Research Square

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Comparing the Efficacy of High-Power and Low-Power Laser Therapy in the Management of Chemotherapy-Induced Oral Mucositis in Pediatric Patients with Acute Lymphoblastic Leukemia: A Randomized Controlled Trial

Lana kassem

lann.aa1993@hotmail.com

Damascus University Faculty of Dentistry

Othman Hamdan

Damascus University Faculty of Medicine

ayman al kayal

Faculty of Biomedical Engineering, Al-Andalus University for Medical Sciences

Aya Dawoud agha

Damascus University Faculty of Dentistry

Mahmoud Abdul-Hak

Damascus University Faculty of Dentistry

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Abstract

Purpose

Chemotherapy-induced oral mucositis (OM) is a common complication in children with acute lymphoblastic leukemia (ALL). This randomized controlled trial compared high-power laser therapy (HPLT), low-level laser therapy (LLLT), and placebo in managing OM in pediatric supportive care.

Methods

This parallel-group, placebo-controlled trial included 30 children (3–13 years) with chemotherapy-induced OM, randomized equally into HPLT, LLLT, or placebo groups (n = 10 each). Treatments were applied once daily for four days. OM severity was assessed at baseline (Day 1), Day 4, and Day 11 using WHO and ChIMES scales. Non-parametric tests (Kruskal–Wallis and Mann–Whitney U) were used ($p < 0.05$).

Results

All participants completed the study without adverse events. Both HPLT and LLLT significantly reduced OM severity compared with placebo at Day 4 and Day 11 ($p < 0.05$). At Day 11, both HPLT and LLLT showed significant improvements versus placebo in WHO and ChIMES scores, with no significant difference between the two laser modalities.

Conclusion

Both HPLT and LLLT are safe and effective in reducing chemotherapy-induced OM in pediatric ALL patients. HPLT showed a non-significant trend toward greater improvement compared with LLLT.

Relevance

Photobiomodulation therapy may be a valuable adjunct in pediatric oncology supportive care to reduce OM severity and improve patient comfort during chemotherapy.

Trial registration: ISRCTN18078092, registered on 23 May 2025.

Introduction

Leukemia is a heterogeneous group of hematologic cancers characterized by the uncontrolled proliferation of abnormal leukocytes, classified into acute or chronic and myeloid or lymphoid subtypes. Among these, Acute lymphoblastic leukemia (ALL) is the most common form in children, accounting for approximately 80% of pediatric leukemia cases

Treatment outcomes in pediatric cancers have improved markedly in recent years, largely due to advances in Chemotherapy, which remains the cornerstone of of cancer treatment, particularly in

resource-limited settings. Despite the increasing availability of chemotherapeutic agents, treatment is frequently associated with significant adverse effects [1]. In addition to systemic symptoms such as nausea and vomiting, Oral Mucositis (OM) is one of the most severe and prevalent complications, affecting approximately 52% to 100% of patients undergoing high-dose chemotherapy [2].

The pathogenesis of OM involves complex interactions between oral epithelial cells, proinflammatory cytokines, and local environmental factors [3]. This process progresses through five overlapping phases: initiation, signaling, amplification, ulceration, and healing. Chemotherapy-induced generation of reactive oxygen species leads to direct cellular and tissue injury, followed by activation of transcription factors such as nuclear factor-kappa B, which promotes cytokine release and amplifies tissue damage. Subsequent bacterial colonization of ulcerated mucosa further intensifies the inflammatory cascade, increasing the risk of pain, infection, and systemic complications, particularly in neutropenic patients. Healing typically begins after cessation of chemotherapy [4]. Clinically, OM develops within 3–10 days of chemotherapy initiation, peaks at 7–14 days, and may persist for up to three weeks [5]

Given its multifactorial nature and clinical burden, effective management of OM remains challenging, leading to increasing interest in light-based therapies such as Photobiomodulation (PBM). PBM utilizes non-ionizing visible and near-infrared light to stimulate mitochondrial activity and modulate biological pathways involved in inflammation, tissue repair, and pain control [6–8]. Its therapeutic effects are dose-dependent, promoting healing and anti-inflammatory responses at lower doses (Low Level Laser Therapy LLLT), while higher doses (high-Power laser therapy HPLT) may contribute to analgesic effects {HPLT) [9–11]

