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Application of Low-Level Laser Therapy for Analgesia of Odynophagia Caused by Head and Neck Radiotherapy: Anatomic Study and Clinical Protocol Proposal

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ABSTRACT

Introduction: Oral and hypopharyngeal mucositis are considered acute effects of great importance of radiotherapy. Patients present painful ulcers, dysphagia, odynophagia and difficulties in speaking, which can lead to malnutrition and treatment discontinuation. Currently, photobiomodulation therapy, using low-level laser therapy is the treatment of choice for oral mucositis.

Objective: To propose the use of extraoral laser therapy to treat odynophagia associated with radioinduced hypopharyngeal mucositis.

Methods: Pilot study divided into two stages: (1) Anatomical study in cadavers, to select the best area of application of the extraoral laser in the cervical region to reach the hypopharynx. In this stage, we opted for the use of low-level light therapy (XXXXX*), continuous mode, $\lambda 660\text{nm}$, 100mW power, 0.028cm² spot. (2) Application of extraoral photobiomodulation for patients with odynophagia associated with oral and hypopharyngeal mucositis. The same low-level laser therapy (XXXXX*) was used, but with $\lambda 808\text{nm}$, 100mW power and 4J energy, 40 pulses per point. Reports of three patients who underwent treatment were collected, transcribed and reviewed qualitatively. Results: (1) The anatomical region that allowed better access of extraoral laser therapy to the hypopharynx was the carotid triangle. (2) Patients reported reduced odynophagia and greater comfort with the use of this treatment.

Conclusion: The carotid trigone was the best extraoral region for laser application to reach the hypopharyngeal region. The laser therapy protocol applied in this region brought comfort to the patients assessed. Further studies are needed to assess the analgesic capacity of this treatment.

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Introduction

Mouth cancer is considered a public health problem in XXXX. An estimated 15,190 new cases are expected to occur in the year 2020 affecting 11,180 men and 4,010 women, this being one of the most frequent malignancies in the XXXX population. Worldwide, 657,000 new cases of oral cavity and pharynx cancer and 330,000 deaths are estimated to occur each year [1,2].

Oncological surgery of the lesion is considered the first treatment option, followed by adjuvant radiotherapy or radiochemotherapy, depending on the stage of the disease. The most common side effects of radiotherapy are: oral, hypopharyngeal and esophageal mucositis, difficulty in chewing and swallowing, hyposalivation, dry mouth, loss of taste, trismus, radiation decay, osteoradionecrosis, among others [3,4].

Oral and hypopharyngeal mucositis are considered acute effects of great importance and depend directly on the radiotherapy dose, the location of the tumor and the type of radiotherapy used. Patients present painful ulcers, dysphagia, odynophagia and difficulties

in speaking, which can lead to malnutrition and treatment discontinuation. Odynophagia is characterized by swallowing pain, often requiring diet changes, which directly impacts the patient's quality of life. Currently, photobiomodulation therapy, using low-level laser therapy is the treatment of choice for oral mucositis [5].

The low-level laser therapy modulates the inflammatory, repairing and analgesic process. This non-invasive and non-drug therapy is able to delay the development of oral mucositis, as well as to attenuate both the severity of the lesions and their duration [6]. Clinical protocols for intraoral photobiomodulation for oral mucositis are consolidated in the literature, but very few reports are available regarding hypopharyngeal mucositis control. The oral mucosa is easily accessible by the low-level laser equipment available on the market, which allows direct contact of the light beam with the altered surface. Thus, a better analgesic effect ensues [7,8].

However, the pharyngeal region is difficult to access intraorally and this is why the light beam is unable to come into direct contact with the injured mucosa of that region, a fact that may reduce the laser therapeutic efficacy. In view of the above, the objective of this study was to propose the use of low-level laser therapy extraoral to treat odynophagia associated with radio-induced

hypopharyngeal mucositis.

Material and Methods

This investigation was approved by the Research Ethics Committee under number CAAE 72989417.0.0000.0121, dated April 9, 2018. It was divided into two stages: 1) Anatomical study in cadavers and 2) Clinical study with the application of extraoral photobiomodulation therapy in patients with odynophagia associated with oral and hypopharyngeal mucositis, with observational cases study.

