Evaluation of the Effect of Preventive Laser on Chemo-induced Oral Mucositis in Patients Submitted to High Doses of Methotrexate

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Avaliação do Efeito do Laser Preventivo na Mucosite Oral Quimioinduzida em Pacientes Submetidos a Altas Doses de Metotrexato

Evaluación del Efecto del Láser Preventivo em la Mucositis Oral Inducida por Quimioterapia en Pacientes Sometidos a Altas Dosis de Metotrexato

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ABSTRACT

Introduction: Chemotherapy, one of the treatments for malignant neoplasms, is associated to innumerous drugs, one of them methotrexate (MTX), of high toxicity, responsible for several health damages and impact on the patient's well-being. One of the main complications is oral mucositis, a clinical manifestation resulting from the oncologic treatment that can interfere in the treatment and cure. **Objective:** To evaluate comparatively through a retrospective study, the effect of preventive laser in the occurrence of chemo-induced oral mucositis in patients with non-metastatic osteosarcoma submitted to high doses of methotrexate (MTX), and the intensity of oral mucositis, using the preventive laser after the chemotherapy cycles containing the drug methotrexate (MTX) in the patients treated at Barretos Children's Hospital/SP. **Method:** Retrospective cohort study with charts review. The patients were divided in two groups, one submitted to low-intensity laser prophylaxis therapy after infusion of MTX and another group not submitted to prophylactic therapy. **Results:** The data obtained showed that preventive laser-therapy reduced the severity of oral mucositis with statistically significant results (p<0.001), corroborating the results found in the literature. **Conclusion:** The use of laser therapy is an important auxiliary therapy in the prevention and reduction of severity of oral mucositis in patients submitted to high doses of MTX, reducing the number of hospitalizations and delays in therapeutic protocol, which reduces costs and improves the patient prognosis.

Key words: Stomatitis/drug therapy; Methotrexate; Low-Level Light Therapy; Pediatric Dentistry.

RESUMO

Introdução: A quimioterapia, uma das formas de tratamento de neoplasias malignas, tem sua administração associada a inúmeras drogas, sendo uma delas o metotrexato (MTX), de alta toxicidade, responsável por inúmeros fatores agravantes para a saúde e bem-estar do paciente. Uma das principais complicações é a mucosite oral, manifestação clínica resultante do tratamento oncológico que pode interferir no tratamento e na cura. **Objetivo:** Avaliar, comparativamente, por meio de um estudo retrospectivo, o efeito do *laser* preventivo na ocorrência da mucosite oral quimioinduzida em pacientes com osteossarcoma não metastático submetidos a altas doses de MTX, bem como a intensidade da mucosite oral, utilizando o *laser* preventivo após os ciclos quimioterápicos contendo o medicamento MTX nos pacientes atendidos no Hospital de Câncer infantojuvenil de Barretos/SP. **Método:** Estudo de coorte com coleta retrospectiva em prontuários. Os pacientes foram divididos em dois grupos, um submetido à terapia profilática com *laser* de baixa intensidade após infusão do MTX e outro grupo não submetido a essa terapia. **Resultados:** Os dados obtidos mostraram que houve redução da gravidade da mucosite oral com o uso da laserterapia preventiva, com resultados estatisticamente significativos (p<0,001), corroborando os resultados encontrados na literatura. **Conclusão:** O uso da laserterapia é uma terapêutica auxiliar importante na prevenção e na redução da severidade da mucosite oral em pacientes submetidos a altas doses de MTX, diminuindo o número de internações por mucosite e os atrasos no protocolo terapêutico, o que reduz gastos e melhora o prognóstico para o paciente.

Palavras-chave: Estomatite/tratamento farmacológico; Metotrexato; Terapia com Luz de Baixa Intensidade; Odontopediatria.

