

Therapeutic associations on the management of chemo-induced oral mucositis in pediatric patients

Associação terapêutica no manejo da mucosite oral quimioinduzida em pacientes pediátricos

Asociación terapéutica en el manejo de la mucositis oral inducida por quimioterapia en pacientes pediátricos

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The objective of this study was to present 10 cases of severe oral mucositis treated with an oral mouthwash solution associated with low potency laser therapy in pediatric oncology patients. The evaluated patients with oral mucositis had acute lymphoblastic leukemia, Osteosarcoma and Wilms's tumor. The lesions presented in the following anatomical sites: vermilion of the lip, labial mucosa and tongue. The mean time for lesion regression was 6.8 ± 3.9 days. The treatment protocol consisted of an oral mouthwash solution (0.9% saline, nystatin, dexamethasone, diphenhydramine, morphine, 2% lidocaine, and vitamin B complex) and photodynamic therapy with low power laser (ECCO Fibers and Devices, n/s -040401; model -BM0004A), calibrated for a wavelength of 670 nm, power of 40mW and energy density of 4 J/cm². All the patients had remission of oral mucositis lesions within 14 days after the initiation of the therapeutic intervention. It was concluded that the protocol used with the use of low-power laser therapy combined with mouthwash solution was effective in the treatment of oral mucositis in pediatric patients undergoing antineoplastic treatment.

Descriptors: Oncology service hospital; Lasers; Mucositis.

O objetivo deste trabalho foi discutir casos de mucosite oral grave quimioinduzida, tratados com solução oral para bochecho associado a laserterapia de baixa potência em pacientes pediátricos oncológicos. As patologias apresentadas pelos pacientes que apresentaram a mucosite foram: Leucemia Linfoblástica Aguda (LLA), Osteossarcoma e Tumor de Wilms. As lesões se apresentaram nos seguintes sítios anatômicos: vermelhão do lábio, mucosa labial, e língua. O tempo médio para regressão das lesões foi de $6,8 \pm 3,9$ dias. O protocolo de tratamento consistiu na utilização da solução para mucosite oral utilizada no Hospital Napoleão Laureano, João Pessoa/PB. Concomitante ao uso da solução oral, iniciou-se a terapia fotodinâmica com laser de baixa potência (ECCO Fibras e Dispositivos; n/s-040401; modelo-BM0004A), calibrado para um comprimento de onda de 670 nm, potência de 40mW e densidade de energia de 4 J/cm². Todos os pacientes tiveram remissão das lesões de mucosite oral em até 14 dias após o início da intervenção terapêutica. Concluiu-se que o protocolo utilizado, com o uso da laserterapia de baixa potência aliado à solução de mucosite oral mostrou-se eficaz no tratamento da mucosite oral em pacientes pediátricos em tratamento antineoplásico.

Descritores: Serviço hospitalar de oncologia; Lasers; Estomatite.

El objetivo de este trabajo fue discutir casos de mucositis oral grave inducida por quimioterapia, tratados con solución oral para buches, asociado a laserterapia de baja potencia en pacientes pediátricos oncológicos. Las patologías presentadas por los pacientes que presentaron la mucositis fueron: Leucemia Linfóide Aguda (LLA), Osteosarcoma y Tumor de Willms. Las lesiones se presentaron en los siguientes sitios anatómicos: enrojecimiento del labio, mucosa labial y lengua. El tiempo promedio para regresión de las lesiones fue de $6,8 \pm 3,9$ días. El protocolo de tratamiento consistió en la utilización de la solución oral para mucositis utilizada en el Hospital Napoleón Laureano, João Pessoa/PB. Con el uso de la solución oral, se inició la terapia fotodinámica con láser de baja potencia (ECCO Fibras y Dispositivos, n/s -040401; modelo-BM0004A), calibrado para una longitud de onda de 670 nm, potencia de 40mW y densidad de energía de 4 J/cm². Todos los pacientes tuvieron remisión de las lesiones de mucositis oral en hasta 14 días después del inicio de la intervención terapéutica. Se concluyó que el protocolo utilizado, con el uso de la laserterapia de baja potencia aliado a la solución de mucositis oral se mostró eficaz en el tratamiento de la mucositis oral en pacientes pediátricos en tratamiento antineoplásico.

