ORIGINAL ARTICLE

Photobiomodulation in Paediatric Chemotherapy Induced Mucositis - A Pilot Study

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ABSTRACT

Introduction: Oral mucositis, seen in up to 80% of children receiving chemotherapy for malignant conditions, causes severe discomfort and can compromise the child's nutrition which might affect the treatment. Despite the prevalence of this condition, no definitive therapeutic treatment has been suggested to mitigate the consequences. Therefore, we decided to study the effect of photobiomodulation (PBMT) in this condition. **Methods:** Ten patients, with grade two or greater mucositis who agreed for laser treatment were treated with 980 nm diode of 0.2W in continuous mode after calculating their power irradiance and time, with another two patients serving as the control group. This was repeated three times a day for seven consecutive days. The degree of oral mucositis according to the WHO scale as well as the pain score using the Visual Analogue Scale (VAS), were measured until day 15 after the start of the intervention. **Results:** The mean pain score of the PBMT group based on VAS at the base line was 8.40 which reduced to a score of 6.20 on the third day and to 0.30 on the 15th day, compared to the non-PBMT group which showed a pain score of eight and 1.50, respectively. **Conclusion:** Our study showed that PBMT can be integrated into the standard treatment modalities for this condition. The small participant size being a major drawback, studies with bigger sample size and randomization would be needed to validate our result.
Malaysian Journal of Medicine and Health Sciences (2025) 21(SUPP13): 52-56. doi:10.47836/mjmhs.21.s13.9

Keywords: oral mucositis, photobiomodulation, low level laser therapy, chemotherapy, paediatric malignancy.

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INTRODUCTION

The incidence of paediatric malignancies appears to have risen over the past few decades with the overall cancer rate in children and adolescents in the United States increasing by approximately 0.80 per 100,000 annually from 1975 to 2022 (1). In the age group one to 14 years, malignancies have been the second most common cause of death in US (after accidents) and among the 15 to 19 years old, it's the fourth cause. However, the bright spot on the horizon is that death rates decreased from 1970 through 2019 by 71% in children (from 6.30 to 1.80 per 100,000) and by 61% in adolescents (from 7.20 to 2.80 per 100,000). This is mainly because of the tremendous advances that have happened in traditional treatment approaches like chemotherapy, surgery and radiotherapy as well as newer modalities like immunotherapy, targeted therapy, etc. But this has come with its own side effects or complications, which might be of comparatively short duration or lifelong. The lifelong effects could be neurologic and/or developmental deficiencies, second malignant neoplasms (in 3 to 12% of survivors, varying with their initial cancer and type of treatment), cardiac damage, delayed or absent puberty, etc (2). The short-term complications include hair loss, nausea and vomiting, mouth sores, infection, constipation, diarrhoea, etc., with oral mucositis (OM) being one of the most common side effects.

In children, OM has been reported in almost 65% of chemotherapy cycles when used for solid and hematologic cancers. Previous study has reported that the incidence of OM was higher in protocols using high-dose methotrexate, with the rate of severe oral mucositis (SOM) being 8.44%. A strong association between SOM and protocols using high-dose methotrexate (10.50%) or a combination of methotrexate and cyclophosphamide (>28.30%) were observed (3).

Oral mucositis can result in these children having severe mouth pain and difficulty in eating which can lead to compromised nutrition or in extreme cases, parenteral nutrition. This may also result in infections of the oral cavity, which can progress to disseminated systemic infections in these immunocompromised children. In the recent past, there have been quite a few studies which have shown promising results in treating oral mucositis with low level laser therapy (LLLT) otherwise known as photobiomodulation therapy (PBMT). So, we decided to conduct a study to evaluate the efficacy of PBMT in diminishing chemotherapy-induced oral mucositis and relieve related symptoms in paediatric patients.

MATERIALS AND METHODS

This study was done at Shirdi Sai Baba Cancer Hospital and Research Centre, Manipal, India. Ethical approval for the research was obtained from KMC & KH Institutional Ethics Committee (IEC572/2015).

This was a prospective, single-center, single blinded, non-randomized, single arm interventional study, Our exclusion criteria were: children undergoing chemotherapy for solid tumours, no history of previous chemotherapy administration, children on radiotherapy, children who underwent other modalities of treatment for mucositis recently, children who were unable to give the pain score using the VAS (Figure 1), head & neck cancers and oral mucositis of grade ≤1 (Table I).