Part 1: Anatomical Study on Cadavers

This stage was carried out strictly to determine the region where it is possible to visualize the propagation of the visible red laser beam through the different tissues of the cervical structures (Figure 1).

The study of the anatomy of the human cervical region was performed on dissected parts of cadavers (Human Anatomical Theater, Department of Morphology). All the cadavers used in this study were previously prepared using a 10% formaldehyde and glycerol medium.

A diode laser (Therapy XT DMC®) was used, at a wavelength of 660nm, continuous mode, 100 mW power, 0.028cm² spot size over all regions of the cervical trigones, for 10 seconds at each observation point, time considered sufficient for visual observation of the red light beam passing through the tissues. Through direct observation, the area in which the visible red beam propagated and reached the hypopharynx region to the point of being seen with the naked eye was assessed.

Part 2: Pilot Study with the Application of the Extraoral Photobiomodulation Technique, with an Observational Case Study.

The extraoral laser therapy clinical treatment proposed for hypopharyngeal mucositis used a diode laser (Therapy XT DMC®), 660nm, 100mW power, continuous mode, 4J energy and 40 seconds per point.

Based on what was proposed in part 1 of this study, the carotid trigone was considered the best extraoral region for laser application allowing to reach the hypopharyngeal region. The anterior margin of the sternocleidomastoid muscle (SCM), one of the boundaries of the carotid trigone, was used as the most favorable application site, for being more easily clinically identified, through palpation. Thus, the low-level laser therapy was applied, in the clinical phase of the study, in 4 points (4J per point) in this pre-determined anatomical region, perpendicularly and in contact with the skin, along the anterior margin of SCM muscle.

Three patients undergoing oncologic head and neck radiation therapy or radiation chemotherapy (radiation doses equal to or greater than 5000cGy), who exhibited oral and hypopharyngeal mucositis associated with odynophagia, were assessed and voluntarily accepted to undergo this photobiomodulation technique on the bilateral carotid artery trigone and reporting about their perception of pain and odynophagia.

Hypopharyngeal mucositis was determined from the report of pain in the region, associated with odynophagia. Clinical care was provided by the team of surgeon dentists at the Hospital Dentistry Center. In addition to using this technique to treat hypopharyngeal mucositis, patients received conventional photobiomodulation therapy to prevent and treat oral mucositis. The diode laser (Therapy XT DMC®), 660nm, continuous mode, 0.028cm² spot size, 100mW power, 1J per point, 54 points was used.

The patients were older than 18 years and, after receiving due information, voluntarily signed a free and informed consent form. Information was collected such as: gender, tumor site, irradiated site, type of treatment performed (radiotherapy and/or radiotherapy associated with chemotherapy), total radiation dose, number of radiotherapy sessions, at what point in time the radiotherapy laser therapy was started, pain complaints and odynophagia and use of nasoenteral tube.

At the end of the treatment, all patients issued a verbal and spontaneous statement about the perception of their symptoms during the photobiomodulation sessions. The statements were recorded and later transcribed in text format.

Results

Part 1: Anatomical Study in Cadavers

The region that allowed the best propagation of the laser beam was the carotid trigone, allowing good access of the light to the hypopharynx. In this region, during application, the visible red laser beam was observed spreading through all muscle and cartilage layers, thus being considered the best extraoral access site for laser application. The laser tip was positioned perpendicularly and in contact with the skin, along the anterior margin of the SCM muscle.

The cadaveric anatomical study was important to establish the extraoral location of laser applications. A total of four points was then established, with 1 cm distance between them, following the direction of the SCM muscle along the carotid trigone, for an improved laser beam penetration and better analgesic effect (Figure 2).

Part 2: Pilot Study with the Application of the Extraoral Photobiomodulation Technique, with an Observational Case Study

The three patients participating in this study were diagnosed with squamous cell carcinoma on the border of the tongue and were treated surgically and with head and neck radiotherapy. As a sequel to treatment, all patients developed oral and hypopharyngeal mucositis, and complained of odynophagia.