In parallel, High-Intensity Laser Therapy -also referred to as high-Power laser therapy (HPLT)- has emerged as an advanced modality. High-power lasers (> 500 mW, Class IV) can be safely applied using techniques that minimize thermal accumulation [12]. At higher energy densities, HPLT produces both photochemical and photothermal effects, enabling deeper tissue penetration and enhanced biological responses, including increased ATP production, improved microcirculation, accelerated edema resolution, and enhanced removal of inflammatory exudates [13]. Pain reduction associated with laser therapies is mediated through multiple mechanisms, including decreased nerve conduction velocity, modulation of inflammatory mediators, increased β-endorphin release, and regulation of neuronal activity [6, 14–18]

Therefore, the aim of the present study is to evaluate and compare the efficacy of low-level and high-level photobiomodulation protocols in the management of chemotherapy-induced oral mucositis in pediatric patients with acute lymphoblastic leukemia.

Materials and methods

Study design and setting

This study was designed as a randomized, single-blinded, placebo-controlled, parallel-group superiority clinical trial with a 1:1:1 allocation ratio to compare the efficacy of high-power laser therapy (HPLT), low-level laser therapy (LLLT), and placebo for the management of chemotherapy-induced oral mucositis in pediatric patients with acute lymphoblastic leukemia (ALL). Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this trial. The study protocol, outcome measures, and statistical analysis plan remained unchanged after trial commencement.

The trial was conducted at the Pediatric Hematology Department of the Children's University Hospital between June 2025 and January 2026. All clinical assessments, treatment procedures, and follow-up evaluations were performed at the study center according to a standardized protocol. Participants were evaluated at three predefined time points: baseline (Day 1, before initiation of treatment), Day 4 (the final day of laser therapy, representing the early treatment response), and Day 11 (one week after completion of treatment) to evaluate both early and sustained therapeutic effects.

Ethics and trial registration

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (1975). Ethical approval was obtained from the Institutional Ethics Committee before participant recruitment commenced. The trial was prospectively registered in the ISRCTN registry (ISRCTN18078092). Written informed consent was obtained from the parents or legal guardians of all participants before enrollment.

Participants: eligibility and recruitment

Pediatric patients aged 3–13 years with a confirmed diagnosis of acute lymphoblastic leukemia (ALL) who were receiving induction chemotherapy consisting of methotrexate, cytarabine, and dexamethasone were screened for eligibility at the Pediatric Hematology Department, Children's University Hospital, Damascus, Syria

Patients were eligible if they developed chemotherapy-induced oral mucositis during treatment, were expected to remain available for at least 10 days of follow-up, were able to achieve a mouth opening greater than 2 cm, and had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2, indicating that they were ambulatory and capable of self-care.

Patients were excluded if they had previously received laser therapy for oral mucositis, presented with dysplastic oral lesions, or had undergone radiotherapy to the head and neck region.

Randomization, allocation concealment, and blinding

Eligible participants were randomly assigned in a 1:1:1 ratio to one of three study groups: HPLT, LLLT, or placebo group. Randomization was computer-generated using GraphPad software. Allocation concealment was maintained until completion of data analysis.

Because of the nature of the interventions, the principal investigator responsible for treatment administration and clinical outcome assessment could not be blinded. However, the statistician remained blinded to treatment allocation throughout the study and analyzed anonymized coded data without access to group assignments.

Interventions

Participants were allocated to one of three treatment groups: high-power laser therapy (HPLT), low-level laser therapy (LLLT), or placebo. All laser applications were performed using the same Class IV diode laser device (Doctor Smile, Italy). Treatments were administered once daily for four consecutive days according to standardized protocols. In addition to the assigned intervention, all participants received the same standard supportive oral care throughout the study.

High-power laser therapy (HPLT)

Participants allocated to the HPLT group received extra-oral high-power diode laser therapy using a Class IV diode laser device (Doctor Smile, Italy) with wavelengths ranging from 635 to 980 nm. Laser irradiation was delivered at an average power of 2.75 W (5 W pulsed at 50%) through a spot size of 0.785 cm^2, resulting in a total energy of 660 J per treatment session and an energy density of 840 J/cm^2.

Treatment was administered in a defocused, non-contact, continuous-wave mode using a rotatory sweeping motion. Each treatment session lasted 240 seconds and was performed once daily for four consecutive days. Laser irradiation was applied extra-orally to six anatomical sites, including the right cheek, left cheek, lips, right cervical (submandibular) region, left cervical (submandibular) region, and submental area. Each site was irradiated for 40 seconds using gentle circular sweeping movements while maintaining the laser tip approximately 1 cm from the skin surface to ensure uniform energy distribution and minimize localized thermal effects.