Descriptor: Servicio de oncología en hospital; Rayos láser, Mucositis.

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INTRODUCTION

Anti-neoplastic therapy is used in chemotherapy, radiotherapy, surgeries and bone marrow transplant, induced as an isolated procedure or associated with others. In the last decades, scientific advances have been making this therapy more efficient¹. However, the numerous comorbidities that result from the treatment are still worrisome, making the management and survival of these patients much more of a challenge².

In the oral cavity, the most frequent alterations are: oral mucositis, reduction in the saliva flow and opportunistic infections^{2,3}. Among these adversities, the oral mucositis is the most prevalent complication, affecting from 40 to 80% of the patients who undergo chemotherapy and almost all of those who are exposed to radiotherapy⁴.

The development of oral mucositis causes severe pain, difficulties in speech, swallowing and mastication, and, consequently, prejudices nutrition, which may lead to an interruption of the treatment⁵.

Clinically, it is manifested through ulcerative and bloody areas, born from the toxicity of chemotherapy medication and/or ionizing radiation. Its symptoms include intense pain, which compromises physiological functions such as speech, swallowing and eating. In addition, this condition leads to a propensity to local and/or systemic infections that make the treatment even longer and more debilitating⁶.

Considering these complications that result from the anti-neoplastic treatment, this condition requires a closer look. Considering that, the protocols of mucositis management described in the literature are numerous⁵⁻⁷. Most of them, however, are limited to preventive procedures, and therapeutic conducts are scarce.

In this perspective, a recent literature meta-analysis revealed that the use of low-potency laser therapy, as well as the rinsing of the mouth with antimicrobial solutions, are effective to treat oral mucositis. Therefore, combining these measures is a strategy that

aims at increasing the chances of good results when dealing with oral mucositis.

With that, the objective of this work was discussing cases of severe chemo-induced oral mucositis, treated with oral solutions for rinsing the mouth, associated with low-potency laser therapy in oncologic pediatric patients.

METHODS

This series include the report of 10 cases of oncologic pediatric patients who were attended during their oncological treatments by the Odontology team of a hospital that is a reference for cancer treatment in the state of Paraíba, the Napoleão Laureano Hospital, from 2013 to 2017.

The monitoring of the patients, as well as the record of information and images, was possible after the Ethics Committee of the Center of Health Sciences approved the investigation, under protocol n. CAAE: 12922113.8.0000.5188.

The patients were supervised during the entire period of their treatment, and the classification of the SOM was performed through the modified Oral Assessment Guide (OAG) index⁹, a guide for oral evaluations that is used worldwide to monitor and measure mucositis in oncologic patients.

RESULTS

The distribution of patients attended in this study can be observed in Table 1, and the clinical conditions treated by the Odontology team are in Image 1.

For all cases exposed in Table 1, the protocol used for treating oral mucositis was that of the Odontology standards of the pediatric sector in the Napoleão Laureano Hospital, in João Pessoa-PB.

The protocol consists in the use of an oral solution four times a day (every 8 hours), in rinsing the mouth for 30 seconds with 10mL of the solution, which is manipulated in the hospital itself and distributed daily (Image 2). The components, dosages and action mechanism of the drugs are described in Table 2.

Table 1. Oncologic pediatric patients with severe oral mucositis treated according to the treatment Odontology protocol of the reference hospital. (2013-2017). João Pessoa, 2017.

Patient	Sex	Age (years)	Diagnostic	Treatment protocol	SOM site	Remission time (days)
1	Female	4	Osteosarcoma	GCBT/GLATO	Vermilion border	7
2	Male	3	Osteosarcoma	GCBT/GLATO	Lip mucosa	8
3	Male	8	ALL	GBTLI - LLA/99	Tongue	6
4	Female	12	ALL	GBTLI - LLA/99	Vermilion border	12
5	Male	5	ALL	GBTLI - LLA/99	Lip mucosa, tongue and vermillion border	14
6	Female	19	Osteosarcoma	GCBT/GLATO	Lip mucosa	5
7	Female	14	Tumor de Wilms	NWTS	Vermilion border	7
8	Male	8	ALL	GBTLI - LLA/99	Lip mucosa	4
9	Male	12	AML	BFM/LMA 98	Lip mucosa	3
10	Male	4	ALL	GBTLI - LLA/99	Vermilion border	7

Source: Odontology. Pediatric Sector. Napoleão Laureano Hospital, João Pessoa/PB.

