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Review

Photobiomodulation therapy on bothrops snake venom-induced local pathological effects: A systematic review

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ABSTRACT

Bothrops snakebite treatment is antivenom therapy, which is ineffective in neutralizing the severe local effects caused by these envenomations. There are evidence that photobiomodulation therapy (PBMT) has emerged as a promising tool to counteract the venom-induced local effects. The purpose was to write a narrative review of the literature about PBMT as a treatment for Bothrops snakebites. We reviewed articles indexed in PubMed, SCOPUS and Scientif Direct database with filter application. Included studies had to investigate local effects induced by Bothrops snake venom in any animal model using any type of photobiomodulation irradiation and at least one quantitative measure of local effects of Bothrops envenomation. Sixteen studies were selected from 54 original articles targeted PBMT (low-level laser or light emitting diode) as a complementary tool for local effects treatment induced by snakebites, and all its assessments. Articles were critically assessed by two independent raters with a structured tool for rating the research quality. PBMT demonstrate to be a promising tool for local treatment effects caused by snakebite by reducing local edema, hyperalgesia, leukocyte influx and myonecrosis and accelerating tissue regeneration related to myotoxicity. However, the mechanism is not well understood and additional studies are needed.

1. Introduction

Data suggest that more than 5 million people are assaulted by snakebites each year, of which 25,000 to 125,000 die (Gutierrez et al., 2015). Moreover, 400.000 amputations are attributed to snakebite accidents in addition to serious health consequences such as infection, tetanus and psychological sequelae (WHO, 2016). As a result, the World Health Organization incorporated snakebite envenoming into its list of neglected disease (www.who.int/negleted_diseases/en; Chippaux, 2017a,b). These snakebites accidents occur mainly in the rural communities of developing countries in Asia, Africa, Oceania and Latin America (Gutierrez et al., 2010; Chippaux, 2017a; b).

In Latin America, the majority of snakebite envenomation are inflicted to Bothrops species, which account for 50–80% of the snakebite in Central America (Oteto-Patinõ, 2009; Chippaux, 2017a; b) and nearly 90% in Brazil (Ministério da Sáude, 1998; Chippaux, 2017a; b). These envenomations are characterized by systemic and local pathophysiological alterations. Systemic effects include alterations in blood coagulation, myoglobinemia, hypercalemia, acute renal failure and cardiovascular shock (Del Brutto and Del Brutto, 2012). At the site of the bite, the development of pathological changes occurs rapidly and is characterized by intense pain, edema formation, blisters, hemorrhage and myonecrosis, which may develop in more severe outcome, such as loss of muscle mass and neuropathy that can lead to amputation (Oteto-Patinõ, 2009).

Currently, antivenom (AV) immunoglobulins, included in the WHO List of Essential Medicines, are the only treatment available for snakebites envenoming (WHO, 2010). In the case of Bothrops envenoming, AV is very effective in reversing venom-induced systemic effects. However, neutralization of venom-induce local effects is difficult, owing to the rapid development of tissue damage after this envenomation (Gutierrez and Ownby, 2003). Due to the severity of the local effect caused by Bothropic envenomation and the lack of AV protection, the search for alternative treatments in order to reduce the local myotoxicity caused by snake venom has been investigated. These alternatives include the use of medicinal plants (Parreño et al., 2017; Harder et al., 2017), substances such as heparin and polyanions (Melo et al., 1993; Rostelato-Ferreira et al., 2010) and the use of recombinant antigen binding domains derived from camelid heavy chain antibodies (Prado et al., 2016). Furthermore, the use of photobiomodulation

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therapy (PBMT) has been proposed to complement AV in the treatment of local effect induced by bothropic venom.

PBMT is a non-invasive form of phototherapy, including low-level laser (LLL) and light emitting diode (LED), that utilizes wavelengths of light between 600 and 1000 nm to deliver low irradiance and doses to the target tissue (Chung et al., 2012). The light triggers biochemical changes within cells where the photons are absorbed by cellular photoreceptors and trigger chemical changes (Chung et al., 2012). Positive effects of PBMT comprise activation of cell differentiation, modulation of the inflammatory process, muscle regeneration contribution and tissue fibrosis preventing (Silva et al., 2016; Carlos et al., 2014; Assis et al., 2013). PBMT also showed favorable effects in the reducing hyperalgesia, edema, hemorrhage and myonecrosis after snake venom injections (Barbosa et al., 2008, 2009; Dourado et al., 2003; Nadur-Andrade et al., 2012, 2016).

The effects of PMBT depend on the irradiation time and frequency, dose, and wavelength. Nevertheless, there are no consensuses on standards of therapy dosimetry or standardization of dosage when using PBMT. It is unknown to which extent it is effective in the treatment of local envenomation. We performed this systematic review to identify animal research defining the effects of PBMT on experimental models of local Bothrops envenomation and determine whether the use of photobiomodulation is an effective treatment.

