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Photodynamic therapy for treatment of oral mucositis: Pilot study with pediatric patients undergoing chemotherapy

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ABSTRACT

Background: Oral mucositis has become a major dose-limiting toxicity of antineoplastic treatment.
Aim: The aim of this study was to evaluate the effect of photodynamic therapy (PDT) and low level laser therapy (LLLT) on the treatment of chemotherapy-induced mucositis in pediatric patients.
Methods: An open, controlled, and blind, randomized clinical trial was conducted with 29 patients, from 10 months to 18 years old, who were divided into two groups. Group A was submitted to photodynamic therapy (0.01% Methylene Blue and red laser, λ660 nm) with 3J energy per point; and Group B submitted to low level laser therapy (λ660 nm) with 1J energy per point. The results were evaluated by using the WHO and ChIMES mucositis scales. The Chi-square, Exact Fisher, Student's-*t* and Mann-Whitney tests, and the mixed linear regression model were used for comparison between the groups, with the maximum error admitted of 5%.
Results: There was no difference between the groups as regards the number of sessions necessary for clinical cure of the oral lesions ($p = 0.954$) or reduction in pain reported by the patients ($p = 0.258$; $p = 0.486$). Within each group, however, there was significant reduction in pain ($p = 0.032$; $p = 0.003$). The number needed to treat (NNT) was 4.75.
Conclusions: PDT or LLLT could be used for treatment of oral mucositis in children/young patients. Each were well tolerated and presented satisfactory results in reducing pain associated with the lesion.

1. Introduction

The new antineoplastic agents being administered and the diverse therapeutic regimes implemented have allowed a significant improvement in the survival rates of pediatric oncological patients, however, this has been associated with greater morbidity [1–3]. Fifty-eight percent of the pain reported by children/young patients are attributed to the side effects of anticancer therapy, and oral mucositis has appeared as one of the most serious and frequent complications [3,4] associated with an increase in mortality of around 40% for severe cases [5].

Defined as an inflammatory, painful and debilitating condition, oral mucositis affects the oral tissues of patient submitted to atineoplastic treatment. It may make it difficult for them to eat, swallow, speak and perform oral hygiene, in addition to serving as the port of entry for infections. In some situations, the patient needs parenteral or enteral nutrition, and even the oncological treatment has to be interrupted, thus negatively interfering in the prognosis of the disease [1,4,6,7].

Its estimated prevalence ranges from approximately 20–40% in patients submitted to conventional chemotherapy [4], but may affect 90–100% of the pediatric patients submitted to aggressive myeloablative chemotherapy regimens [1]. Severity varies as a result of various factors, some related to the treatment, such as type, dose and agenda for administering the cytotoxic medications; and others related to the patient, such as age, nutritional condition, type of malignancy, neutrophil counts and degree of oral hygiene. Children with hematological tumors experience the condition more frequently and more severely than those diagnosed with solid tumors [8,9].

Various studies have sought to prevent or minimize the severity of oral mucositis, but the majority of these have been conducted in adults. Among the possible interventions suggested are the use of oral care protocols [2,3,10,11]; mouth washes [8,9]; morphine [12]; glutamin [9]; photobiomodulation [7,10,13–16] and the use of keratinocyte growth factors [7,10]. However, up to now, there has been no consensus about the level of evidence presented by these studies, or any

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agreement about the best therapeutic option [6,7,9,10,15].

Over the last few decades, researchers have turned their attention to low level laser therapy as an effective modality for preventing oral mucositis and reducing the symptoms associated with it [17]. The studies have revealed the angiogenic power of laser favoring microcirculation and facilitating regeneration, in addition to its anti-inflammatory and analgesic action [15,18,19]. In the treatment of oral mucosa, short wavelength lasers (600–900 nm) have reduced the severity of mucositis, shortened its duration and minimized the pain [17].

Because of the diversity of microorganisms in the oral cavity environment, mucositis lesions are frequently associated with infections making it necessary to disinfect the area to achieve adequate healing. Photodynamic therapy (PDT) appeared as a promising method and its effectiveness has been demonstrated in different odontogenic processes [20]. The technique has been used by health professionals to eliminate tumor cells and/or microorganisms [21]. The procedure is local, easy to implement, and has no significant adverse effects. However, up to now, there are only two published studies that have evaluated the action of PDT in the treatment of oral mucositis: one was developed in an animal model [21] and the other in humans [20].

In view of the need to reduce the symptoms associated with oral mucositis in children/young patients, the present study was developed with the aim of evaluating and comparing the effectiveness of two interventions described in the literature as being easy to handle and free of side effects: photodynamic therapy (PDT) and low level laser therapy (LLLT). The hypothesis tested was that PDT would present similar or superior results to those of LLT in the control of chemotherapy induced oral mucositis in pediatric oncological patients.