Key: ALL (Acute Lymphoblastic Leukemia); GCBT/GLATO (Protocol of the Latin American Group for the Treatment of Osteosarcoma); GBTLI - LLA/99 (Protocol of the Brazilian Group for the Treatment of Leukemia in Childhood); NWTS (Protocol of the National Wilms Tumor Study Group); BMF/LMA 98 (Protocol of the European Berlin-Frankfurt-Münster Group, BFM, for the treatment of Acute Myeloid Leukemia, AML, in children and adolescents of 15 years of age or less).

Image 1. Pediatric patient diagnosed with severe oral mucositis according to the OAG index. João Pessoa, 2017.

Source: Odontology. Pediatric Sector. Napoleão Laureano Hospital.

Table 2. Pharmacological description of the solution for the treatment of severe oral mucositis. Napoleão Laureano Hospital, 2017.

Component	Quantity	Action
Nystatin	20ml	Antifungal
Decadron (Dexamethasone)	2mg/ml; 1mL ampoule.	Anti-inflammatory
Morphine	10mg/ml; 1mL ampoule.	Analgesic
Diphenhydramine	50mg/ml; 1mL ampoule.	Antiallergic
Lidocaine 2%	10ml	Anesthetic (local)
B vitamins	1 1mL ampoule	Adjuvant in tissue recovery
Saline Solution 0.9%	250ml	Excipient

Source: Odontology. Pediatric Sector. Napoleão Laureano Hospital, João Pessoa/PB.

The use of the oral solution took place, in all cases, together with the photodynamic therapy with low potency laser (from ECCO Fibras e Dispositivos; s/n -040401; model - BM0004A), calibrated for a

670nm wavelength, with a potency of 40mW and an energy dosage of 4J/cm², with targeted application for 30 seconds, daily, until the remission of the lesions could be observed (Image 2).

Image 2. Therapeutic management of pediatric oncology patients (rinsing with the oral mucositis solution and low potency laser therapy). Low potency laser therapy (A/B) associated with rinsing solution (C/D). João Pessoa, 2017.



Source: Odontology. Pediatric Sector. Napoleão Laureano Hospital, João Pessoa/PB.

In each consultation of the patients, oral hygiene guidance was also offered. Lesion remission varied from 3 to 14 days after the beginning of protocol. After this period, the

patients being monitored could already eat normally, after complete remission and healing of the lesions (Image 3).

Image 3. Pediatric patient after SOM treatment with oral solution and laser therapy. João Pessoa, 2017.



Source: Odontology. Pediatric Sector. Napoleão Laureano Hospital.

DISCUSSION

This study presents a series of 10 clinical cases of oncological pediatric patients, showing the positive effects for the course of oral mucositis, especially in serious cases, of the therapeutic association of an oral solution and a low potency laser, which were effective in the solving of chemotherapy induced oral lesions.

Oral mucositis in children and adolescents is even more worrying than it is in adults, as it affects these individuals with more severity¹⁰.

Many factors contribute to that. The immaturity of tissues, the constant cellular renovation, the oral microbiota still in formation, the compromised defense system and the local injuries are the main factors to this aggressivity¹⁰.

The SOM may advance due to oral health negligence, which can occur with hospitalized patients, due to the stress of the treatment, which leads to changes in the patient's routine¹¹.

Odontological attention for pediatric patients undergoing cancer treatment is

paramount to promote, prevent, and to conduct interventions that make oral health improvements possible. The odontological team in the oncological treatment sector emerges as one of the main allies in the success of the treatment, considering that the oral cavity may be a potential pathway to access to information⁶.

