on 4th/7th day ($p \leq 0.05$).

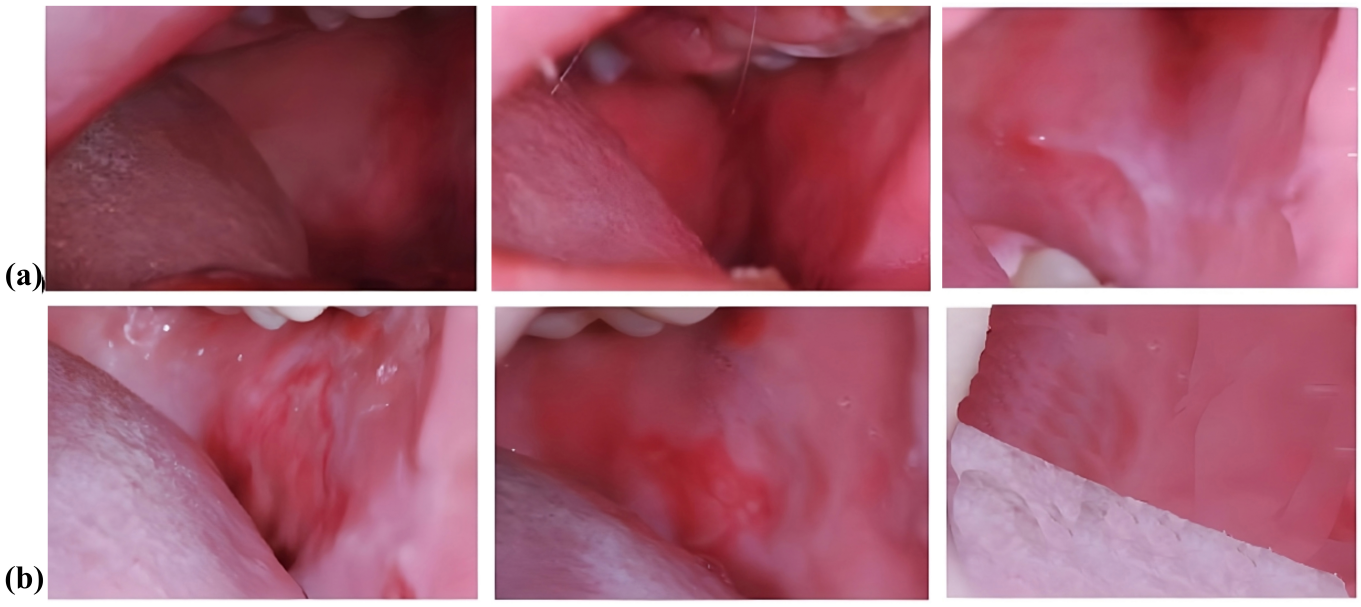

FIGURE 7. Clinical image displaying difference pre-treatment to post-treatment. Progressive improvement of oral mucositis in a pediatric patient treated with (a) photodynamic therapy; and (b) LL laser therapy, as observed on day 1, Day 4 and Day 7. Images demonstrate the gradual reduction in inflammation, erythema and ulcerations, with restoration of healthy mucosal tissue over time.

diversity of treatment practices used in paediatric oncology and varying levels of patient cooperation and adherence also present challenges, especially when children need parental consent to participate in research [5, 32].

In recent years, there have been many studies involving photo-bio-modulation, a treatment that uses light energy [23, 28, 35]. However, these studies have primarily focused on adults, and studies in children have produced mixed results. This difference may be due to differences in how children and adults respond to therapy due to differences in pharmacokinetics, receptor distribution, and patient compliance, thus justifying a study focusing only on paediatric patients [1, 12, 18, 23, 28, 35].

Viewed from a biological perspective, one might anticipate that interventions proven effective in adults would yield similar results in children. However, this is not always the case. Discrepancies in effectiveness can be attributed to variances in how drugs are processed and their effects are experienced in the body, variations in the distribution of receptors targeted by specific treatments, as well as potential challenges related to the cooperation of paediatric patients. These factors can significantly influence outcomes and provide rationale for conducting research exclusively with paediatric patients [36].

A group of researchers explored paediatric patients when provided adequate oral care; the application of photo-bio-modulation did not yield any advantages in preventing or reducing oral mucositis among individuals aged from 3 to 18 undergoing chemotherapy or bone marrow transplantation [37].

Nonetheless, a different research team displayed the effectiveness of lasers in alleviating the pain linked to mucositis in children, although they did not observe a reduction in the severity of mucositis [18]. Conversely, several other authors have reported positive outcomes from low-level laser therapy in both reducing mucositis and alleviating the associated pain [12, 24, 38, 39].

