




Window therapeutic of extraoral photobiomodulation for prevention of oral mucositis in HSCT patients: additional arm

Letícia Beatriz da Cruz Santos¹ · Mariana Bitu Ramos-Pinto¹ · Rodolfo Maestrello Zerbato¹ · Maria Emilia Mota Galdino Ferreira¹ · Jayr Schmidt-Filho² · Manoela Domingues Martins³ · Fabio Abreu Alves^{1,4} 

Received: 20 September 2023 / Accepted: 6 December 2023
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2023

Abstract

Purpose This study aimed to evaluate the efficacy of 1W extraoral photobiomodulation (EOPBM) and to compare with our previous results of 2W EOPBM and intraoral photobiomodulation (IOPBM) protocols in the management of oral mucositis (OM) related to hematopoietic stem cell transplantation (HSCT).

Methods A total of 30 patients underwent autologous or allogenic HSCT. Experimental protocol of 1W EOPBM was performed daily beginning in the first day of the conditioning regimen until 5 days after transplantation. The application areas included six points on the face and three points on the cervical area. Additional application of IOPBM was performed if patients had ulcerated mucositis. Its severity was assessed daily according to WHO (World Health Organization) and NCI (National Cancer Institute) scales. Oral and oropharynx pains were scored daily by visual analogue scale (VAS).

Results The 1W EOPBM protocol was well tolerated without any complaints. Of total, 13 patients were male and 17 were female and the mean age was 49.3 years old. Most patients (21 patients — 70%) received autologous HSCT, and 24 patients (80%) underwent myeloablative conditioning (MAC) regime and 6 patients (20%) reduced intensive conditioning regime. Nineteen patients (63.3%) developed OM according to WHO criteria, 3 patients grade I, 10 grade II and 6 grade III. NCI mucositis grades were similar to WHO grades. OM outcomes of 1W EOPBM were similar when compared to our previous groups and no significant differences were observed. No differences were found between pain and the protocols (1W EOPBM, IOPBM and 2W EOPBM).

Conclusion This 1W EOPBM protocol seemed to be as effective as IOPBM and 2W EOPBM in the prevention of OM in HSCT patients. In addition, we might assume that there is a window of application on EOPBM.

Keyword Hematopoietic stem cell transplantation · Oral mucositis · Photobiomodulation · Extraoral photobiomodulation

Comment

Oral mucositis (OM) is a debilitating and painful complication that affects most of the patients who underwent hematopoietic stem cell transplantation (HSCT). Severe OM impairs the normal oral functions, increases supportive care, and may interrupt the oncological treatment [1]. Photobiomodulation (PBM) has been recommended for the prevention of OM in HSCT patients through intraoral low-power lasers or LEDs due to its ability to reduce the incidence and severity of OM [2].

New PBM perspectives have emerged and extraoral photobiomodulation (EOPBM) has minimize the mouth opening discomfort [3–5]. However, adjustments of the dosimetry such as the use of Infrared wavelengths and higher potency are necessary for better tissue penetration of photons in deeper

✉ Fabio Abreu Alves
falves@accamargo.org.br

¹ Stomatology Department, A.C. Camargo Cancer Center, R: Prof. Antônio Prudente, 211, Bairro: Liberdade, São Paulo 01509-900, Brazil

² Hematology Department, A.C. Camargo Cancer Center, São Paulo, Brazil

³ Department of Oral Pathology, School of Dentistry, Federal University of Rio Grande Do Sul, Porto Alegre, RS, Brazil