Low-level laser therapy (LLLT)

Participants assigned to the LLLT group received intra-oral low-level diode laser therapy using the same Class IV diode laser device (Doctor Smile, Italy) with wavelengths ranging from 635 to 980 nm. The laser was delivered at an average power of 0.25 W with a spot size of 0.785 cm^2, providing a total energy of 60 J per treatment session and a fluence of 76.43 J/cm^2.

Treatment was applied in a defocused, non-contact, continuous-wave mode using a rotatory sweeping motion. Each treatment session lasted 240 seconds and was administered once daily for four consecutive days. Laser irradiation was delivered intra-orally to eight mucosal sites: the right buccal mucosa, left buccal mucosa, upper labial mucosa, lower labial mucosa, dorsal tongue, ventral tongue, floor of the mouth, and soft palate.

Placebo

Participants assigned to the placebo group received sham laser therapy using an identical laser device with the same appearance, operating sounds, indicator light, treatment duration, and application procedure as the active interventions. However, no therapeutic laser energy was emitted during treatment, thereby preserving participant masking while avoiding active irradiation.

Standard supportive care

All participants received standard oral care and supportive management according to the pediatric oncology department's routine clinical protocol. Supportive care included oral hygiene measures, antifungal therapy when clinically indicated, topical anesthetic sprays, and nutritional support as required.

To avoid interference with pain assessment, topical anesthetic sprays or other analgesic interventions were not administered immediately before outcome evaluations. Standard supportive care was provided uniformly across all three study groups throughout the study period.

Outcome measures

The primary outcome was the change in oral mucositis severity from baseline (Day 1) to Day 11, assessed using the WHO Oral Mucositis Grading Scale and the ChIMES score. Treatment effects were expressed as change scores (Δ = Day 11 − Day 1) and used for between-group comparisons to assess sustained efficacy.

Secondary outcomes included early response, defined as change from Day 1 to Day 4 (Δ = Day 4 − Day 1), corresponding to completion of laser therapy. Mucositis-related symptom changes were evaluated at all time points using the same instruments.

Sample size calculation

An a priori sample size calculation was performed using G*Power software (version 3.1) for a one-way analysis of variance (ANOVA) with three parallel groups. Assuming a significance level (α) of 0.05 and a statistical power of 90%, the analysis indicated that a minimum sample size of 18 participants (six per group) would be sufficient to detect a very large effect size (Cohen's $f = 0.96$). The effect size was estimated based on the findings reported by Ludovichetti et al. [19]

The anticipated effect size was supported by preliminary evidence demonstrating substantial differences between treatment groups, together with the practical and ethical constraints associated with recruiting pediatric oncology patients. Given the exploratory nature of this clinical trial and the expected magnitude of the treatment effect, this assumption was considered appropriate.

To improve study robustness and compensate for potential participant attrition, the final recruitment target was increased beyond the minimum required sample size. Consequently, 30 participants were

enrolled, with 10 participants allocated to each study group.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize baseline demographic characteristics and outcome variables.

Data distribution was assessed for normality before inferential analyses. As the outcome variables were not normally distributed, non-parametric statistical methods were applied.

The primary analysis evaluated changes in WHO and ChIMES scores from baseline to Day 11 (Δ = Day 11 − Day 1) to determine the sustained treatment effect. Early treatment response was evaluated by calculating changes from baseline to Day 4 (Δ = Day 4 − Day 1).

Between-group comparisons of change scores were performed using the Kruskal–Wallis test. When statistically significant differences were identified, pairwise comparisons were conducted using the Mann–Whitney U test. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

Results

A total of 30 pediatric patients with chemotherapy-induced oral mucositis were enrolled and randomized equally into three groups (n = 10 per group). All participants completed the study without losses to follow-up, exclusions, or protocol deviations and were included in the final analysis (Fig. 1). No treatment-related adverse events were observed during the study period (Figs. 2 and 3).

Baseline characteristics were comparable among groups with no significant differences in age ($H = 0.536$, $p = 0.765$) or sex distribution ($\chi^2 = 1.09$, $p = 0.581$) (Table 1).

