Publication status: This preprint has been published elsewhere.
DOI of the published preprint: https://doi.org/10.1590/1807-2577.20260016

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https://doi.org/10.1590/SciELOPreprints.16864

Submitted on: 2026-07-10
Posted on: 2026-07-13 (version 1)
(YYYY-MM-DD)

e20260016
Original Article

Antimicrobial photodynamic therapy in the treatment of experimentally induced dental alveolitis in animals

Terapia fotodinâmica antimicrobiana no tratamento de alveolite experimentalmente induzida em animais

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How to cite:

Garcia VG, Lopes Júnior W, Theodoro LH. Antimicrobial photodynamic therapy in the treatment of experimentally induced dental alveolitis in animals. Rev Odontol UNESP. 2026;55:e20250016. https://doi.org/

Resumo

Introdução: A reparação alveolar em áreas infectadas ainda carece de estudos adicionais, especialmente no que diz respeito a terapias adjuvantes ou alternativas. **Objetivo:** Este estudo teve como objetivo analisar histologicamente o processo de reparação em feridas infectadas após extração dentária tratadas com terapia de fotobiomodulação (FBM) isoladamente ou em combinação com um fotossensibilizador (FS) na terapia fotodinâmica antimicrobiana (aPDT). **Material e método:** Quarenta e oito ratos foram submetidos à extração do incisivo superior direito e após, receberam a indução da alveolite experimental. A seguir, foram aleatoriamente divididos em 4 grupos (n=12) que receberam os seguintes tratamentos: Grupo controle (C), sem tratamento intra ou extra-alveolar; Grupo FS, irrigação alveolar com azul de metileno (100 µg/mL); Grupo FBM, os alvéolos foram submetidos à irradiação com laser de baixa potência (685nm, 0,05W, 240s, 12J); Grupo aPDT: O tratamento foi semelhante ao do grupo FS, com um tempo de pré-irradiação de 60 segundos, seguido imediatamente da irradiação com laser, em condições semelhantes às do grupo FBM. Os animais foram eutanasiados no pós-operatório nos dias 7, 15, 21 e 28. Foram realizadas análises descritivas do processo do reparo alveolar em três locais. **Resultado:** As feridas do grupo C apresentaram atraso na cronologia da reparação alveolar. O grupo FS apresentou uma melhor resposta inflamatória inicial em comparação ao grupo controle. Os animais tratados com FBM e aPDT apresentaram reparação óssea mais

acelerada do que os do grupo C. **Conclusão**: Conclui-se que houve atraso do processo de reparação alveolar; que o uso isolado do FS minimizou os efeitos deletérios da alveolite sobre o reparo ósseo; que as terapias fotônicas beneficiaram o reparo alveolar, principalmente quando a aPDT foi utilizada.

Descritores: Alveolite seca; terapia por luz de baixa intensidade; fotoquimioterapia; regeneração óssea; ratos.

Abstract

Introduction: Alveolar repair in infected areas still lacks further studies, especially regarding adjuvant or alternative therapies. **Objective:** This study aimed to histologically analyze the repair process in infected wounds after tooth extraction treated with photobiomodulation (PBM) therapy alone or in combination with a photosensitizer (PS) in antimicrobial photodynamic therapy (aPDT). **Material and method:** Forty-eight rats underwent extraction of the right upper incisor and subsequently received experimental alveolitis induction. They were then randomly divided into 4 groups (n=12) that received the following treatments: Control group (C), no intra- or extra-alveolar treatment; PS group, alveolar irrigation with methylene blue photosensitizer (MB, 100 μg/mL); PBM group, the alveoli were subjected to PBM therapy mediated with a low-power laser (685nm, 0.05W, 240s, 12J); aPDT Group: The treatment was similar to that of the PS group, with a pre-irradiation time of 60 seconds, followed immediately by laser irradiation, under conditions similar to those of the PBM group. The animals were euthanized post-operatively on days 7, 15, 21, and 28. **Result:** The wounds in group C showed a delay in the chronology of alveolar repair, PS group showed an improved initial inflammatory response compared to the control group. The animals treated with PBM and aPDT showed faster bone repair than those

in group C. **Conclusion:** It is concluded that there was a delay in the alveolar repair process; that the isolated use of the PS minimized the alveolitis deleterious effects on bone repair; those photonic therapies benefited alveolar repair, especially when aPDT was used.