⁴ Stomatology Department, School of Dentistry, Sao Paulo University, Sao Paulo, Brazil

tissues and improve PBM efficacy. In a previous study, our group observed that the protocol of EOPBM infrared diode laser (Gemini Ultradent, 810 + 980 nm, 2W, 4.07 J/cm², 4.91 cm², 10 s, 20 J per point) presented similar results to well established IOPBM red diode laser (MMOptics DUO, 660 nm, 0.1W, 0.03 cm², 33.3 J/cm², 10 s, 1 J per point) [6] in prevention of OM in HSCT patients. New parameters of EOPBM should be evaluated to develop this modality as possible standard care for OM in oncological patients. Therefore, the purpose of this study was to evaluate the efficacy of another protocol, 1W EOPBM, and to compare with our previous results of 2W EOPBM and IOPBM protocols in the management of OM related to HSCT (Table 1). This controlled clinical trial in accordance with the Declaration of Helsinki was approved by the Ethics Committee of the A. C. Camargo Cancer Center, Sao Paulo, Brazil (no. 3146/2). A total of 30 patients underwent autologous or allogenic HSCT was evaluated. The same inclusion and exclusion criteria of the previous study were used. Experimental protocol of 1W EOPBM (Gemini Ultradent, 810 + 980 nm, 1W, 6.11 J/cm², 4.91 cm², 30 s, 30 J per point) was performed daily beginning in the first day of the conditioning regimen until 5 days after transplantation

(day + 5). The application areas included 6 points on the face (2 on both right and left cheeks, and 1 on the lips) and three points on the cervical area (right/left submandibular and submental regions) (Fig. 1). The OM severity was assessed daily according to WHO (World Health Organization) [7] and NCI (National Cancer Institute) [8] criteria. Mucositis topography was also evaluated. Oral and oropharynx pain was scored in a daily basis by visual analogue scale (VAS) and the patients were instructed to classify the pain as follow: “0” without pain and “10” the maximum pain.

Patients who developed ulcerated OM (grade II according to WHO scale) before day + 5 started an intraoral treatment protocol combined with 1W EOPBM. Patients who developed ulcerated OM after day + 5 received only the intraoral treatment protocol until the lesions healing following our previous study.

Of the total, 13 patients were male and 17 were female and the mean age was 49.3 years old. Regarding underlying diseases, 11 patients (36.7%) had multiple myeloma, 11 (36.7%) lymphomas, 7 (23.3%) leukemias and 1 (3.3%) germ cell tumors. Most patients (21 patients — 70%) received autologous HSCT, 24 patients (80%) underwent

Table 1 Photobiomodulation parameters of all protocols

Parameters	Prior preventive protocols (Ramos Pinto et al., 2021)		Present protocol	Curative protocol
	IOPBM	2W EOPBM		
Groups	IOPBM	2W EOPBM	1W EOPBM	IOPBM
Manufacturer	MMOptics®	Ultradent®	Ultradent®	MMOptics®
Source of light	Laser	Laser	Laser	Laser
Wavelengths (nm)	660	810 + 980 (50%/50%)	810 + 980 (50%/50%)	660
Operational mode	Continuous	Pulsed	Pulsed	Continuous
Frequency (Hz)	~ 50/60	50	50	~ 50/60
Pulse duration (ms)	Continuous	2	2	Continuous
Work cycle (%)	-	10	10	-
Peak power (W)	0.01	20	10	0.01
Average power (mW)	100	2000	1000	100
Polarization	Yes	No	No	Yes
Beam area (cm ²)	0.03	4.91	4.91	0.03
Irradiated Area (cm ²)	0.03	4.91	4.91	0.03
Beam shape	Round	Round	Round	Round
Beam profile	Gaussian	Gaussian	Gaussian	Gaussian
Irradiance (mW/cm ²)	3333	407	203	3333
Fluence (J/cm ²)	33.3	4.07	6.11	10
Photon fluence (p. J/cm ²)	6.30	5.29	6.10	6.30
Photon fluence (Einstein)	1.40	1.17	1.35	1.40
Application time per point (sec.)	10	10	30	3
Energy per point (J)	1	20	30	0.3
Application technique	Contact	Contact	Contact	Contact
Application distance	Contact	Defocused	Defocused	Contact
Number of irradiated points	34	6	6	On the ulcers
Number and frequency of treatment sessions	1 ×/day — Daily	1 ×/day — Daily	1 ×/day — Daily	1 ×/day — Daily



Fig. 1 Schemes of both extra (a) and intra (b) photobiomodulation protocols

myeloablative conditioning (MAC) and 6 patients (20%) reduced intensive conditioning.

