Research, Society and Development, v. 11, n. 5, e24611528283, 2022
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v11i5.28283

Use of photodynamic therapy in the prevention and treatment of osteonecrosis of the jaw: an integrative literature review

Uso de terapia fotodinâmica na prevenção e tratamento de osteonecrose dos maxilares: uma revisão de literatura integrative

Uso de la terapia fotodinámica en la prevención y tratamiento de la osteonecrosis de los maxilares: una revisión integrativa de la literature

Received: 03/20/2022 | Reviewed: 03/26/2022 | Accept: 03/29/2022 | Published: 04/04/2022

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Abstract

The aim of this study was to evaluate the use of photodynamic therapy (PDT) in the prevention and treatment of osteonecrosis of the jaw through an integrative literature review. Thus, a search was carried out in 8 scientific bases (MEDLINE, Cochrane Library, Scopus, ISI Web of Science, LILACS, BBO, SciELO and ClinicalTrials) using pre-established descriptors and search strategies, without language restrictions, date of publication and country where the study was carried out. Screening was carried out based on titles, abstracts and the full reading of studies by 2 evaluators, simultaneously and independently. The search identified 309 studies and 2 additional references were manually identified. After excluding duplicates, 236 studies were selected for analysis based on titles and abstracts, and 17 articles were fully read. After reading articles, 11 met the inclusion criteria and were included in this review. Among them, 8 are case reports or case series, 2 are *in vivo* studies with animal models and 1 was an *in vitro* study. It was observed that despite the diversity of protocols found, studies pointed out that PDT can be considered a supporting therapy useful in the prevention and treatment of osteonecrosis of the jaw. However, due to the absence of

randomized clinical trials on the subject, it is suggested the development of further studies in order to have stronger scientific evidence and to more safely support the use of PDT in the treatment of osteonecrosis of the jaw.
Keywords: Osteonecrosis; Photodynamic therapy; Low-level light therapy; Bisphosphonate-associated osteonecrosis of the jaw.

Resumo

O objetivo desse estudo foi avaliar o uso da terapia fotodinâmica (TFD) na prevenção e tratamento da osteonecrose dos maxilares, por meio de uma revisão integrativa da literatura. Foi realizada uma busca em 8 bases científicas (MEDLINE, *Cochrane Library*, *Scopus*, *ISI Web of Science*, LILACS, BBO, SciELO e *Clinical Trials*) utilizando descritores e estratégias de busca pré-estabelecidos, sem restrição de idiomas, data de publicação e país de estudo. Procedeu-se uma triagem baseada nos títulos, resumos e leitura completa dos estudos por 2 avaliadores, de forma simultânea e independente. Foram identificados 309 estudos e 2 referências adicionais manualmente. Após a exclusão dos duplicados, 236 estudos foram selecionados para análise baseada nos títulos e resumos, e 17 tiveram seus textos analisados integralmente. Após a leitura dos artigos, 11 preencheram os critérios de inclusão e foram incluídos neste estudo. Dentre os 11, 8 são relatos de caso ou série de casos, 2 estudos *in vivo* com animais e 1 estudo *in vitro*. Observou-se que apesar da diversidade de protocolos encontrados, os estudos apontaram que a TFD pode ser considerada uma terapia coadjuvante útil na prevenção e no tratamento da osteonecrose dos maxilares. Entretanto, devido à ausência de ensaios clínicos randomizados sobre a temática, sugere-se que esses estudos sejam desenvolvidos, a fim de que se tenha uma evidência científica mais forte e apoiar com maior segurança o uso da TFD no tratamento da osteonecrose dos maxilares.
Palavras-chave: Osteonecrose; Terapia fotodinâmica; Terapia de luz de baixa intensidade; Osteonecrose mandibular associada a bisfosfonatos.

Resumen

El objetivo de este estudio fue evaluar el uso de la terapia fotodinámica (TFD) en la prevención y el tratamiento de la osteonecrosis de los maxilares, através de una revisión integradora de la literatura. Se realizó una búsqueda en 8 bases de datos científicas (MEDLINE, Cochrane Library, Scopus, ISI Web of Science, LILACS, BBO, SciELO y Clinical Trials) utilizando descriptores y estrategias de búsqueda preestablecidos, sin restricciones de idioma, fecha de publicación y país de estudio. Se realizó un cribado en base a títulos, resúmenes y lectura completa de los estudios por 2 evaluadores, de forma simultánea e independiente. Se identificaron 309 estudios y 2 referencias adicionales manualmente. Después de excluir los duplicados, se seleccionaron 236 estudios para el análisis en función de los títulos y resúmenes, y se analizaron los textos en su totalidad en 17. Después de leer los artículos, 11 cumplieron los criterios de inclusión y fueron incluidos en este estudio. Entre los 11, 8 son informes de casos o series de casos, 2 estudios en animales *in vivo* y 1 estudio *in vitro*. Se observó que a pesar de la diversidad de protocolos encontrados, los estudios mostraron que la TFD puede considerarse una terapia adyuvante útil en la prevención y tratamiento de la osteonecrosis de los maxilares. Sin embargo, debido a la falta de ensayos clínicos aleatorizados sobre el tema, se sugiere que estos estudios se desarrollen para tener evidencia científica más sólida y para respaldar de manera más segura el uso de la TFD en el tratamiento de la osteonecrosis de los maxilares.
Palabras clave: Osteonecrosis; Terapia fotodinámica; Terapia de luz de bajo nivel; Osteonecrosis de la mandíbula asociada a bisfosfonatos.