Primary outcome (Day 1 to Day 11)

Significant differences were observed among the three groups for both WHO ($H = 11.254$, $p = 0.004$) and ChIMES scores ($H = 16.851$, $p < 0.001$). For WHO, improvement was highest in the HPLT group (Δ = 2.10), followed by LLLT (Δ = 2.00), and lowest in placebo (Δ = 1.00). For ChIMES, the greatest reduction was seen in HPLT (Δ = 14.40), followed by LLLT (Δ = 13.44), compared with placebo (Δ = 6.50) (Fig. 4).

Pairwise comparisons showed no significant difference between HPLT and LLLT for WHO ($p = 0.538$) or ChIMES ($p = 0.303$). However, both HPLT and LLLT were significantly superior to placebo for WHO (HPLT $p = 0.002$; LLLT $p = 0.006$) and ChIMES (HPLT $p = 0.001$; LLLT $p < 0.001$).

Secondary outcome (Day 1 to Day 4)

For WHO, significant differences were observed among groups (H = 14.263, p = 0.001), with greatest improvement in HPLT (Δ = 1.30), followed by LLLT (Δ = 0.89), and placebo (Δ = 0.30).

For ChIMES, differences were also significant (H = 18.100, p < 0.001), favoring HPLT (Δ = 8.50), followed by LLLT (Δ = 6.33), and placebo (Δ = 2.70) (Fig. 5).

Pairwise analysis showed no significant difference between HPLT and LLLT for WHO (p = 0.051) or ChIMES (p = 0.126). Both laser groups showed significantly greater improvement than placebo for WHO (HPLT p = 0.001; LLLT p = 0.012) and ChIMES (both p < 0.001), indicating superior efficacy of laser therapy over placebo (Table 2).

Table 1
Baseline demographic characteristics of the study participants

Variable		HPLT	LLLT	Placebo	Test statistic	P-value
Age, median (years)		8.20	8.40	7.60	H = 0.536	0.765
Sex:	male, n (%)	7 (70%)	5 (50%)	5 (50)	χ^2 = 1.09	0.581
	female, n (%)	3 (30%)	5 (50%)	5 (50)		

Table 2
Intergroup analysis of the improvement in oral mucositis severity measured by WHO and ChIMES scales between baseline (Day 1) and follow-up assessments (Day 4 and Day 11).

Tool scale	Outcomes	Groups	Kruskal–Walli's test	Pairwise comparisons	Mann–Whitney U test
WHO	**Δ Day 1 → Day 11**	**HPLT G.**	H = 11.254 P = 0.004	**HPLT vs LLLT**	U = 42.500, P = 0.538
		LLLT G.		**HPLT vs Placebo**	U = 12.500, P = 0.002
		Placebo G.		**Placebo vs LLLT**	U = 17.500, P = 0.006
	Δ Day 1 → Day 4	**HPLT G.**	H = 14.263 P = 0.001	**HPLT vs LLLT**	U = 28.000, P = 0.051
		LLLT G.		**HPLT vs Placebo**	U = 10.500, P = 0.001
		Placebo G.		**Placebo vs LLLT**	U = 18.500, P = 0.012
ChIMES	**Δ Day 1 → Day 11**	**HPLT G.**	H = 11.254 P = 0.004	**HPLT vs LLLT**	U = 36.500, P = 0.303
		LLLT G.		**HPLT vs Placebo**	U = 6.000, P = 0.001
		Placebo G.		**Placebo vs LLLT**	U = 2.000, P < 0.001
	Δ Day 1 → Day 4	**HPLT G.**	H = 14.263 P = 0.001	**HPLT vs LLLT**	U = 26.500, P = 0.126
		LLLT G.		**HPLT vs Placebo**	U = 3.000, P < 0.001
		Placebo G.		**Placebo vs LLLT**	U = 3.000, P < 0.001

* Statistically significant at $p < 0.05$

Discussion

Oral mucositis (OM) is one of the most frequent and debilitating complications of chemotherapy in pediatric oncology patients. Although OM is generally considered a self-limiting condition [20], it can cause severe pain, impaired oral intake, nutritional compromise, increased risk of infection, prolonged hospitalization, and interruption of anticancer treatment, all of which may negatively affect prognosis and quality of life [21]. Consequently, identifying effective supportive therapies capable of reducing OM severity and accelerating healing remains a major clinical priority.

Low Level Laser therapy (LLLT) has emerged as a clinically effective and safe approach for both the prevention and treatment of OM in oncologic settings. Evidence from multiple systematic reviews and international guidelines, including MASCC/ISOO, WALT, and NICE, supports the use of laser therapy for reducing the incidence, severity, pain, and duration of OM while improving patients' quality of life and facilitating continuity of cancer treatment [22]. Nevertheless, despite the growing body of evidence supporting LLLT, pediatric-specific data remain limited, and optimal treatment parameters have not yet been clearly established [23].