The 1W EOPBM protocol was well tolerated without any complaints. Nineteen patients (63.3%) developed OM according to WHO criteria, 3 patients grade I, 10 grade II

and 6 grade III. NCI mucositis grades were similar to WHO grades (Fig. 2).

The present OM outcomes were compared to our previous results [6]. No significant differences were observed between the Groups (1W EOPBM, 2W EOPBM and IOPBM) in all OM scores according to both WHO and NCI scales (Fig. 2).

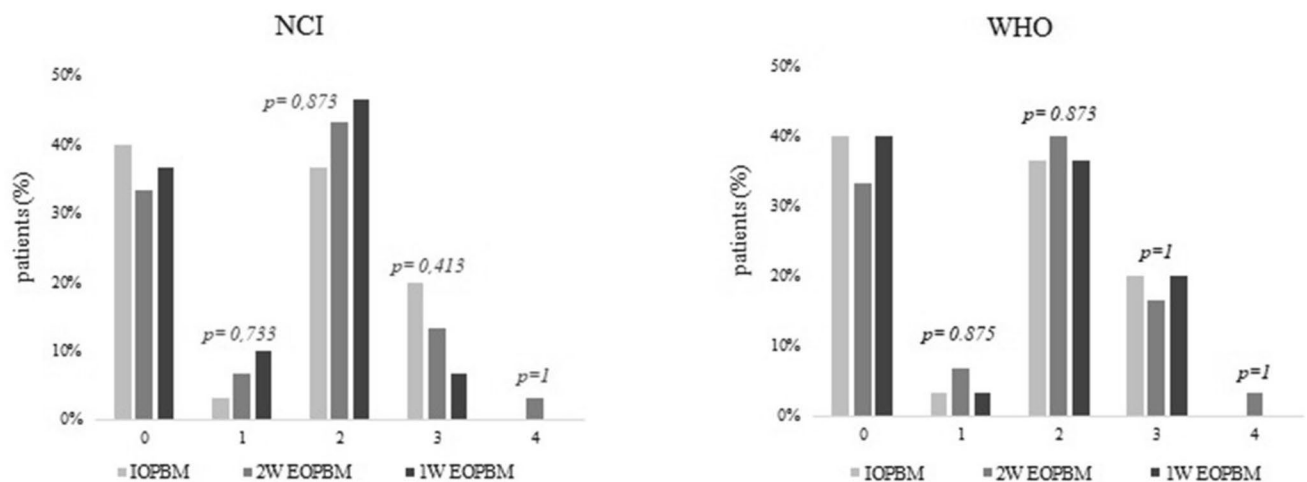


Fig. 2 Oral mucositis scores according to WHO and NCI. No differences were found between Groups

There was no statistical difference in the mean daily oral pain ($p=0.790$) and throat pain ($p=0.553$) between the PBM parameters. According to logistic regression statistics, there was no difference between 1W EOPBM and previous protocols (IOPBM and 2W EOPBM) to develop ulcerated OM.

Intraoral PBM is a well-consolidated therapy in the management of OM related to both radiotherapy and HSCT [2]. According to our Group (8 residents and 6 dentists), IOPBM is an exhaustive task which is performed daily in around 30 patients per day (data of our service). Taking that into account and patient's discomfort during the sections, we have been studying the benefits of EOPBM [6]. Moreover, other studies have demonstrated OM control using such therapy [5, 9–12] Both 1W EOPBM and 2W EOPBM protocols were well tolerated by the patients. The 1W EOPBM patients presented similar OM-related pain scores when compared to the previous PBM protocols.

In the face of the results of this study, we might assume that there is a “window” of parameters for EOPBM application, whereas 1W EOPBM yielded similar results in the management of OM in HSCT patients when compared with 2W EOPBM and IOPBM. However, more dosimetry studies and clinical trials are urged on this topic to set the EOPBM as a standard of care for the management of OM in HSCT patients.