RESUMEN

Introducción: La quimioterapia, es uma de las formas de tratamiento de las neoplasias malignas, tiene su administración asociada a numerosas drogas siendo una de ellas el metotrexato (MTX), de alta toxicidad, responsable de numerosos factores agravantes para la salud y bienestar del paciente. Una de las principales complicaciones es la mucositis oral, manifestación clínica resultante del tratamiento oncológico que puede interferir en el tratamiento y cura. **Objetivo:** Evaluar, comparativamente, a través de um estudio retrospectivo, el efecto del láser preventivo em la aparición de la mucositis oral quimio inducida em pacientes com osteosarcoma no mestastásico sometido a altas dosis de MTX, bien como la intensidade de la mucositis oral, utilizando el láser preventivo después de los ciclos quimioterápicos que contiene el medicamento MTX en los pacientes antendidos en el Hospital del Cáncer Infantojuvenil de Barretos/SP. **Método:** Estudio de coorte con colección retrospectiva en prontuários. Los pacientes fueron divididos em dos grupos, uno sometido a terapia profiláctica con láser de baja intensidade después de la infusión de MTX y otro grupo no sometido a terapia profiláctica. **Resultados:** Los dados obtenidos mostraron que hubo una reducción en la severidad de la mucositis oral con el uso de la terapia láser preventiva, con resultados estáticamente significativos (p<0,001), corroborando los resultados encontrados em la literatura. **Conclusión:** El uso de la terapia con láser es una terapia auxiliar importante en la prevención y reducción de la severidad de la mucositis oral em pacientes sometidos a altas dosis de MTX, diminuendo el número de internaciones por mucositis y retrasos en el protocolo terapéutico, lo que reduce los gastos y mejora el pronóstico para el paciente.

Palabras clave: Estomatitis/tratamiento farmacológico; Metotrexato; Terapia por Luz de Baja Intensidad; Odontología Pediátrica.

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INTRODUCTION

Nearly 40% of the patients who submitted to chemotherapy develop buccal side effects and it reaches 90% when the child is younger than 12 years old[1]. Several buccal complications can be noticed during the oncologic treatment as mucositis, xerostomia, dysgeusia, radiation caries and osteoradionecrosis[2].

Oral mucositis is the main change in the buccal cavity resulting from oncologic treatment, defined as possibly chemotherapy[3] or radiotherapy induced inflammation of the buccal mucosa. It may start with dry mouth evolving to erythema and ulcerations, causing pain and difficulty of deglutition involving the entire gastrointestinal tract, further to favoring opportunistic infections[4,2]. Mucositis occurs because of drugs action and radiotherapy in cellular proliferation, maturation and substitution. The indirect effect holds associations with myelosuppressive drugs, deregulating the immune system and process of reparation[5].

Methotrexate (MTX) is a folic acid antimetabolite interfering in phase S of mitosis. Is a highly toxic chemotherapic for the organism and closely related to the appearance of mucositis, being utilized in high doses in the treatment of osteosarcoma[6]. This is a type of rare bone tumor below 5 years old[7], its peak happens in the adolescence when growth intensifies[4,8,9].

The side effect of the antineoplastic treatment associated to mucositis tends to cause a series of harming factors, causing discomfort and pain, with possible nutritional limitation, leading to the interruption or modification of the drug administration, increasing the time of hospitalization, with more costs and in some cases, the risk of death is considerable[2,10-12].

Oral mucositis can be classified in four grades according to the World Health Organization (WHO): grade 0 - absence of alterations; grade I – presence of erythema; grade II – presence of erythema, ulcers and solid feeding; grade III – ulcers and liquid feeding; and grade IV – unable to feed orally[13].

The literature describes several treatments for oral mucositis as low-level laser therapy which has analgesic, anti-inflammatory and healing effect[14-17]. Laser therapy has been used in the treatment and prevention of mucositis. Innumerous articles demonstrate the reduction of the oral mucositis intensity when preventive laser is used, although there is no consensus about the potency and the protocol to be utilized[1]. Clinical evidences-based protocols developed by the Multinational Association for Supportive Care in Cancer (MASCC) recommend that the therapy with photobiomodulation is relevant in reducing pain in incidence of oral mucositis in patients submitted to high doses of chemotherapy for hematopoietic stem cells transplantation and in patients submitted to head and neck radiotherapy during the moment of immunosuppression[18-22].

Laser therapy has biologic effects as pain control and inflammation modulation, capacity of modulation of a range of cellular metabolic events and has healing properties[11,12,20-22].

Low-level laser therapy increases the cellular metabolism, stimulating the mitochondrial activity, functioning as analgesic, anti-inflammatory and healer of the mucosa lesion. They provoke several biologic events as epithelial proliferation and of fibroblasts as well as its maturation, locomotion, and transformation in myofibroblasts. Cellular and vascular alterations occur, depending of the laser wavelength among other factors. Collagen, elastin and proteoglycans, revascularization, contraction of the wound, increase of phagocytosis by the macrophages, increase of the proliferation and activation of the lymphocytes and tension strength still occur, accelerating the healing process[14-16].

The presence of the dentist-surgeon is important in the multi-professional team of an oncologic hospital for the diagnosis, prevention, and management of oral mucositis and other buccal complications. Odontology care must be directed to promote and keep the integrity of the tissue and prevent buccal complications, improving the quality of life, reducing the time of hospitalization and costs of the treatment[11,16].