The dental surgeon, as a member of the multiprofessional health team, allows for the oncological pediatric patient to maintain and guarantee their oral health, providing favorable conditions for their nutrition, and, consequently, a better quality of life for the patient during their treatment, with lower chances of chemotherapy interruptions and higher chances of cure for the patient.

The average time, in this study, for oral mucositis to manifest, from the first moment of chemotherapy, was that of 6.8 ± 3.9 days. A study showed that after the treatment with low potency laser therapy associated with the use of the oral mucositis solution, there was an improvement in approximately 9 days¹², corroborating the findings of the present study.

The protocol for the treatment of severe oral mucositis in the pediatric ward of the Napoleão Laureano Hospital includes daily (4x/day) rinsing with 10mL of a solution for mucositis consisting of: Saline Solution, Nystatin, Decadron, Diphenhydramine, Morphine, Lidocaine 2%, and B vitamins, manipulated in the hospital itself, together with daily sessions of low potency laser calibrated for a 670nm wavelength, with a 40-60mW potencies and a dosage of 4J/cm², applied for thirty seconds in the reddened and ulcerated regions with or without pseudomembrane¹³.

Nystatin is an important component of the solution, since it is efficient in the treatment of fungal infections such as candidiasis. When candidiasis makes the mucositis worse, rinsing with nystatin is recommended to prevent the worsening of the situation¹⁴.

Another option for its use in hospital odontology is to start it together with an anti-neoplastic therapy, since the use of antifungal medication diminishes the incidence of

ulcerations, limiting mucositis to erythema areas¹⁵. This fact should be considered in the elaboration of hospital protocols, since it is possible to make prophylactic use of it; it does not have to wait for the disease to be installed.

The Decadron (dexamethasone) is a corticosteroid that aids in almost all stages of the inflammatory process, that is, the dexamethasone is used to treat the ulcerations and inflammations of the mucosa, preventing the progression of inflammatory responses and tissue destruction¹⁶, which explains its presence in the oral solution for the treatment of SOM.

Recent studies have shown other substances that can be used in the SOM treatment, as the stimulant for colonies of recombining human granulocytes and the apigenin, both more effective than dexamethasone^{17,18}. Still, studies with therapies for oral mucositis, especially severe cases, have been very well accepted, since the knowledge in this field is yet limited, which may aid in the creation of a universal protocol.

The use of morphine in the SOM treatment is justified due to its extremely effective analgesic capabilities. However, it has an unpleasant taste, and this is the main difficulty in using it according to an ideal posology (4x/day), which may result in a higher period before the remission of the lesions.

Therefore, more researches should be conducted aiming at diminishing the concentration of morphine or replacing it with other components that cause less collateral effects, thus making the use of the solution easier. One example is the melatonin, recently described¹⁹.

The symptoms caused in SOM cases have repercussions in the quality of life of the patients, leading to the use of local anesthetics and central analgesics, such as morphine²⁰.

Lidocaine blocks the initiation and conduction of the nervous impulse, diminishing the permeability of the neuron membrane for sodium ions. Solutions with lidocaine may be used in isolation or in combination. Topic anesthesia is an obvious choice for a palliative action to deal with the pain caused by mucositis. It has minimal

systemic consequences and a very good response when associated to diphenhydramine²¹. The most commonly used agents are the lidocaine and the benzocaine²².

The use of the A, B and E vitamins significantly reduces the degree and produces relief of the mucositis symptoms which can be associated to the anti-inflammatory actions of the substance^{23,24}, this corroborating this study, which presents in its formulation of the oral solution B vitamins, whose adjuvant action aids in the tissue recovery after severe oral mucositis.

With that, the components in the pharmacological protocol of the oral solution to treat mucositis have effective therapeutic results, with analgesic, anti-inflammatory, anti-edema and healing effects. The action of these drugs allows for an improvement in the quality of life of oncologic patients, with an increase in the survival rates²⁵.

According to the findings of this study, laser therapy was effective against the mucositis lesions, independently of the type of neoplasia and of the treatment being conducted. Studies suggest the use of prophylactic laser therapy, although a consensus on the issue has not yet been reached^{5,26,27}.