Descriptors: Dry socket; low-level light therapy; photochemotherapy; bone regeneration; rats.

INTRODUCTION

Dental alveolitis is a clinical condition that requires rapid diagnosis and prompt professional intervention, occurring after tooth extractions, especially of third molars. It can also be referred to as dry or wet alveolitis. Diagnosis is based on the symptoms of intense pain after extraction in the dental socket region that radiates to the ear, eyes, and neck, peaking between 1 to 3 days, which may be accompanied by the presence of a totally or partially disintegrated blood clot[1,2]. Consequently, patients report a foul odor and bad taste, and lymph node swelling may also occur.

Various synonyms define this clinical condition, such as dry socket (absence of blood clot), fibrinolytic osteitis, alveolar osteitis, postoperative osteitis, alveolalgia, and purulent/suppurative alveolitis when infection and pus are present (wet alveolitis). Its incidence occurs in 10% of patients[3], 1% to 5% of extractions, and 38% in lower third molar extractions[1]. With an etiology that is not yet fully clarified, many factors are associated, such as traumatic extractions, smoking, advanced age, oral contraceptives, infections at the extraction site, systemic diseases like diabetes mellitus, bone disorders, blood clotting problems, irradiation, and non-compliance with post-extraction instructions[1,4,5].

Several treatment methods are reported in the literature[6] and indicated according to the clinical presentation (dry or wet), such as irrigation with saline solution and 0.2% chlorhexidine gluconate to remove food debris and bacteria, debridement of the bone socket to reactivate new blood clot formation, blood products (fibrin-rich plasma, PRF), antibiotics, intra-alveolar medications (Alveogil, zinc oxide and eugenol, metronidazole, thermosensitive gel with lidocaine), and photobiomodulation (PBM) therapy with low-power laser[7-14].

The benefits of PBM mediated by low-power laser have shown encouraging results in reducing pain, inflammation, and alveolar repair events in experimental animal studies[15,16] and in humans[17,18]. However, publications attesting to the effectiveness of antimicrobial photodynamic therapy (aPDT) in the alveolar repair of infected dental extraction wounds are still scarce. Thus, the purpose of this study was to histologically evaluate in animals the repair of infected dental sockets treated with PBM and aPDT, with clinical similarity to wet alveolitis. The hypothesis of this study is that sockets treated with photonic therapies (PBM or aPDT) will present better histological patterns of bone repair in infected wounds compared to controls. The null hypothesis is that none of the treatments will benefit the biological response in the treatment of alveolitis.

MATERIAL AND METHOD

Animals

The research protocol was approved by the Ethics Committee on Animal Use (CEUA) of the School of Dentistry of Araçatuba, in accordance with the standards of the National Council for the Control of Animal Experimentation (CONCEA). Forty-eight male Wistar rats (Rattus norvegicus albinus), aged 90 to 120 days and weighing between 180 to 250 grams, were used. The animals were kept in appropriate plastic

cages (4 animals per cage) in a temperature-controlled room (22 ± 2°C) with a 12/12-hour light cycle and ad libitum access to balanced food and water.

Experimental Procedures

All procedures were in compliance with the ARRIVE guidelines for animal studies. The animals were anesthetized with general anesthesia via intramuscular injection of ketamine hydrochloride (0.7 mL/kg) combined with xylazine (0.3 mL/kg). To obtain a homogeneous suspension of purulent secretion, 10 animals were used following previously described methodology[19]: after extraction of the right upper incisor, a sterile absorbent paper point soaked in a millesimal adrenaline solution was inserted into the sockets for 60 seconds. After this period, animals were observed for 60 to 90 seconds to confirm the absence of bleeding and clot formation. Three days later, the sockets showed edge edema and purulent secretion, confirming the diagnosis. The secretion was collected by introducing sterile paper points into the socket for one minute. These were transferred to vials containing transport medium (MRT), agitated for 30 seconds, fractionated, and preserved in liquid nitrogen to ensure bacterial viability[20].