(LLLT) were significantly more effective than placebo in reducing the severity of chemotherapy-induced oral mucositis in pediatric patients with acute lymphoblastic leukemia over the study period from Day 1 to Day 11. However, HPLT achieved the greatest overall reduction in both WHO mucositis grades and ChIMES scores, indicating superior efficacy in improving both clinical severity and patient-reported oral function.

These findings support the growing evidence regarding the beneficial role of photobiomodulation therapy (PBMT) in the management of oral mucositis in oncology patients. International guidelines, including MASCC/ISOO, WALT, and NICE, recognize PBMT as a safe and effective supportive intervention capable of reducing OM severity, pain, and treatment-related complications while improving quality of life and facilitating continuity of cancer therapy [22].

The superior therapeutic outcomes observed with HPLT may be explained by its enhanced tissue penetration and stronger biostimulatory effects compared with LLLT. Experimental studies have shown that high-power laser irradiation stimulates mitochondrial activity, increases ATP production, enhances angiogenesis and microcirculation, and modulates inflammatory cytokines, thereby accelerating epithelial regeneration and tissue repair [24]. These biological mechanisms may account for the greater reductions in mucositis severity and symptom burden observed in the HPLT group.

Our findings are generally consistent with previous pediatric studies evaluating laser therapy for OM management. [25] reported significant reductions in oral pain and analgesic use among pediatric patients treated with LLLT, while [26] concluded that LLLT may provide clinically beneficial effects in reducing oral pain and severe mucositis despite variability among protocols and outcomes. Similarly, [23] demonstrated that LLLT reduces OM severity and oral pain in pediatric and young cancer patients, although the authors emphasized the need for standardized laser parameters and additional high-quality clinical trials.

Evidence regarding HPLT in pediatric oncology remains relatively limited; however, available studies support its promising therapeutic potential. [27] demonstrated rapid improvement in oral lesions, pain, and oral functional outcomes following HPLT in pediatric patients with chemotherapy-induced OM. Likewise, [28] reported significant reductions in mucositis severity and pain, with faster lesion healing in the HPLT group compared with placebo. These findings are in agreement with the present study, in which HPLT achieved the greatest overall improvement in both WHO and ChIMES scores.

An important strength of the present study is the combined use of the WHO grading system and the ChIMES scale. While the WHO scale provides clinician-based assessment of mucosal injury severity, the ChIMES scale evaluates multiple patient-centered dimensions including pain, swallowing, eating, drinking, and analgesic requirement. The integration of both measures allowed a comprehensive evaluation of treatment response encompassing both clinical and functional aspects of oral mucositis.

To the best of our knowledge, this study is among the few pediatric investigations directly comparing high-power laser therapy, low-level laser therapy, and placebo in chemotherapy-induced oral mucositis using both clinical and patient-reported outcome measures. The findings suggest that although both laser modalities are effective, HPLT may provide superior overall therapeutic benefits in pediatric patients undergoing chemotherapy for acute lymphoblastic leukemia.

Beyond statistical significance, the observed clinical improvements may have important practical implications. Reduction in OM severity and oral pain may improve nutritional intake, hydration, oral function, and adherence to chemotherapy protocols while potentially reducing hospitalization and the need for analgesic medications. Consequently, effective OM management may contribute to improving overall quality of life and supportive care outcomes in pediatric oncology patients.

Despite these promising findings, several limitations should be acknowledged. The sample size was relatively small, and the follow-up duration was limited to the acute treatment period, which may affect the generalizability of the results. Nevertheless, this study provides important comparative evidence regarding the effectiveness of HPLT and LLLT in pediatric oral mucositis management. Future multicenter randomized controlled trials with larger sample sizes and standardized laser protocols are warranted to establish optimal treatment parameters and evaluate long-term outcomes.

Conclusion

Chemotherapy-induced oral mucositis remains a common and clinically relevant complication in pediatric acute lymphoblastic leukemia, contributing to significant morbidity and treatment burden. In this randomized placebo-controlled trial, both high-power laser therapy (HPLT) and low-level laser therapy (LLLT) demonstrated clinically meaningful reductions in mucositis severity compared with placebo, with benefits observed at both early and late follow-up assessments.