Author contributions Study design and concepts: F.A., M.M. and J.S.F. Data collection: L.S., M.R.P., R.Z. and M.E.M. Data analysis: L.S., M.R.P. and F.A. Manuscript draft: L.S., M.R.P. and F.A., M.M. Manuscript final and approval: All authors.

Funding Not applicable. All author declare that no funding was received.

Data availability We declare that all data used in the study are available if necessary.

Declarations

Competing interests The authors declare no competing interests.

Ethics approval and consent of participate The study was approved by the Ethics Committee of the A. C. Camargo Cancer Center, Sao Paulo, Brazil (no. 3146/2). Written informed consent was obtained from all participants.

References

- Berger K, Staudenmaier T, Cenzer I et al (2020) Epidemiology, patient adherence, and costs of oral mucositis in routine care in stem cell transplantation. *Support Care Cancer* 28:3113–3123. <https://doi.org/10.1007/s00520-019-05107-2>
- Zadik Y, Arany PR, Fregnani ER et al (2019) Systematic review of photobiomodulation for the management of oral mucositis in cancer patients and clinical practice guidelines. *Support Care Cancer* 27:3969–3983. <https://doi.org/10.1007/s00520-019-04890-2>
- Hodgson BD, Margolis DM, Salzman DE et al (2012) Amelioration of oral mucositis pain by NASA near-infrared light-emitting diodes in bone marrow transplant patients. *Support Care Cancer* 20:1405–1415. <https://doi.org/10.1007/s00520-011-1223-8>
- Soto M, Lalla RV, Gouveia RV et al (2015) Pilot study on the efficacy of combined intraoral and extraoral low-level laser therapy for prevention of oral mucositis in pediatric patients undergoing hematopoietic stem cell transplantation. *Photomed Laser Surg* 33:540–546. <https://doi.org/10.1089/pho.2015.3954>
- Treister NS, London WB, Guo D et al (2016) A feasibility study evaluating extraoral photobiomodulation therapy for prevention of mucositis in pediatric hematopoietic cell transplantation. *Photomed Laser Surg* 34:178–184. <https://doi.org/10.1089/pho.2015.4021>
- Ramos-Pinto MB, de Lima Gusmão TP, Schmidt-Filho J et al (2021) Intraoral versus extraoral photobiomodulation therapy in the prevention of oral mucositis in HSCT patients: a randomized, single-blind, controlled clinical trial. *Support Care Cancer* 29:6495–6503. <https://doi.org/10.1007/s00520-021-06228-3>
- World Health Organization (1979) Handbook for reporting results of cancer treatment, vol 48. Offset Publication, Geneva, pp 15–22
- National Cancer Institute, National Institutes of Health, US Department of Health and Human Services (2018) Common terminology criteria for adverse events (CTCAE) version 5.0. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/
- Whelan HT, Connelly JF, Hodgson BD et al (2002) NASA light-emitting diodes for the prevention of oral mucositis in pediatric bone marrow transplant patients. *J Clin Laser Med Surg* 20:319–324. <https://doi.org/10.1089/104454702320901107>
- Moraes JJC, Queiroga AS, Biase RCCG et al (2009) The effect of low level laser therapy in different wavelengths in the treatment of oral mucositis—proposal for extra-oral implementation. *Laser Phys* 19:1912–1919. <https://doi.org/10.1134/S1054660X09170150>
- Hodgson BD, Margolis DM, Salzman DE et al (2012) Amelioration of oral mucositis pain by NASA near-infrared light-emitting diodes in bone marrow transplant patients. *Support Care in Cancer* 20:1405–1415. <https://doi.org/10.1007/s00520-011-1223-8>
- Soto M, Lalla RV, Gouveia RV et al (2015) Pilot study on the efficacy of combined intraoral and extraoral low-level laser therapy for prevention of oral mucositis in pediatric patients undergoing hematopoietic stem cell transplantation. *Photomed Laser Surg* 33:540–546. <https://doi.org/10.1089/pho.2015.3954S>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.