Groups and Treatments

All animals underwent induction of clinical alveolitis. After confirmation, they were randomly distributed into: Control Group (C): Gentle cleaning of the coronal portion (soft tissue); no intra-alveolar treatment; PS Group: Gentle cleaning of the coronal portion followed by alveolar irrigation with methylene blue (MB, 100 µg/mL); PBM Group: Gentle surgical cleaning of the coronal portion followed by low-power

laser irradiation; aPDT Group: Gentle surgical cleaning of the coronal portion, application of PS, and after a 60-second pre-irradiation time, low-power laser irradiation.

PBM and aPDT Therapy

In the PS and aPDT groups, 1 mL of methylene blue (Apothicário Farmácia de Manipulação, Araçatuba, SP, Brazil) at a concentration of 100 μg/mL was deposited into the alveoli and remained in the area for 60 seconds prior to irradiation. Subsequently, the alveoli were irradiated with a low-power laser.

In group PBM and aPDT a GaAlAs diode laser (Laser Beam®, Rio de Janeiro, RJ, Brazil) was used with the following protocol: 685 nm (visible red), single application, point contact on the vestibular soft tissue at the middle portion of the socket, 50 mW (0.05 W) power, 240 s exposure time, 12 J energy, and 600 J/cm² energy density, 2 mm² elliptical spot.

Euthanasia and Histologic procedures

Animals were euthanized via anesthetic overdose at 7, 15, 21, and 28 days post-treatment. Specimens were removed, fixed in 10% formalin for at least 24 hours, and processed for histological analysis. After 48 hours in 10% formalin it was washed in running water, dehydrated, cleared, impregnated, embedded in paraffin and sectioned in a microtome with 4 μm thick. Semi-serial sections were performed and captured on histological slides. The histological sections were submitted to staining with hematoxylin-eosin (HE).

Histomorphological analysis of the samples

Sample analyses were performed by an expert examiner, who was blinded to the samples. Histological sections were analyzed under bright field illumination in an optical microscope (Axiolab, Carl Zeiss). A descriptive analysis of biological events was conducted across the cervical, middle, and apical thirds of the alveoli for all time periods. The evaluation included the presence of blood clots, inflammatory infiltrate, connective tissue organization (cells, fibers, and vessels), bone tissue formation, the alveolar bone crest, and the oral mucosal epithelium.

RESULT

Histological events are detailed in Table 1 and documented in Figure 1.

Table 1: Descriptive histological analysis in each group and period

Group	Location	7 days	15 days	21 days	28 days
C	Cervical	Unorganized blood clot, presence of macrophages, lymphocytes, and neutrophils. Slight fibroblast and capillary proliferation.	Unorganized blood clot, high neutrophils in some cases. Most lack connective neoformation.	Filled with well-developed connective tissue, rich in collagen. Some small new bone spicules.	Occupied by thin bone trabeculae, wide inter-trabecular spaces. Well-developed undifferentiated connective tissue.
	Middle	Extensive areas of connective tissue, moderate fibroblasts, small new bone spicules. Moderate macrophages/lymphocytes.	New bone tissue characterized by thin trabeculae with intense osteoblastic activity.	Developed trabeculae near the wall; large amount of undifferentiated connective tissue in center.	Thicker bone trabeculae throughout the extension.
	Apical	Same as middle.	Same as middle.	Same as middle.	Same as middle.
PS	Cervical	Unorganized blood clot with numerous macrophages. Slight fibroblast/capillary proliferation near the wall.	Filled with new connective tissue and small bone trabeculae. Moderate lymphocytes and macrophages.	Partially occupied by thin bone trabeculae. Undifferentiated connective tissue in the center.	Thick bone trabeculae near lingual wall. Thinner trabeculae and undifferentiated tissue in remote areas.
	Middle	New connective tissue, numerous fibroblasts/capilla	Trabeculae more developed than cervical.	Occupied by generally thick bone	Bone tissue is more developed, showing thick