The present retrospective study had the objective of evaluating comparatively the effect of preventive laser in chemo-induced oral mucositis in patients with non-metastatic osteosarcoma submitted to high doses of MTX at Barretos Children's Hospital, SP.

METHOD

Cohort study with retrospective collection of charts with population of patients diagnosed with non-metastatic osteosarcoma at the diagnosis submitted to the protocol GLATO (chemotherapy – doxorubicin, cisplatin, dexamethasone and MTX + surgery), consulted at Barretos Children's Hospital/SP followed up at the odontology sector. The patients were divided in two groups: 1) patients treated or in treatment for non-metastatic osteosarcoma receiving three to five preventive laser therapy sessions since the infusion of chemotherapic MTX as of 2012; 2) patients treated for non-metastatic osteosarcoma who did not submit to preventive laser therapy during the chemotherapy treatment before 2012.

The equipment utilized for the laser therapy was MM Optics Twin Laser, diode laser, red light, wavelength of

660 nm, 100 mw of potency, output spot of 0.03 cm^2, in ten seconds, reaching dose of 33.3 J/cm^2.

The patients were consulted at the Infusion Center (D0) and in the odontology room (other applications) under the universal ocular protection norms recommended for therapeutic laser. Laser were applied after the infusion of MTX (D0) and during three to five consecutive days, with 24 hours interval. The spots of application were jugal and labial mucosa, soft palate, buccal floor, and lingual belly in direct contact distributed in 36 spots. The assessment of the incidence and severity of oral mucositis was carried out pursuant to WHO grading parameters for ten consecutive days since the onset of the symptoms until its resolution.

The Institutional Review Board of Barretos Children's Hospital/SP reviewed and approved the study, CAAE: 64161817.5.0000.5437 and report number 1.905.452, in compliance with Directive 466/12 of the National Health Council and the Declaration of Helsinki.

The sample size developed was based in the mean of mucositis grade. According to Cowen et al.[23], the group of patients who did not receive preventive laser had mean score of mucositis of 225.7 (standard deviation: 40.5), anticipating a reduction of 50 scores in the mean score of mucositis in patients who received preventive laser, generating an effect size of 1.23. The comparison of the mean between two independent groups by test T, with power of 80%, level of significance of 5% and possible loss of information of 10% resulted in a sample of 12 participants in each group, totaling 24 participants in the study.

Because of the sample size (n=24) non-parametric tests were adopted. The program REDcap was used to generate the results presented[24].

Data were submitted to statistical descriptive analysis through distribution of univariate and bivariate frequencies and mean and standard deviation measures. The chi-square tests of Pearson and Fisher exact test were used for the associations among variables, considering the level of statistical significance of 5%. The software SPSS v.21.0 was used for the statistical analysis.

RESULTS

The sample consisted of 24 patients who submitted to osteosarcoma treatment at the Barretos Children's Hospital from 2009 to 2017. The patients of the sample were divided sequentially in two groups with 12 participants each, by the grade of laser therapy they were submitted to and who did not submit to laser therapy, reaching 288 episodes of evaluation between the weeks of infusion of MTX where each patient underwent 12 weeks of chemotherapic. Sociodemographic characteristics of the sample indicated that 58.3% were males and 41.7%, were females. Most of the patients originated from the Southeast Region, mainly from the State of São Paulo (28.6%).

Of the participants who claimed they were Caucasian, eight were not submitted and four submitted to laser therapy, but the self-reporting as Brown race was inversely proportional, four did not submit and eight did submit to laser therapy. Regarding nutritional diagnosis, the group without laser had 50.0% of the patients mal-nourished or with low weight, 33.3%, eutrophic and 16.7%, overweight or obese. For the laser group, 50% were mal-nourished or with low weight, 16.7 eutrophic and 33.3%, overweight or obese, showing nutritional balance among groups.

Comparing the grades I and II of oral mucositis among the groups, the participants of the laser group had more mucositis (41) than the non-laser group (10); the severe oral mucositis (III and IV) was higher in the non-laser group (9). It is noticeable that seven episodes of mucositis failed to be graded, according to Table 1.

Figure 1 shows the distribution of the episodes of oral mucositis and its grading scores with level of significance ($p<0.001$).