Since its efficiency was not yet proved, prophylactic laser therapy is, as of now, not conducted in the NLH. A study²⁶ found that laser therapy has prophylactic effects in OM of a degree > 3 (severe oral mucositis), when compared to patients who do not undergo the therapy.

However, it is still necessary to conduct studies with bigger samples. Additionally, many different protocols exist, making necessary studies that establish a universal protocol to determine dosage, length of application, number of laser sessions and method to be used^{4,6}.

However, the dosage of the wavelength is adequate, between 660nm and 670nm, as well as the potency between 40 and 60 Mw and the energy dosage from 2 to 7 J/cm²,^{2,26}.

CONCLUSION

Considering the cases shown and registered in the present study, the protocol which was used, with low potency laser therapy used in conjunction with an oral solution, has shown itself to be effective in the treatment of severe oral mucositis in pediatric patients undergoing an anti-neoplastic treatment.

REFERENCES

1. Grabois MF, Oliveira EX, Carvalho MS. Access to pediatric cancer care in Brazil: mapping origin-destination flows. *Rev Saúde Pública*. 2013; 47(2):368-78.
2. Hespanhol FL, Tinoco EMB, Teixeira HGC, Falabella MEV, Assis NMSP. Manifestações bucais em pacientes submetidos à quimioterapia. *Ciênc Saúde Coletiva*. 2010; 15(Supl. 1):1085-94.
3. Velten DB, Zandonade E, Miotto MHMB. Prevalence of oral manifestations in children and adolescents with cancer submitted to chemotherapy. *BMC Oral Health*. 2017; 17(1):49.
4. Campos MIDC, Campos CN, Aarestrup FM, Aarestrup BJV. Oral mucositis in cancer treatment: natural history, prevention and treatment. *Mol Clin Oncol*. 2014; 2(3):337-40.
5. Lima AG, Villar RC, Castro G, Antequera R, Gil E, Rosalmeida MC, et al. Oral mucositis prevention by low-level laser therapy in head-and-neck cancer patients undergoing concurrent chemoradiotherapy: a phase III randomized study. *Int J Radiat Oncol Biol Phys*. 2012; 82(1):270-5.
6. Cheng KK-F, Leung S, Liang RH, Tai JW, Yeung RM, Thompson DR. Severe oral mucositis associated with cancer therapy: impact on oral functional status and quality of life. *Support care cancer*. 2010; 18(11):1477-85.
7. Rodrigues GH, Jaguar GC, Alves FA, Guollo A, Camandoni VO, Damascena AS, et al. Variability of high-dose melphalan exposure on oral mucositis in patients undergoing prophylactic low-level laser therapy. *Lasers Med Sci*. 2017; 32(5):1089-95.
8. Carneiro-Neto C, Moura LB, Menezes JDS, et al. Estadiamento TNM para o tratamento de câncer bucal. *Rev Odontol (ATO)*. 2016; 16(3):100-8.