		ries. Alveolar wall shows moderate resorption.	Connective tissue is vascularized and rich in fibroblasts.	trabeculae. Alveolar crest is remodeled.	and organized trabeculae.
	Apical	Same as middle.	Same as middle.	Same as middle.	Same as middle.
PBM	Cervical	Unorganized blood clot with numerous neutrophils. Slight new connective tissue near the wall.	Partially occupied by thin, unorganized bone trabeculae and connective tissue rich in fibroblasts.	Generally thin bone trabeculae regularly filling the area.	Thin bone trabeculae, thicker only in small areas near the wall.
	Middle	New connective tissue, rich in fibroblasts. Some small new bone spicules with osteoblasts at edges.	More intense ossification. Thin trabeculae surrounded by numerous osteoblasts.	Trabeculae show same characteristics as cervical, thicker near the alveolar wall.	More developed bone tissue; thick trabeculae in almost entire extension.
	Apical	Same as middle.	Same as middle.	Same as middle.	Same as middle.
aPDT	Cervical	New connective tissue, rich in fibroblasts. Small new bone spicules near the wall.	Well-developed bone trabeculae, except for areas far from the wall.	Filled with thick, well-developed bone trabeculae. Remodeled crest.	Occupied by thick, well-developed bone trabeculae.
	Middle	Thin new bone trabeculae and large amount of undifferentiated connective tissue.	More developed trabeculae, except near the center. New bone formation at the crest.	Same as cervical.	Same as cervical.
	Apical	Same as middle.	Same as middle.	Same as cervical.	Same as cervical.

DISCUSSION

The results obtained demonstrated that wounds treated with PS, PBM, and aPDT exhibited an accelerated repair process compared to those that received no treatment (Group C). Among the histological findings, greater organization and neoformation of connective tissue, increased fibroblastic proliferation, and earlier and more extensive bone remodeling and neoformation were observed. These

characteristics were most prominent in wounds treated with aPDT, followed by those treated with PBM and PS, across all evaluation periods.

In the specimens from the PS group, the ability of the phenothiazine derivative (MB) to promote benefits in the repair of infected wounds when applied alone was demonstrated. Greater bone formation was noted in all periods, with well-vascularized connective tissue rich in fibroblasts and a lower degree of inflammation compared to control wounds. The observed reduction in the inflammatory process is likely due to the anti-inflammatory action of MB, which interferes with nitric oxide synthesis through an important signaling pathway (iNOS/NO), consequently promoting vasoconstriction in the area. It is known that MB is deeply related to its anti-inflammatory effect, which occurs through a variety of pathways and functions, decreasing the expression level of pro-inflammatory cytokines in several ways, including the inhibition of iNOS/NO signaling[21,22]. There is also evidence that the reduction of oxidative stress promoted by MB results in an increase in collagen synthesis[23]. These benefits of the PS are likely also due to the ability of phenothiazines to modulate the metabolism of macrophages, inducing the accumulation of intracellular reactive oxygen species (ROS), promoting the activation of autophagy and lysosomal activity, and thus increasing their bacterial destruction capacity. The increase in ROS contributes to the elimination of intracellular bacteria through direct microbial death, as well as by promoting lysosomal acidification and inducing autophagy[24].

PBM therapy mediated by low-power laser has demonstrated established results in different conditions, both in dental extraction wounds under normal conditions[16,18] and in infected extraction wounds[25]. Studies have shown that PBM effects may occur through the direct action of light on bacteria, acting on endogenous porphyrins which, when stimulated, release free radicals capable of damaging the cytoplasmic protein

membrane and DNA[26,27]. Other studies have demonstrated the effects of PBM on the viability of microorganisms both in vitro[28] and in vivo[29]. An important factor to consider is the action of laser energy on the host response, promoting an indirect antimicrobial effect by increasing local blood flow and oxygenation[30,31], which favors the presence of host defense cells in the area and, consequently, improves bone repair. Furthermore, PBM therapy is capable of inducing an increase in extracellular matrix synthesis and angiogenesis[32].

The benefits of aPDT on biological events in infected areas proved to be superior to the other groups, becoming evident from the initial period of repair, with neoformation of connective tissue, bone formation, and reduction of the inflammatory process. These findings are likely due to three important hypotheses: first, the initial action of the PS on microorganisms, which remained in the area for sixty seconds (pre-irradiation time), sufficient for bacterial absorption and a primary action as previously described; second, the photodynamic action itself—the interaction of visible red light with MB capable of forming reactive oxygen species (ROS) resulting from Type I photosensitization (electron transfer leading to the production of superoxide anion [O_2-], hydroxyl radical [OH-], and hydrogen peroxide [H_2O_2]) and Type II (energy transfer producing excited singlet oxygen [$1O_2$]). Each of these ROS can combine with biomolecules, leading to subsequent oxidation and degradation, a reaction sufficient to cause cell/bacterial death[33]. The third hypothesis is the capacity of laser light to promote benefits in accelerating bone repair (photobiomodulation). Studies have demonstrated the benefits of aPDT in alveolar repair for the prevention of alveolitis in humans[34] and as a preventive therapy for implant placement in animals[35].