12 patients receiving chemotherapy for haematological malignancies and who were suffering from oral mucositis (grade ≥2) were enrolled for this study. The age of the patients ranged from 7 to 12 years, with the mean age being 9.75 (1.42) years. Of these 12, two patients refused the proposed intervention just before the commencement of the study. These two patients who were nine and 10 years old, were included in the non-PBMT/control group. After explaining the various aspects of the proposed treatment, informed consent was obtained from the patients as well as their parents. All patients underwent dental and oral health evaluation. Oral hygiene kits with paste and soft brushes were distributed to all participants. Oral hygiene was monitored daily by the research team, throughout the study. The 2 patients who were included in the non-PBMT group were also monitored throughout the study and received only oral hygiene instructions. None of the children received any analgesics during the study

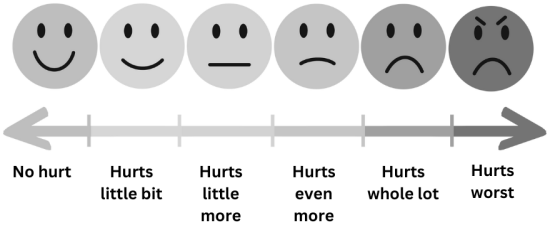

Figure 1: Visual analogue scale

Table I: World Health Organization Grades of Mucositis

Grade	Description
0	No changes
1	Soreness/erythema
2	Soreness/erythema + ulceration + ability to eat solid foods
3	Soreness/erythema + ulceration + ability to use a liquid diet only
4	Soreness /erythema + ulceration + no possible oral alimentation

period. The data were analyzed using IBM SPSS Statistics version 27 with descriptive statistics.

Laser parameters and protocol

Diode laser 980nm with wave length of 0.2 W was used in continuous mode on a focal spot of 1cm^2, using an intraoral approach. Power irradiance and time was calculated for each patient based on their toxicity score of mucositis that ranged from 4-16 J/cm^2 and time ranging from 15-60 sec. This was repeated 3 times a day for 7 consecutive days. The therapy dosing was calculated based on the formula E=P x T (Energy = Power x Application Time). which was then calculated for the targeted surface area. The dosage ranged from 4-16 J/cm2 and time ranging from 15-60 sec. (grade 4=15 J for 60 sec, grade 3=8 J for 30 sec and grade 2=4J for 15 sec).

Evaluation

A paediatric oncology palliative care nurse was trained in the VAS as well as WHO Oral Toxicity score scale interpretation but was blinded to the treatment and control groups. All the patients were evaluated for their pain score and oral toxicity score of mucositis at baseline and up to the 15th day, by the same person. The degree of oral mucositis was measured according to the WHO scale (4) until day 15 after the start of the intervention. The pain score was recorded using the VAS at the same time. Children were asked to score their pain experienced using the pain rating scale that was provided. Personal data of each patient was also collected.

RESULTS

The mean age of the participants in our study was 9.75 (1.42) years. All 12 patients who were enrolled for the study were undergoing similar type of chemotherapy but were not suffering from the same type of malignancy, nor were the doses of the chemotherapeutic agents same. Of these 12, four patients had a mucositis score of four, six patients had a score of three and two patients had a score of two.

In the group that underwent PBMT there were four patients with mucositis score of four, another four patients with a score of three and two patients with a score of two. The mean pain score of this group based

on VAS at the base line was 8.40 (0.52) which reduced to a score of 6.20 (1.03) on third day. In the non-PBMT group, both patients had a mucositis score of three and a pain score of eight at base line as well as on the third day (Tables 2 & 3). On the fifth day the PBMT group showed six patients with a toxicity score of two and four patients with a score of one. The mean pain score was reduced to 2.60 (0.52) compared to the non-PBMT group which showed a pain score of seven and a mucositis score of three. (Tables II & III). On the seventh day, in the PBMT group pain reduced to mean score of 2.40 (0.52) compared to non-PBMT group which showed a mean pain score of 5.00 (0). The severity of mucositis also reduced in the PBMT group, with two patients in grade 0, four patients in grade 1 and four patients in grade 2 toxicity score (Tables II & III). On the 15th day the mean pain score in the PBMT group reduced to 0.30 (0.48) with eight patients showing a grade of 0 compared to the non-PBMT group which showed a pain score of 1.50 (0.71) (Tables II & III).