In the most recent revision of the practical manual for managing oral mucositis by the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology, it is advised to employ treatments of low-level (LL) laser (at 650 nm) [15]. A clinical guideline grounded in evidence also proposed the utilisation of laser therapy for the prevention and reduction of mucositis [13].

The aim of the current pilot study, a randomised, controlled, triple-blind clinical trial, was to evaluate the effectiveness of two treatments-LL using a 660 nm laser and photodynamic (PD) therapy using curcumin-in children and adolescents. The rationale for using PD therapy was based on its effectiveness against oral infections associated with oral mucositis [40, 41]. Interestingly, previous human-detailed studies on the use of PD therapy in the treatment of oral mucositis had not been published prior to this study [42, 43]. Curcumin has been identified as an active agent in the photodynamic therapies to display strong anti-microbial and anti-inflammatory effects [35].

Prior to the commencement of this study, there were no comprehensive investigations available regarding the application of PD therapy for treating oral mucositis in humans. A team of researchers conducted a comprehensive examination encompassing clinical, biochemical, and histological aspects to assess PD therapies impact on the healing process of mucositis lesions induced in hamsters [37]. Their findings indicated that the therapy effectively lessened the severity of mucositis, promoted increased collagen deposition within the lamina propria, and established its safety for use.

In this study, based on the information from the Saudi Arabia National Cancer Registry, indicated that leukaemia was the predominant form of cancer. All of the patients underwent treatment that incorporated the chemotherapeutic drug methotrexate, which can predispose to mucositis. However, there were differences in chemotherapy protocols between different patients.

In the oncology centres under investigation, preventive laser therapy was regularly employed, and clinical observations indicated a potential decrease in the occurrence of mucositis following its implementation. This study, however, did not aim to assess the effectiveness of preventive laser therapy in preventing mucositis lesions. Instead, the analysis focused on examining the relationship between patients' self-reported severity of oral mucositis and whether they had received prophylactic phototherapy. Nevertheless, no statistically significant correlation was identified.

Regarding pain assessment, a comparable approach was adopted. Although numerous studies employed the VAS scale, it couldn't be utilised in this case due to the inclusion of young participants ranging from 3 years to 15 years old, as young children lack the capacity to comprehend it. Instead, the ChIMES scale was utilised [32], enabling the assessment of pain intensity and function through the use of visual representations of facial expressions. This approach allowed interpretation by children aged 8 years or older and by their guardians if the children were less than 8 years of age.

The challenges of the study were the lack of standardised laser parameters and a generally accepted method for evaluating mucositis. Despite these challenges, patients tolerated both LL laser treatment and PD therapy well. Although there were no statistically significant differences in the results between the two treatment groups, pain was significantly reduced in the LL laser therapy group.

Limitations of the study include, among others, the lack of evaluation of combination therapy, variable laser parameters, and a special focus on children and adolescents. Future studies could delve into factors such as medication use, nutritional status, haematological conditions and oral health to better understand treatment effects. Furthermore analyzing the systemic parameters like the neutrophil, eosinophil and platelet counts can help in further detailed analysis on the affect of the PD and LL therapies.

5. Conclusions

In conclusion, both PD- and LL-laser therapy are viable options for the management of OM in children and young patients. These therapeutic options are well-received and demonstrated positive outcomes in alleviating the pain associated with the condition. The management of oral mucositis in childhood cancer patients presents unique challenges due to the diversity of childhood cancers, treatment practices, patient

cooperation, and the lack of standardised treatment parameters. Although some treatments such as photo-bio-modulation laser and PD therapy show promise, more focused research is needed to establish effective treatments for this vulnerable population.

ABBREVIATIONS

OM, oral mucositis; ChIMES, Children's International Mucositis Evaluation Scale; PBM, photo-bio-modulation; PD, photodynamic; CONSORT, Consolidated Standards of Reporting Trials; LL, low level; WHO, World Health Organization; NHL, Non-Hodgkin Lymphoma; HDM, high dose of metotrexate; LDM, low dose of methotrexate; SD, standard deviation.

AVAILABILITY OF DATA AND MATERIALS

The detailed data is available under the materials and methods section.

AUTHOR CONTRIBUTIONS

ZQ, MS, NSA, AB and CS—designed the research study. ZQ, RNR and SV—performed the research. ZQ and MS—provided help and advice on improving the sample size. NSA and CS—analyzed the data. ZQ, AB and CS—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of Riyadh Elm University, Riyadh, Saudi Arabia (FRP/2023/519). All the patients/guardians signed the consent form.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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