2. Materials and methods

2.1. Ethical aspects

The present study was elaborated in accordance with the CONSORT guidelines – *Consolidated Standards of Reporting Trials* [22], submitted to the Research Ethics Committee of the "Universidade Federal de Pernambuco" (UFPE) and approved under number 1.810.409/2016. In the Brazilian Register of Clinical Trials "Registro Brasileiro de Ensaios Clínicos (ReBEC)" the study was approved under identification number UTN: U1111-1190-9887.

2.2. Pilot study

The pilot study consisted of a randomized, open, controlled and triple-blind trial, composed of two groups: Group A (study group) made up of children/adolescents submitted to photodynamic therapy for the control of oral mucositis; and Group B (control) made up of young persons submitted to low level laser therapy.

2.3. Sample selection

The patients were evaluated in the period from November 2016 to March 2017 in the pediatric oncology units of two reference hospitals in the treatment of childhood cancer, in the state of Pernambuco, Brazil.

Twenty-nine patients, with ages ranging from 10 months to 18 years of age, submitted to chemotherapy, and with oral mucositis > 1, according to the World Health Organization (WHO) Toxicity Criteria, were included in the sample. Patients with malignant neoplasia, or clinically evident severe infection in the oral cavity, or in a serious medical condition that would prevent their participation in the research, were excluded from the sample.

The potential participants were identified by dentists of the services, who were not directly connected with the study, and the patients were referred to the main researcher. After applying the eligibility criteria, this researcher explained the details of the research to the children's guardians and young persons over the age of 12 years and requested them to sign the term of free and informed consent. Afterwards, by means of a simple randomization process of choosing a sealed opaque envelope that contained identification of the therapy to be implemented, the patient was allocated to one of the study groups.

The beginning of each chemotherapy cycle was considered a new case, and the patients were submitted to a new randomization process if they presented a new episode of oral mucositis [16].

2.4. Intervention

At a time before the first laser session, the patients were instructed about the importance of maintaining adequate oral hygiene throughout the oncological treatment, and to perform at least 2 daily tooth brushing sessions with a soft toothbrush and children's toothpaste. They were given a follow-up chart to use for noting the tooth brushing sessions they performed, and their oral health condition was inspected. If the researcher found at least one open caries cavity, a root remainder, or gingival bleeding associated with the presence of dental biofilm identified without the help of a plaque disclosing agent, the patient was categorized as having an unfavorable oral condition. The patients were also asked whether they had previously been submitted to prophylactic laser therapy.

The entire attendance procedure was performed at the bedside of hospitalized patients; or in the case of outpatients, they were seated on conventional chairs in the outpatient clinic, and were examined under room lighting with the help of a clinical flashlight.

2.4.1. Group A (PDT)

The patients randomized in Group A received photodynamic therapy as the form of treatment for oral mucositis. At the sites where lesions were identified, 0.01% Methylene Blue was applied with a cotton bud, until the ulcerated area was completely colored. After a three-minute waiting time for the coloring agent to act, red laser was administered at a minimum distance from the tissue (that is, without touching the tissue) by the punctual technique, perpendicular to the tissue. The equipment *Therapy EC (DMC®)*, with a wavelength of 660 nm was used in continuous mode, with the following parameters: *spot size* 0.028 cm^2; mean power (*output)* of 100 mW; 3J energy per point; energy density 107J/cm^2 and irradiation time of 30 s per point. The number of points was calculated according to the size of the lesion, in a ratio of 1 laser application per cm^2 of the lesioned area. The procedure was repeated daily, until clinical cure of the lesions was achieved.

Clinical cure was considered the absence of painful symptomatology accompanied by re-established function (chewing, swallowing and phonation) and clinical signs of tissue regeneration.

Before each time of use, the tip of the laser was disinfected with 70% alcohol and covered with plastic film. The patient and operator used specific glasses to protect the eyes and all the biosafety measures were adopted during therapy.

2.4.2. Group B (LLLT λ = 660 nm)

The Control Group was composed of patients who received red laser on a daily basis. The treatment began as soon as the oral mucositis was diagnosed, and continued until clinical cure of the lesions was obtained. The light was applied at a minimum distance from the tissue in a punctual and perpendicular manner. The same equipment *Therapy EC (DMC®)*, with a wavelength of 660 nm was used in continuous mode, with the following parameters: *spot size* 0.028 cm^2; mean power (*output)* of 100 mW; 1J energy per point; energy density 35J/cm^2 and irradiation time of 10 s per point. The number of points was also calculated according to the total size of the lesion, in a ratio of 1 application per cm^2 of the lesioned area. The same procedures of care taken with protection and biosafety were adopted, as those described for the study group.