DISCUSSION

According to the systematic review and meta-analysis done by Mengxue He, et al (5) OM occurs in approximately 52 to 80% of children receiving chemotherapeutic treatment. Beech N, et al (6) state that the rapid cellular turnover of the basal layer of the oral mucosa makes it susceptible to injury and cell death and this coupled with the incapacity of the mucosa to heal, leads to the development of oral mucositis. Mucosal cells lining the oral cavity as well as the rest of the gastrointestinal tract reproduce rapidly and so are susceptible to destruction by the chemotherapeutic agents. OM usually present as erythematous, atrophic, and painful lesions that are the result of a string of molecular as well as cellular occurrences which end up in epithelial damage and death. Stephen T Sonis (7) distinguishes the underlying molecular and cellular pathobiology of OM in five phases: initiation, the primary damage response, signaling and amplification, ulceration, and healing. He states that it is the epithelial stem cells which are the targets in a dynamic process in which reactive oxygen species, transduction and transcription pathways, signaling and functional mediators, and bacteria play important roles in the development and resolution of mucositis.

OM usually sets in within a week of starting the chemotherapeutic regime. Depending on the severity it can act as a hindrance in starting the next course of the regime or a dose reduction, concomitantly resulting in prolonged hospital stay, soaring costs, diminished quality of life and decreased survival rate (8).

Studies suggest that pain is one of the most distressing symptoms experienced by patients with oral mucositis, making inclusion of a pain scale essential in any assessment tool (9). In our study also pain was the reason why the children as well as their parents agreed to be part of the study. While pain assessment in pediatric mucositis is undeniably challenging, it remains a critical reason why oral mucositis warrants further study. Sonis et al. (10) argued that pain can be influenced by the use of analgesia, which might lead investigators to underreport the severity of mucositis. Consequently, they suggested that pain should not be included in scales used for research but in our study analgesics, oral or parenteral, were not.used during the duration of the study. Our study demonstrated a reduction in both pain and the severity of mucositis following PBMT. This aligns with the findings of Redman MG, et al (11) who

Table II: Comparison of VAS (Visual Analog Scale) scores between the groups

Timeline	PBMT group (n=10) Mean (SD)	95% CI	Non-PBMT group (n=2) Mean (SD)	95% CI
Baseline	8.40 (0.52)	8.03,8.77	8.00 (0)	8.00,8.00
3 days	6.20 (1.03)	5.46,6.94	8.00 (0)	8.00,8.00
5 days	2.60 (0.52)	2.23,2.97	7.00 (0)	7.00,7.00
7 days	2.40 (0.52)	2.03,2.77	5.00 (0)	5.00,5.00
15 days	0.30 (0.48)	-0.05,0.65	1.50 (0.71)	-4.85,7.85

Table III: Oral Mucositis grading of the groups following treatment, based on WHO criteria.

Groups	Grading	Baseline n (%)	3 days n (%)	5 days n (%)	7 days n (%)	15 days n (%)
PBMT group	Grade 0	-	-	-	2 (20.0)	8 (80.0)
	Grade 1	-	-	4 (40.0)	4 (40.0)	2 (20.0)
	Grade 2	2 (20.0)	4 (40.0)	6 (60.0)	4 (40.0)	-
	Grade 3	4 (40.0)	6 (60.0)	-	-	-
	Grade 4	4 (40.0)	-	-	-	-
Non PBMT group	Grade 0	-	-	-	-	1 (50.0)
	Grade 1	-	-	-	-	1 (50.0)
	Grade 2	-	-	-	2 (100.0)	-
	Grade 3	2 (100.0)	2 (100.0)	2 (100.0)	-	-
	Grade 4	-	-	-	-	-

observed in their meta analysis that PBMT may reduce the severity of mucositis and associated oral pain.

Mengxue He, et al (5) in their meta-analysis found that prophylactic as well as therapeutic PBMT reduces the overall risk of oral mucositis and severe mucositis (grade III or higher) and decreases the average severity of oral mucositis in pediatric and young patients with cancer or undergoing haematopoietic stem cell transplantation (HSCT). According to them, it is not just the effects of therapeutic PBMT on the duration of OM that was promising but also the effects of prophylactic PBMT on the duration of OM & oral pain. Our study did not include prophylactic PBMT and focused only on the therapeutic effect of PBMT.

How PBMT brings about these positive effects have not been understood very clearly. According to a study in 2012 (12), this is brought about by the conversion of laser light input through photophysical and biochemical processes.. Bensadoun R and Nair RG's (13) in vitro testing suggested that energy absorption by photoreceptors during PBMT might be promoting cellular proliferation due to positive cell metabolic process, resulting in improved tissue repair. Another in vitro study (14) on the effect of PBMT on proliferation, cell cycle distribution, and apoptosis in fibroblasts showed that PBMT increased fibroblast proliferation significantly ($P < 0.01$). When oral mucositis-related inflammatory cytokines were used to challenge oral fibroblasts, it was shown that PBMT counteracted the negative effects of high concentration of inflammatory cytokines, especially IL-6 and IL-8 on gingival fibroblast functions directly related to the wound-healing process (15).