2. Scope and methods

2.1. Literature search strategy

During December 2017, a systematic review of available literature was conducted by searching the databases PubMed, Science Direct, and SCOPUS for papers that compared the effects of PBMT with the effects of local injury caused by *Bothrops* snake venom. No restrictions by publication period were employed. The following keywords, individually or combined, were used: photobiomodulation, PBMT, low-level laser therapy, LLLT, light emitting diode, LED, snake venom, *Bothrops* snake venom. We also reviewed the retrieved articles to identify possible additional studies (Fig. 1). The search was repeated following review of the eligible papers to specifically search for experimental methodologies and outcomes and parameters of PBMT.

Titles and abstracts of retrieved articles were screened by two independent authors and irrelevant studies were excluded. Articles obtained from the previous step were then read and assessed by the two authors (LMGS and SAS) for inclusion criterion to the full studies. Conflicts were resolved through a third independent researcher (PTC). The following inclusion criteria were used: (a) access to the full content of the article; (b) live animal subjects: (c) experimental local injury model induced by snake venom; (d) type of LLL or LED irradiation was provided as an intervention to at least one of the treatment groups: (e) a quantitative or semi-quantitative measure; (f) *Bothrops* species (g) the article was written in English.

In vitro studies, monographs, letters to the editor, conference papers and unpublished data were excluded from the review.

2.2. Quality assessment

The quality of the included studies was assessed independently by two authors and was printed, reviewed, and critically consider for quality rating. To assess the appropriateness, we used a quality rating scale for an animal/tissue research scale (QATRS) questionnaire designed to assess the quality of animal studies (Bashardoust Tajaliv et al., 2010). The QATRS is a 20-point graded assessment chart designed to evaluate randomization, blindness, animal/tissue model similarity with human applications, standardization and reliability of measurement techniques, management of study surveys, and appropriateness of statistical methods.

2.3. Data extraction, data analysis

The data were extracted from the included articles by two independent authors using a standardized data collection form, which contained the following information: authors, animal type, age, gender, groups and sample sizes, site of injury, venom dose, interventions, type of laser, energy settings, treatment period and main outcomes. Data analysis was performed with a qualitative design.

3. Results

3.1. Study selection

Fifty-four studies were found matching our keyword search in the selected databases. Abstracts were used to identify research that repeatedly appeared in more than 1 database (duplication of the same study) ($n = 31$). Additionally, one study was identified by manual search, and was included in the final analysis. Thus, we prescreened 24 studies for full review. Among the 24 studies analyzed, 8 were excluded for not meeting the inclusion criteria of this systematic review: without evaluation of local effects ($n=3$); *in vitro* study ($n = 2$), abstract only ($n = 1$), study with other species than *Bothrops* ($n = 1$), unpublished data (1). The remaining sixteen articles were considered as high methodological quality and included in the final analysis and screening using a standardized pre-quality assessment (Fig. 1).

3.2. General characteristics of included studies

Study characteristics of the selected experimental controlled animal such as sample sizes, type of animal chosen, the breed of the animals being studied, the age of the animals, their weight, the site of the venom injection, the snake venom species and the dose of each study are summarized in Table 1. The studies were analyzed by a series of methodological rigor called QATRS, addressing several aspects that allow a better quality control of the experimental studies. Scores ranged from 16 to 18 points on a scale of 0–20 points. All included studies were venom-induced local effects compared to the effect of PBMT or with an AV treatment. Fourteen studies used Swiss mice and two studies used Wistar rats, the weight of subjects included in the studies ranged from 18 to 40 g for mice and 250–350 g for the rats. The studies used several experimental models of venom-induced local effects, and all of them were distributed in intramuscular injection (10/16), intradermally injection (4/16), intradermally and intraperitoneal injection (1/16) and intramuscular and intradermally injection (1/16). Fifteen studies used male animals and one did not mention the gender. The species of the snake venom studied was *B. moojeni* venom (7/16), *B. jararacussu* (5/16), *B. newviedi* (1/16) and *B. jararaca* (1/16), in addition one study used BthTx-I and −II myotoxins isolated from *B. jararacussu* snake venom and another used the Mjtx-I and −II myotoxins isolated from *B. moojeni* snake venom (Table 1).

3.3. Study results

Treatment protocol and laser parameters varied among studies and are summarized in Table 2. Thirteen studies used LLL, one study used LED and two studies compared LLL and LED in their studies. The energy density varied from 2.2 to 10.5 J/cm^2 with the wavelengths varying between 632.8 and 945 nm and an output power ranging from 10 to 120 mW. Regarding the number of sessions of PBMT application, the studies ranged from 1 to 88 sections depending on the type of analysis performed. The beginning of treatment period varied from 3 h to 21 days. Moreover, the onset of PBMT application varies from 0 to 3 h after the venom injection (Table 2).

The studies used several experimental models of injury induction and in most studies more them one type of injury was used, and all of them were distributed in myonecrosis (8), edema formation (6),