Table 1. Distribution of figures and percentage of oral mucositis grading among the groups

	Group without laser		Group with laser	
Oral mucositis	**N**	**%**	**N**	**%**
Absent	119	82.6%	99	68.8%
Grade 1	2	1.4%	23	16.0%
Grade 2	8	5.6%	18	12.5%
Grade 3	5	3.5%	1	0.7%
Grade 4	4	2.8%	2	1.4%
Without grading	6	4.2%	1	0.7%

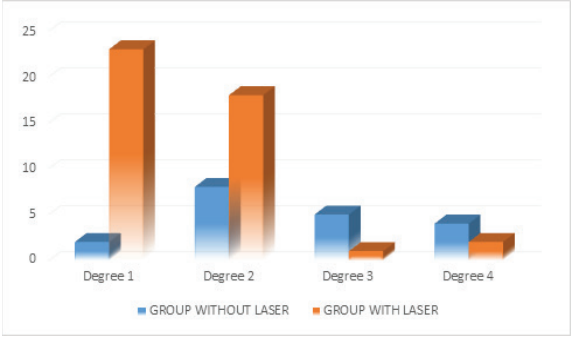

Figure 1. Episodes of oral mucositis in relation to the grade of intensity among the groups ($p<0.001$)

When compared the laser group and non-laser group regarding admission by mucositis, the non-laser group had an increase of 4.9% in relation to the laser group. With the Pearson chi-square statistic test, it was not encountered statistic relevance when the two groups are compared (p=0.06) as Table 2 shows.

The results of the evaluation of the delay of the protocol of oral mucositis showed there was an increase of the number of episodes of delay among non-laser patients. 11 episodes of the non-laser and 1 episode of the laser group were found. Based in Pearson chi-square statistic test, significant statistical difference was found when the two groups are compared (p=0.005) as described in Table 3.

Regarding the evaluation of the presence of oral mucositis in relation of the toxicities presented, the results showed there was increase of the number of episodes of oral mucositis in the patients with hepatic alterations with statistical relevance (p=0.001), not being noticed significant alterations in relation to nausea, vomits, neutropenia, renal dysfunction and plateletopenia according to Table 4.

Table 2. Distribution of admissions by oral mucositis, per episode among the groups

Admission by mucositis	Group without laser		Group with laser		Total	
	N	%	N	%	N	%
No	135	93.8	142	98.6	277	96.2
Yes	9	6.3	2	1.4	11	3.8
Total	144	100	144	100	288	100

Caption: Value of p=0.06.

Table 3. Distribution of the delay of the protocol due to oral mucositis per episode among the groups

Delay of the protocol	Group without laser		Group with laser		Total	
	N	%	N	%	N	%
No	130	92.2	139	99.3	269	95.7
Yes	11	7.8	1	0.7	12	4.3
Total	141	100	140	100	281	100

Caption: Value of p=0.005 (statistically significant).

Table 4. Distribution of oral mucositis because of toxicity-related factors among the groups

Toxicities		Oral Mucositis			
		No		Yes	
		N	%	N	%
Nausea	Absent	35	100.0%	219	86.9%
	Present	0	0.0%	33	13.1%
Vomit	Absent	35	100.0%	204	81.3%
	Present	0	0.0%	47	18.7%
Neutropenia	Absent	15	41.7%	137	54.4%
	Present	21	58.3%	115	45.6%
Liver dysfunction (p=0.001)	Absent	0	0.0%	62	24.7%
	Present	36	100.0%	189	75.3%
Kidney dysfunction	Absent	29	80.6%	230	91.3%
	Present	7	19.4%	22	8.7%
Plateletopenia	Absent	29	80.6%	222	88.1%
	Present	7	19.4%	30	11.9%

DISCUSSION

The present study evaluated preventive laser effect of chemo-induced oral mucositis in patients submitted to high doses of MTX to treat osteosarcoma at the Barretos Children's Hospital/SP to assess the response of mucositis to this therapy.

Oral mucositis is considered a high morbidity clinical condition in patients submitted to high doses of MTX and deserves special multi-professional and interdisciplinary attention in the diagnosis, treatment, and rehabilitation of the patient for improvement of the quality of life.

Therefore, laser therapy is a relevant technology for oncologic patient care, in special, pediatric, improving the quality of life while reducing the main adverse effect of the antineoplastic therapeutic. The emphasis in the multi-disciplinary team reinforces that oral mucositis does not belong to a single professional segment, it is necessary to integrate several members from other health areas, among which, stands out odontology because it addresses the buccal cavity of the patient, mostly.

The study population profile showed that 58.3% were males and 41.7% were females. Most of the patients came from the Southeast Region, from the State of São Paulo. It was found balance between the groups regarding race and nutritional diagnosis.

Most of the patients (75.69%) presented some grade of oral mucositis according to WHO. In the present study, there was prevalence of mucositis grades I and II in patients submitted to prophylactic laser therapy when compared with patients who did not submit, this is justified because of the retrospective nature of the study. For the non-laser group, some data were underestimated, mainly because of lack of dental follow up prior to 2012; follow up was more effective only after the creation of an exclusive dental team at Barretos Children's Hospital.