9. Cheng KK, Chang AM, Yuen M. Prevention of oral mucositis in paediatric patients treated with chemotherapy: a randomised crossover trial comparing two protocols of oral care. *Eur J Cancer*. 2004; 40(8):1208-16.
10. Lopes IA, Nogueira DN, Lopes IA. Manifestações orais decorrentes da quimioterapia em crianças de um centro de tratamento oncológico. *Pesqui Bras Odontopediatria Clin Integr*. 2012; 12(1):113-9.
11. Sung L, Yanofsky R, Klaassen RJ, Dix D, Pritchard S, Winick N, et al. Quality of life during active treatment for pediatric acute lymphoblastic leukemia. *Int J Cancer*. 2011; 128(5):1213-20.
12. Mendonça MA, Araújo MD, Levy CE, Morari J, Silva RA, Yunes JA, et al. Oral mucositis in pediatric acute lymphoblastic leukemia patients: evaluation of microbiological and hematological factors. *Pediatr Hematol Oncol*. 2015; 32(5):322-30.
13. Ribeiro ILA, Valença AMG, Bonan PRF. Treatment of severe oral mucositis in a pediatric patient undergoing chemotherapy. *Rev Gaúcha Odontol*. 2015; 63(4):467-71.
14. Júnior OR, Borba AM, Júnior JG. Prevenção e tratamento da mucosite bucal: o papel fundamental do cirurgião-dentista-revisão. *Arch Oral Res*. 2010; 6(1):57-62.
15. Lanzós I, Herrera D, Santos S, O'Connor A, Peña C, Lanzós E, et al. Mucositis in irradiated cancer patients: effects of an antiseptic mouthrinse. *Med Oral Patol Oral Cir Bucal*. 2010; 15(5):e732-8.
16. Peres P, Queiroz A, Moreira M, Faquim J, Ferrari M. Pediatric dentistry applied to childhood cancer-clinical manifestations and protocol service. *J Manage Prim Health Care*. 2013; 4(3):191-9.
17. Liang G, Du W, Ke Q, Huang B, Yang J. The effects of recombinant human granulocyte colony-stimulating factor mouthwash on radiotherapy-induced oral mucositis in locally advanced nasopharyngeal carcinoma patients. *Adv Clin Exp Med*. 2017; 26(3):409.
18. Molina Prats P, Gómez Garcia F, Martínez Diaz F, Amaral Mendes R, Lopez-Jornet P. The therapeutic effects of apigenin and dexamethasone on 5-fluorouracil-induced oral mucositis—a pilot study using a Syrian hamster model. *J Oral Pathol Med*. 2017; 46(2):142-7.
19. Onseong K, Johns NP, Khuayjarernpanishk T, Subongkot S, Priprem A, Hurst C, et al. Beneficial effects of adjuvant melatonin in minimizing oral mucositis complications in head and neck cancer patients receiving concurrent chemoradiation. *J Altern Complement Med*. 2017; 23(12):957-63.
20. Wong PC, Dodd MJ, Miaskowski C, Paul SM, Bank KA, Shiba GH, et al. Mucositis pain induced by radiation therapy: prevalence, severity, and use of self-care behaviors. *J Pain Symptom Manage*. 2006; 32(1):27-37.
21. Madden Kirk L, Brown SD, Luu Y, Ogle A, Huffman J, Lewis PO. Beyond-use dating of lidocaine alone and in two "magic mouthwash" preparations. *Am J Health System Pharm*. 2017; 74(9):e202-210.
22. Barasch A, Elad S, Altman A, Damato K, Epstein J. Antimicrobials, mucosal coating agents, anesthetics, analgesics, and nutritional supplements for alimentary tract mucositis. *Support Care Cancer*. 2006; 14(6):528-32.
23. Bonan P, Lopes M, Alves F, Almeida O. Aspectos clínicos, biológicos, histopatológicos e tratamentos propostos para a mucosite oral induzida por radioterapia: revisão da literatura. *Rev Bras Cancerol*. 2005; 51(3):235-42.
24. Cardoso MdFA, Novikoff S, Tresso A, Segreto RA, Cervantes O. Prevenção e controle das seqüelas bucais em pacientes irradiados por tumores de cabeça e pescoço. *Radiol bras*. 2005; 38(2):107-15.
25. Carneiro TV, Ribeiro ILA, Alves CV, Bonan PRF, Neto EdAL, Valença AMG. Factors associated with health-related quality of life among children with cancer from the standpoint of patients and caregivers. *J Public Health*. 2017; 25(4): 371-7.
26. Figueiredo ALP, Lins L, Cattony AC, Falcão AFP. Laserterapia no controle da mucosite oral: um estudo de metanálise. *Rev Assoc Méd Bras*. 2013; 59(5):467-74.
27. Oberoi S, Zamperlini-Netto G, Beyene J, Treister NS, Sung L. Effect of prophylactic low level laser therapy on oral mucositis: a systematic review and meta-analysis. *PLoS one*. 2014; 9(9):e107418.

CONTRIBUTIONS

Raphael Cavalcante Costa, Rebecca Rhuanny Tolentino Limeira and Laís Guedes Alcoforado de Carvalho contributed in the conception, design, data collection and writing. **Paulo Rogério Ferreti Bonan, Ana Maria Gondim Valença and Isabella Lima Arrais Ribeiro** took part in the conception, design, guidance, supervision of data collection, as well as in the writing.

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