These findings support the potential role of photobiomodulation as an effective supportive care strategy in pediatric oncology. HPLT may offer practical advantages due to its extra-oral application and wider tissue coverage, while LLLT provides a more localized intra-oral approach. Further large-scale multicenter trials are required to confirm these findings and optimize treatment protocols.

Declarations

The study was approved by the Institutional Ethics Committee of the Children’s University Hospital and conducted in accordance with the Declaration of Helsinki. It was registered in the ISRCTN registry

(ISRCTN18078092). Written informed consent was obtained from parents or legal guardians.

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Authors' contributions

The study was designed by the principal investigator also Patient recruitment, treatment administration, and data collection were performed by the principal investiga. Statistical analysis was conducted with input from a blinded statistician. All authors contributed to data interpretation, manuscript drafting, and critical revision, and approved the final version.

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Data availability

Data are not publicly available due to confidentiality restrictions but can be requested from the corresponding author.

Conflicts of interest

The authors declare no conflicts of interest.

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Figures

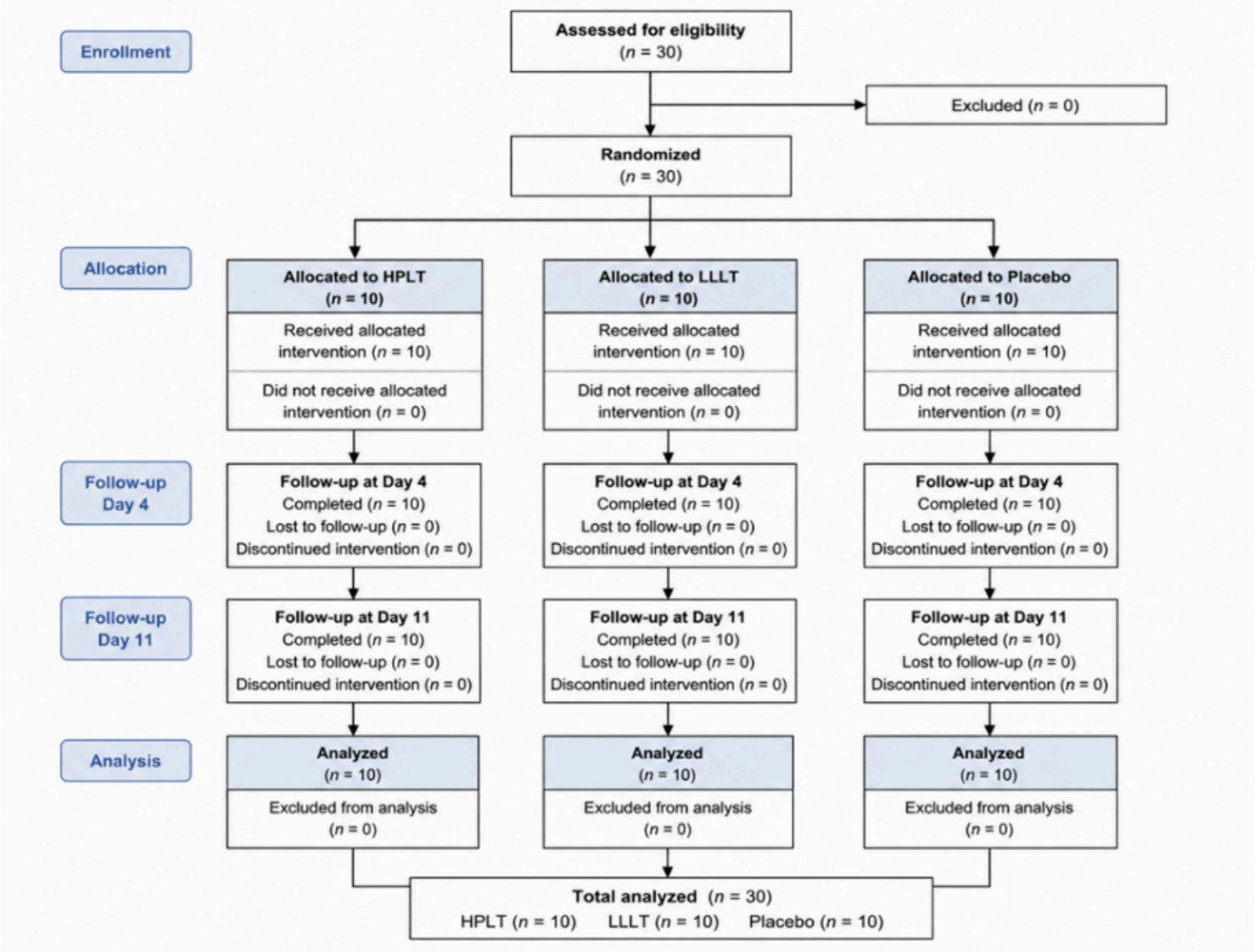


Figure 1

Flow chart of study participants



Figure 2

Clinical appearance of oral mucositis treated with HPLT on (A) Day1 WHO:4 ChIMES: 21 (B) Day 4 WHO: 2 ChIMES: 8, and (C) Day 11 WHO: 0 ChIMES:0



Figure 3

Clinical appearance of oral mucositis treated with LLLT on (A) Day1 WHO:4 ChIMES: 23 (B) Day 4 WHO: 3 ChIMES: 16, (C) Day 11 WHO: 1 ChIMES:7

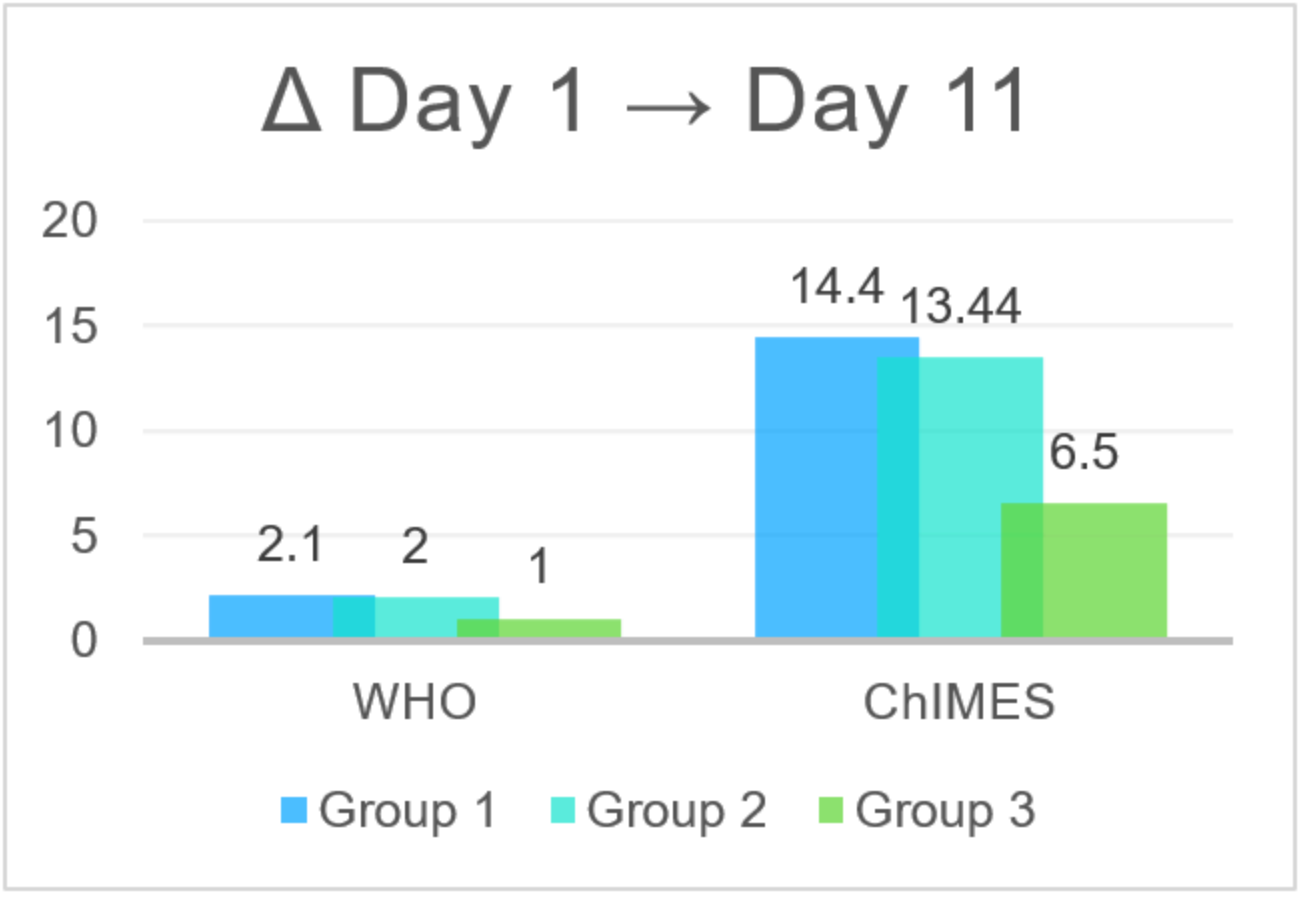


Figure 4

Comparison of the mean reduction in oral mucositis severity between Day 1 and Day 11, as assessed by the WHO and ChIMES scales in the HPLT, LLLT, and placebo groups.