It is known that different conditions can interfere with laser effects on biological tissues, such as wavelength, power, number of applications, light interaction with the

PS, physiological state of the cell, light absorption, emission and irradiation mode, exposure time, beam diameter, medium pH, tissue color, water content, thermal conductivity, and organic matrix.

The present study demonstrated the effective action of PBM and aPDT on alveolar repair in infected sockets. In the present study, a single session of PBM and aPDT therapy was used based on results from previous research developed in our research group[25,28,35]. However, future research may prove whether a greater number of sessions of these therapies could contribute to more favorable results in the repair of infected alveoli.

In addition, further studies are necessary, both in animals and clinical trials in humans, to build a more solid scientific basis for the development of treatment protocols for this condition, which can be difficult to manage. It should be noted that this animal study sought similarity with clinical conditions but presented limitations such as the sample size, laser clinical parameters, number of treatment sessions, and the need for a broader range of analyses.

CONCLUSION

Based on the results obtained, it can be concluded that there was a delay in the alveolar repair process in the control group; the isolated use of the PS minimized deleterious effects on bone repair; and photonic therapies benefited alveolar repair, with more favorable results achieved when aPDT was utilized.

AUTHORS' CONTRIBUTIONS

Contextualization and project development: VGG, LHT; Project execution: WLJr, VGG; Documentation: WLJr, VGG; Writing: WLJr, VGG, LHT; Text correction and adaptation: VGG, LHT.

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CONFLICTS OF INTERESTS

None of the authors have a conflict of interest to disclose.

DATA AVAILABILITY

The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author.

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Received: April 17, 2026

Accepted: July 6, 2026

Figure and Legend:

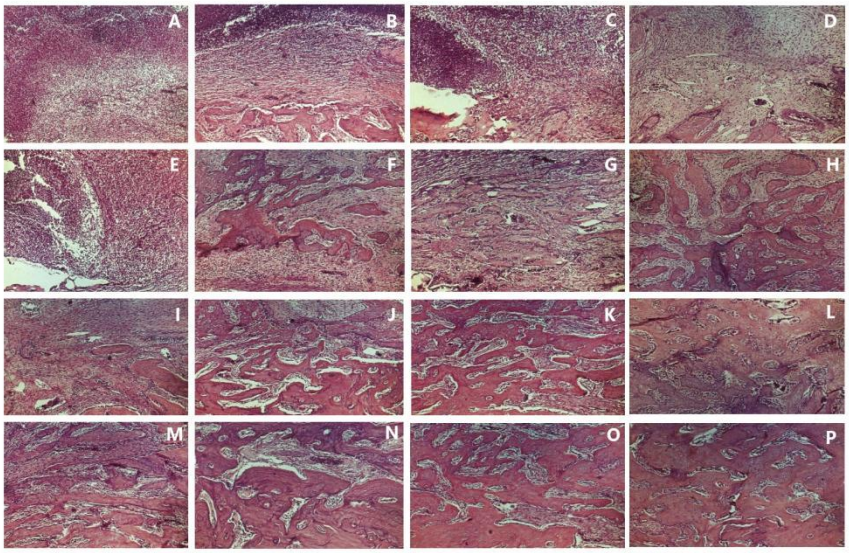

Figure 1. Histological events across different groups, periods, and treatments: Control group (A, 7 days, cervical third; E, 15 days, cervical third; I, 21 days, cervical third; M, 28 days, cervical third); PS group (B, 7 days, cervical third; F, 15 days, cervical third; J, 21 days, cervical third; N, 28 days, cervical third); PBM group (C, 7 days, cervical third; G, 15 days, cervical third; K, 21 days, cervical third; O, 28 days, cervical third); aPDT group (D, 7 days, cervical third; H, 15 days, cervical third; L, 21 days, cervical third; P, 28 days, cervical third). Hematoxylin & Eosin. Original magnification: 63X.

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