Grade II mucositis was the most found, which shows that low intensity laser therapy when applied in patients submitted to high doses of MTX is effective to control the severity of oral mucositis. According to the literature, mucositis is expected in 40% to 80% of the patients because of chemotherapy, it is notorious that the complications in buccal cavity increase from 40% to 90% in children younger than 12 years because cellular division is faster[1,2,7,9,20-22].

Laser prophylaxis and laser therapy have been increasingly used in this group of patients for prevention and treatment of oral mucositis[22,23]. Innumerous articles show concern with the correct use of this therapeutic modality in relation to the type of laser, dose, frequency and timing of application[1,8,21,22].

Through the results obtained, it was observed that the severity of oral mucositis reduced clinically with significant statistical results ($p<0.001$) corroborating the results encountered in the literature[15,17,21,23,25].

The measures of buccal care prior to chemotherapy are essential to reduce the symptoms in these patients[11]. In this study it was not possible to encounter buccal hygiene data because it was retrospective and the data failed to be duly registered in the charts reviewed.

Most of the patients in this study who presented severe oral mucositis (grades III and IV), during the infusion of MTX did not submit to preventive laser. These results concur with the literature which shows lower severity of mucositis in patients submitted to prophylactic laser therapy[14,26,27].

Hospitalization of patients with severe oral mucositis was higher than for patients with mucositis grades I and II in concurrence with the literature. Lopes et al.[28] concluded that the hospitalization of patients with severe oral mucositis would be from two to six days longer than patients with mucositis grades I and II or absent.

Oral mucositis may lead to increased hospitalization for patients, special care, including barbiturate intravenous infusion, other drugs, and parenteral feeding, which together increases economic costs[15,17,21-23].

The effectiveness of laser therapy has been demonstrated for more than 30 years in France with patients treated with chemotherapics including 5-fluorouracil and MTX, the frequency and severity of oral mucositis were reduced with laser therapy and the incidence of oral complications dropped from 43% to 6%[22]. Cancer treatment was optimized by reducing the comorbidities with laser therapy and diminishing of unexpected interruptions, ensuring the continuation of chemotherapy[3,22]. Prophylactic laser therapy reduces the global risk of oral mucositis and other measures of the severities of mucositis including its duration in patients with cancer[14,22]. It was noticed as well a relevant reduction of 1.4% of the admissions by mucositis in patients submitted to laser therapy and 6.3% in the group without laser and although with no statistical significance ($p=0.06$), the admissions among the groups increased. Because of oral mucositis in the non-laser group, an interruption of the chemotherapeutic cycles was noticed in 7.8% of the episodes while in the laser group only 0.7% occurred, proving statistically significant results ($p=0.005$).

Regarding onset and resolution of oral mucositis, the literature shows that with laser a relevant reduction of the severity and days until healing was noticed[22]. However, it was not possible to evaluate this data in this retrospective study because the relevant information were not described in the charts.

In relation to toxicity, the literature brings pertinent information, but these are expected events from the use of MTX as demonstrated in Table 4; in this study, nevertheless, it was observed an increase of mucositis in patients with liver function change, which calls for consideration in relation to deem relevant the raise of these toxicity parameters. It is possible to infer about the influence of MTX serum levels that dosage changes impact the onset of mucositis as the delayed excretion or intoxication increasing the time of action of the drug in the organism, however, this data was not evaluated for serum dosage in this retrospective study and some data to obtain this information failed to be described in the charts analyzed, which demands future studies[5,9,21,27].

All the participants who had mucositis reported nausea and vomits, after reviewing these variables, and it can be explained because of the irritating action and pH reduction upon release of the gastric juice resulting from vomit[5,21,27].

More clinical indicators could be presented in the study had mucositis onset and resolution been included, however, these disadvantages do not reduce the generalization of the results to the population investigated and strengthen the necessity of prospective study.

CONCLUSION

The use of laser therapy investigated in this study has been shown to be an important auxiliary therapeutic for the prevention and reduction of the serious oral mucositis in patients submitted to high doses of MTX.

The intensity of oral mucositis was observed in higher grading (III, IV) in patients of the group who did not submit to prophylactic therapy with laser (statistical significance), being also observed more episodes of admission by mucositis and interruption of the treatment because of mucositis in this group.

CONTRIBUTIONS

All the authors contributed for the study conception and/or design, collection, analysis and/or interpretation of the data, wording and/or critical review and final approval of the version published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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