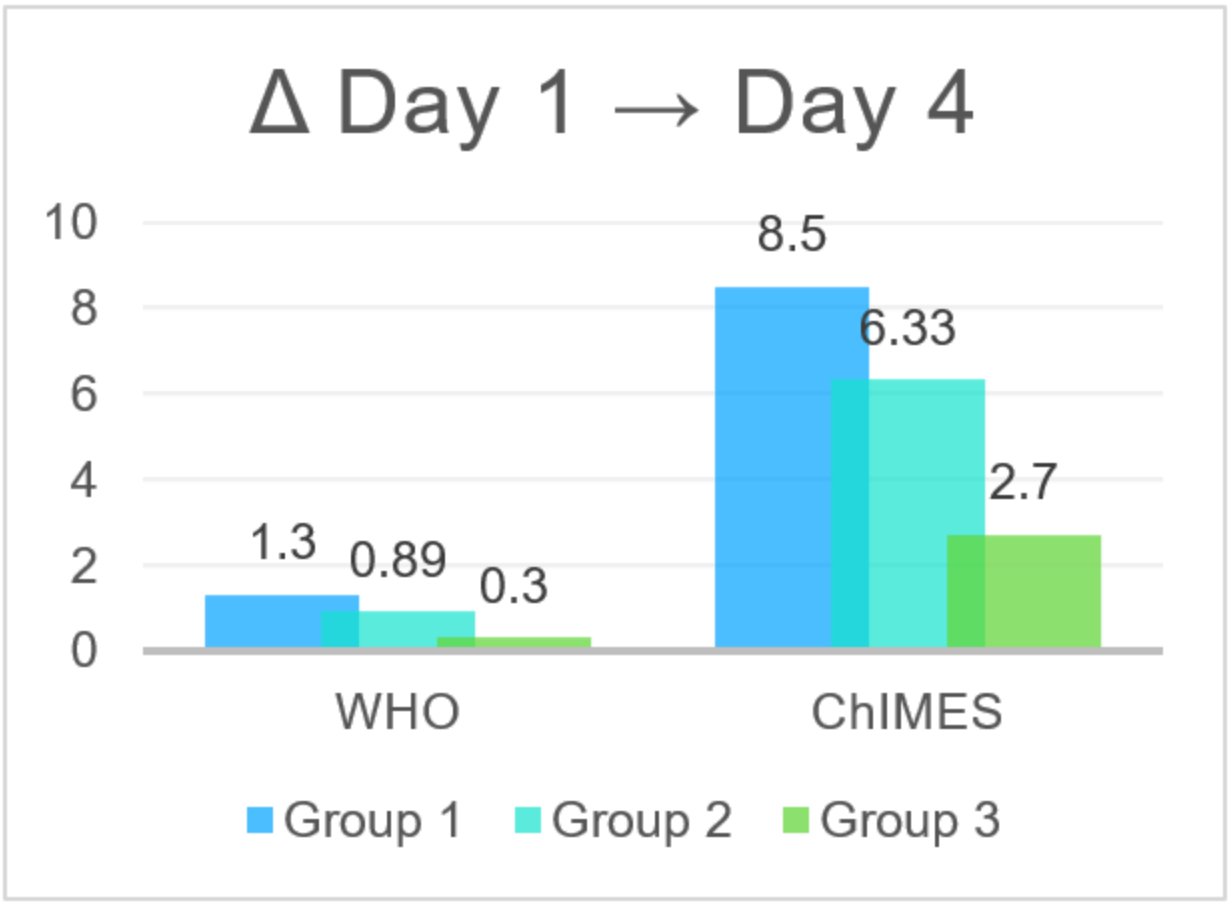


Figure 5

Comparison of the mean reduction in oral mucositis severity between Day 1 and Day 4, as assessed by the WHO and ChIMES scales in the HPLT, LLLT, and placebo groups.