Table 1 presents information related to patients. Patients 1 and 2, who started oral and hypopharyngeal photobiomodulation on the same day they started radiotherapy, developed oral and hypopharyngeal mucositis, reporting mouth pain and odynophagia; both patients maintained exclusively oral feeding throughout the cancer treatment. Throughout the treatment, both patients reported symptoms improvement in the oral cavity, but only patient 1 reported odynophagia improvement. The maximum score of mucositis they developed was grade 3, according to the classification of Sonis, et al. [9].

Patient 3 was referred to the Hospital Dentistry Center, only when he was already in the sixteenth (16th) radiotherapy session, exhibiting grade 4 oral mucositis, according to the Sonis, et al., classification and using a nasoenteral tube [9]. After performing oral and hypopharyngeal photobiomodulation, the patient reported unmeasured pain improvement both in the oral cavity and in swallowing.

The three patients voluntarily and spontaneously orally reported about their experiences and sensations when being attended by the Hospital Dentistry Center team of surgeon dentists. The transcribed reports are presented below:

Patient 1: "(...) Mouth sores appeared after one week of

radiotherapy, it hurt a lot, I felt a lot of pain when swallowing, I choked a lot, I always had to drink some water after food intake to be able to swallow. As soon as the laser was applied, I already felt better; it didn't stop hurting totally, but I managed to eat soon after. The laser applied on my neck helped me a lot with the pain to swallow (...)"

Patient 2: "(...) In the first days of radiotherapy I lost my sense of taste, I already had a sore throat and mouth injuries. In the mouth I didn't feel much pain, but I felt a lot of pain to swallow, I couldn't eat properly. I wish there was something penetrating in my throat to relieve the pain, just like the laser has worked into the mouth (...)"

Patient 3: "(...) I felt pain all over my mouth and pain when swallowing, I couldn't even rinse my mouth with water, or brush my teeth; I had to use a probe for eating. I started to recover very well after the laser application; with each session I felt better, mainly swallowing (...)"

Discussion

Mucositis is the most undesirable consequence of radiotherapy or radiochemotherapy treatments due to severe pain, causing dysphagia, weight loss and reduced treatment adherence [10,11].

The low-level laser therapy has important therapeutic properties in the treatment of mucositis. For best results, the laser tip should be positioned as close as possible and perpendicular to the injured tissue [12]. In oral mucositis, this is possible due to easier access to the tissues [4,7,8,11,13]. In contrast, in hypopharyngeal mucositis, this direct contact between the tip of the laser device and the mucosa is unfeasible, and it is necessary to develop an extraoral laser therapy treatment that allows the laser to penetrate through the anatomical structures of the neck and, thus, provide an analgesic effect on the mucosa. The learning of the cervical anatomy in cadavers allowed the handling of tissues, the observation of the laser positioning in relation to the hypopharynx. The lack of more prominent topographic characteristics and the content of important structures, in particular vessels and nerves, have led to the common use of the subdivision of the neck into triangular-shaped areas. These are three-dimensional triangles, surrounded by muscles and bones and with different fascial layers. The carotid trigone has the anterior border of the median portion of the SCM muscle as a posterolateral boundary, the upper belly of the omohyoid muscle as an anteroinferior boundary and the posterior belly of the digastric muscle and stylo-hyoid muscle as an upper limit. In this study, the laser at the visible red wavelength was applied externally along the cervical structures, seeking to observe from which anatomical region the light would reach the hypopharynx region. Therefore, the criterion used, was only visual. The carotid trigone was shown to be the region with the least amount of tissue between the skin surface and the hypopharyngeal mucosa, allowing the red light beam to reach the hypopharyngeal mucosa [14].

Although there is a vast literature on the application of intra-oral laser in oral mucositis, no clinical studies are available on the effects of photobiomodulation therapy in the hypopharyngeal region [3,7,8,13,15,16]. However, in animal studies, significant effects have already been observed in the use of extraoral laser in the treatment of oral mucositis [16].

Likewise, no studies were found that evaluate swallowing in a clinical or instrumental way to verify the effect of applying the laser therapy protocol in dysphagia. In the study by Gautam, et al., comparing a group submitted to oral laser therapy with a placebo group, the authors found that the need and duration of parenteral nutrition was significantly lower in the group treated with laser to control

radiotherapy-induced oral mucositis [17]. The authors considered the practice feasible to prevent and treat oral mucositis and minimize pain and dysphagia; however, similar studies that used laser in the hypopharynx region have not been described in the literature.