The WALT position paper (16) mentions that the biologic effects are due to a number of variables - namely, the location of the cells in the field of exposure, cell type, molecular and redox state of the cell, the tissue microenvironment, PBM parameters such as wavelength, power density, type of delivery as in pulsing or continuous, beam or spot size, and duration of exposure.

A systematic review and meta-analysis on efficacy of PBMT for treatment of cancer oral mucositis found that PBMT brought about a 62% risk reduction of severe mucositis on the seventh day of evaluation (RR = 0.38 [95% CI, 0.19-0.75])"(17). When they analyzed subgroups, they found that RR (Relative Risk) was 0.28 (95% CI 0.17-0.46) in the adult studies and 0.90 (95% CI, 0.46-1.78) in the studies with children and adolescents. They showed a mean reduction of 4.21 days in the time of complete resolution of OM (CI - 5.65 to - 2.76) in favor of LLLT. In their study, there was moderate evidence that PBMT is effective in resolving OM lesions in adult patients undergoing cancer therapy. They are of the opinion that PBMT has the capability to reduce the healing time of OM lesions by around 4.21 days. In our study by the 5th day, the pain score had reduced from the baseline of 8.40 to around 2.60 and the toxicity score had come down to two in six patients and one in the other four patients. A recent randomized controlled trial (18) to evaluate the effectiveness of PBMT for chemotherapy-induced oral mucositis (OM) in leukemic children found significant reduction of pain on day 10 in the test group compared to the control group ($p < 0.001$). There was also a significant decline in the OM grades between the two groups on day 14 ($p = 0.003$). Our study also reflected similar effects by the 10th day. Even though there are reports of side effects like burning sensation of the treated area (14) following PBM therapy, none of our patients complained of any side effects or complications which is similar to the findings in this randomized controlled trial (18). In the study by Chermetz M, et al (19) also all the included patients had reduction in pain sensation as well as mucositis, by the 11th day. Ludovichetti FS, et al (20) used high power laser therapy (HPLT) to treat OM in 14 oncohematological paediatric patients and concluded that it is a safe and efficacious method for managing the condition.

The small number of participants and the lack of randomization are major limitations of our study. The absence of randomization may have unintentionally introduced selection bias. Another limitation could be that, although both groups received oral hygiene instructions, the PBMT group might have received more attention inadvertently because they were receiving the additional treatment, again possibly leading to a performance bias.

CONCLUSION

Despite the above limitations, our study suggests that photobiomodulation therapy could be integrated into standard care protocols for children with chemotherapy induced oral mucositis providing a non-invasive and effective method to alleviate chemotherapy-induced oral mucositis. Based on our findings we would like to suggest future studies that randomize patients to balance the confounding factors in OM which might be patient-related, treatment-related or disease-related.

ACKNOWLEDGEMENT

We are grateful to the children who agreed to be part of this study and their parents too, for permitting their children to be part of this study.

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A : Cancer Statistics, 2022.CA Cancer J Clin. 2022;72(1):7–33. doi: 10.3322/caac.21708.
2. Kee Kiat Yeo, MD., Overview of Pediatric Cancer, MSD MANUALS, Jan 2023