No equipment is available on the market that will allow intraoral laser access to the hypopharynx region. Device tips, which allow intimate contact of the laser with the mucosa, similar to those used in videolaryngoscopy exams, would be desirable. Given the above, the extraoral application of the laser seems to be a good alternative for the treatment of the hypopharyngeal mucositis.

The laser photons, when crossing a material, can be absorbed or scattered, which can cause attenuation in the light intensity. This is why, a λ range between 600nm and 1200nm is widely used for the treatment of deep tissues (up to ~2cm) [18]. The λ 808nm diode laser is used in clinical practice for the therapeutic effects on deeper tissues. There are laser therapy protocols for postoperative surgeries that use this treatment to reduce edema, assisting in lymphatic drainage and reducing the use of anti-inflammatory medication, for example [19-21].

Other authors, whose studies have evaluated the effect of low-level laser therapy applied extraorally, highlight the lack of investigation reports on the subject covered by our protocol. In addition, dosimetry revealed to be quite complex for these cases [16]. Thus, more studies are needed to understand how much energy actually reaches the oropharyngeal mucosa, so that more effective protocols can be proposed [16].

In this article, we are suggesting the use of diode laser (Therapy XT DMC), λ 808nm, 4 points of 4J each, 1 cm apart, applied perpendicularly along the anterior belly of the SCM muscle, bilaterally. In this way, a total of 32J is applied to the neck skin, in the region of the carotid trigone, and so far it is impossible to know how much of this energy actually reaches the hypopharyngeal mucosa.

The lack of measurable criteria when attending patients, lead us to opt for qualitative analysis through three observational case studies, seeking to understand how each patient understood empirically his individual reality without extrapolating these impressions to a whole group [22]. Despite being a pilot study, this report allows an initial analysis of how promising this triangle technique is and can further be studied and improved, in an attempt to solve one of the major problems that cancer patients experience during treatment, which is the radio-induced hypopharyngeal mucositis, which is associated with pain and dysphagia, hampering the patient's quality of life, as well as increasing the possibility of cancer treatment discontinuation [23].

Based on the patients' reports, it is believed that laser therapy targeting the carotid trigone region caused analgesia in the hypopharynx: Patient 1: "As soon as the laser was applied, I already felt improvement; it never stopped hurting totally, but I was able to eat soon after" and patient 3: "I started to recover very well after the laser applications; in each session I felt better, especially to swallow". Although patient 2 did not report improvement in odynophagia, it can be inferred that the laser application contributed to patients 1 and 2 continuing to feed exclusively orally and patient 3 progressing to oral feeding, considering that it is known that, during radiotherapy in the head and neck region, the need to use an alternative feeding route can reach 61% of cases, due to pain, weight loss and dysphagia conditions [23].

The importance of developing a laser application protocol for hypopharyngeal mucositis was also perceived in another statement by patient 1: “*The laser applied on my neck helped me a lot with the swallowing pain*”. Patient 2 reported that he did not feel much pain relief with extraoral applications, but reveals that “... *I wish there was something that entered my throat to relieve the pain, just as laser has worked out in my mouth*”.

It is believed that the development of a protocol in the extraoral region of laser therapy for the treatment of hypopharyngeal mucositis is important to reduce swallowing pain, allowing the patient to enjoy a better diet and keeping his/her body nourished to face the antineoplastic treatment.

One of the limitations of this study was the difficulty in measuring the energy that can reach the hypopharyngeal mucosa through the extraoral application of laser therapy, a methodology that represents a great challenge. In addition, clinical studies are required to be able to classify the degree of hypopharyngeal mucositis and that better assess the analgesia achieved by this suggested laser therapy protocol in an extraoral region of the carotid trigone.

Conclusion

Within the limitations of this study, the carotid trigone was defined as the best extraoral region for laser application, in order to extend the benefits of photobiomodulation to the treatment of hypopharyngeal mucositis. Although most patients have reported improvement with the laser application in this region, further studies are needed to gather evidence of laser therapy effects, as well as the best protocols to be used.

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