3. Curra M, Gabriel AF, Ferreira MBC, Martin MAT, Brunetto AT, Gregianin LJ et al. Incidence and risk factors for oral mucositis in pediatric patients receiving chemotherapy. Support Care Cancer. 2021; 29: 6243-6251.doi: 10.1007/s00520-021-06199-5. Epub 2021 Apr 12.
4. World Health Organization. Vol. 48. WHO Offset Publication. 1979. pp. 15-22 https://iris.who.int/handle/10665/37200
5. He, M., Zhang, B., Shen, N., Wu, N., & Sun, J. A systematic review and meta-analysis of the effect of low-level laser therapy (LLLT) on chemotherapy-induced oral mucositis in pediatric and young patients. European Journal of Pediatrics. 2017: 177(1), 7–17. doi:10.1007/s00431-017-3043-4
6. Beech N, Robinson S, Porceddu S, Batstone M. Dental management of patients irradiated for head and neck cancer. Australian Dental Journal. 2014;59(1), 20-28. doi:10.1111/adj.12134
7. Stephen T Sonis. Pathobiology of oral mucositis: novel insights and opportunities. J Support Oncol. 2007 Oct;5(9 Suppl 4):3-11.PMID: 18046993.
8. Linda S Elting, Catherine Cooksley, Mark Chambers, Scott B Cantor, Ellen Manzullo, Edward B Rubenstein .The burdens of cancer therapy: clinical and economic outcomes of chemotherapy-induced mucositis. Cancer. 2003 Oct 1;98(7):1531-9. doi: 10.1002/cncr.11671.
9. Jaroneski, L.A., 2006. The importance of assessment rating scales for chemotherapyinduced oral mucositis. Oncol. Nurs. Forum 33, 1085–1090. DOI: 10.1188/06.ONF.1085-1093
10. Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, Bekele BN, Raber-Durlacher J, Donnelly JP, Rubenstein EB; Mucositis Study Section of the Multinational Association for Supportive Care in Cancer; International Society for Oral Oncology. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer. 2004 May 1;100(9 Suppl):1995-2025. doi: 10.1002/cncr.20162. PMID: 15108222.
11. Melody Grace Redman, Katherine Harris, Bob S Phillips Low-level laser therapy for oral mucositis in children with cancer. Archives of Disease in Childhood, 2021, № 2, p. 128-133 https://doi.org/10.1136/archdischild-2020-321216
12. de Castro JFL, Abreu EGF, Correia AVL, de Mota Vasconcelos Brasil C. Low-level laser in prevention and treatment of oral mucositis in pediatric patients with acute lymphoblastic leukemia. Photomed Laser Surg. 2013; 31(12):613–618. https://doi.org/10. 1089/pho.2012.3327)
13. Bensadoun R, Nair RG. Low-level laser therapy in the prevention and treatment of cancer therapy-induced mucositis: State of the art based on literature review and meta-analysis. Curr Opin Oncol. 2012 Jul;24(4):363-70. doi: 10.1097/CCO.0b013e328352eaa3.
14. Schartinger VH, Galvan O, Riechelmann H. Differential responses of fibroblasts, non-neoplastic epithelial cells, and oral carcinoma cells to low-level laser therapy. Support Care Cancer. 2012 Mar;20(3):523-9. doi: 10.1007/s00520-011-1113-0.
15. Basso FG, Soares DG, Pansani TN, Cardoso LM, Scheffel DL. Proliferation, migration and expression of oral-mucosal healing-related genes by oral fibroblasts receiving low-level laser therapy after inflammatory cytokines challenge. Lasers Surg Med. 2016 Dec;48(10):1006-1014. doi: 10.1002/lsm.22553.
16. Robijns J, Nair RG, Lodewijckx J, Arany P, Barasch A, Bjordal JM, et al. Photobiomodulation therapy in management of cancer therapy-induced side effects: WALT position paper. Front Oncol. . 2022 Aug 30:12:927685. doi: 10.3389/fonc.2022.927685.
17. Anschau F, Webster J, Capra MEZ, de Azeredo da Silva ALF, Stein AT Efficacy of low-level laser for treatment of cancer oral mucositis: a systematic review and meta-analysis. Lasers Med Sci. 2019 Aug;34(6):1053-1062. doi: 10.1007/s10103-019-02722-7.
18. Reyad FA, Elsayed NM, El Chazli Y. Photobiomodulation for chemotherapy-induced oral mucositis in leukemic children: A randomized controlled clinical trial. Oral Dis. 2023 Jul;29(5):2239-2247. doi: 10.1111/odi.14217. Epub 2022 May 4. PMID: 35460304.
19. Chermetz M, Gobbo M, Ronfani L, Ottaviani G, Zanazzo GA, Verzegnassi F, et al. Class IV laser therapy as treatment for chemotherapy-induced oral mucositis in onco-haematological paediatric patients: a prospective study. Int J Paediatr Dent .2014; 24(6):441–9.doi: 10.1111/ipd.12090. Epub 2013 Dec 25.
20. Ludovichetti FS, Costa G, Signoriello AG, Stellini E, Zerman N, Biffi A, Mazzoleni S. Evaluating high power laser therapy (HPLT) as treatment for chemotherapy-induced oral mucositis in paediatric patients with oncohematological diseases. Int J Paediatr Dent. 2023 May;33(3):269-277. doi: 10.1111/ipd.13050. Epub 2023 Mar 10. PMID: 36692188.