1. Introduction

Osteonecrosis of the jaw can be defined as a delayed-healing oral lesion primarily associated with the continuous use of some bisphosphonate-class drugs (Bisphosphonate-related osteonecrosis of the jaw - BRONJ) and, more recently, as a result of the use of other drugs that act in bone remodeling and antiangiogenesis (Medication-related osteonecrosis of the jaws - MRONJ), which adversely affects quality of life, producing significant morbidity (Ruggiero et al., 2014; Ribeiro et al., 2018; Poli et al., 2019).

Clinically, MRONJ is defined as an area of exposed bone or bone that can be probed through an intra or extra-oral fistula in the maxillofacial region that persists for more than 8 weeks, with no history of radiotherapy at the site or metastatic disease in the jaws. MRONJ patients should avoid elective dentoalveolar surgical procedures, as they may result in additional areas of exposed necrotic bone (Ruggiero et al., 2014).

In addition, MRONJ can be classified into: stage 0 (no clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes, and symptoms), stage 1 (exposed and necrotic bone, or fistulae that probes to the bone in patients who are asymptomatic and have no evidence of infection), stage 2 (exposed and necrotic bone, or fistulae that probes

to the bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone, with or without purulent drainage) and stage 3 (exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone resulting in pathologic fracture, extraoral fistula, oral-antral/oral-nasal communication or osteolysis extending to the inferior border of the mandible of sinus floor) (Ruggiero et al., 2014; AlDhalaan et al., 2020).

The management of osteonecrosis remains controversial and there is no definitive management pattern for the disease, but stable mucosal coverage is the main treatment objective in order to prevent secondary infections. Non-surgical, conservative and minimally invasive therapies are considered useful in controlling lower stages of the disease (Fliefel et al., 2015) and when conservative measures are unsuccessful, surgical treatments are usually indicated (Rugani et al., 2013).

The following are among treatments proposed and most commonly used: use of antibiotics (Bermúdez-Bejarano et al., 2017), mouthwashes (Khan et al., 2015), surgical debridement (Silva et al., 2016), surgeries (Momesso et al., 2020), hyperbaric chamber therapy (Ceponis et al., 2017) and laser therapy (Li et al., 2020; ,Sánchez et al., 2020), which can be used in isolation or in association (Sanchez et al., 2020); however, they may not reach the resolution of the clinical condition, and prevention, through the pre-therapeutic establishment of optimal oral health conditions and continuous dental supervision, is a crucial factor (Rugani et al., 2013).

Current studies have shown that Photodynamic Therapy (PDT) can be useful both in prevention (Poli et al., 2019; Tartaroti et al., 2020) and treatment of osteonecrosis of the jaw (Poli et al., 2018); however, there are few studies that have evaluated this therapy in the management of the disease, and studies that have carefully compiled and analyzed methodological designs, protocols and results related to this theme have not been identified in literature.

PDT has been considered a valid non-invasive therapy against several microorganisms and in the acceleration of the tissue repair process through its photobiomodulatory effects secondary to antimicrobial action. In this therapy, photosensitizer is applied to the lesion, which when excited by non-thermal light source and with specific wavelength, releases reactive oxygen species responsible for the death of microbial cells. These properties supported the use of PDT to treat osteonecrosis lesions (Poli et al., 2019; Rugani et al., 2013; Ervolino et al., 2019).

Tandon et al. (2019) point out that PDT can be a viable treatment even in cases of more advanced stages of osteonecrosis, considered difficult to treat, and that the excellent results obtained by case reports should encourage future clinical trials. Therefore, this study aimed to evaluate the use of PDT in the prevention and treatment of osteonecrosis of the jaw through an integrative literature review.

2. Methodology

Searches for studies were carried out between May 8 and 10, 2020 on the following scientific bases: MEDLINE via PubMed (www.pubmed.gov), Cochrane Library (www.cochrane.org), Scopus (www.scopus.com), ISI Web of Science (www.isiknowledge.com), Latin American and Caribbean Health Sciences Literature (LILACS) via Virtual Health Library - VHL (www.bvsalud.org), Scientific Electronic Library Online (SciELO) (www .scielo.org), Brazilian Dentistry Bibliography (BBO) via VHL (www.bvsalud.org) and ClinicalTrials - US National Library of Medicine (www.clinicaltrials.gov).

"Photodynamic Therapy", "Photodynamic Therapies", "Photochemotherapy", "Photochemotherapies", "PDT", "aPDT", "Osteonecrosis" and "Avascular necrosis" descriptors were used, combined according to the specificities of each base, and using one combination of keywords related to disease and treatment. There was no restriction on languages, date of publication and country where the study was carried out.

Laboratory studies (in vitro), animal studies, case reports, case series, case-control studies, cohorts, non-randomized and randomized clinical trials and systematic reviews with or without meta-analysis were considered. Only studies that

evaluated the use of PDT, in isolation or as adjunct to other therapy in the prevention or treatment of osteonecrosis of the jaw were included, published as an article in scientific journals. With regard to PDT, only studies using photosensitizers for local administration were included and there was no predilection for the light source used.

Narrative literature review studies and those that evaluated PDT in osteonecrosis of other regions of the body, in osteoradionecrosis or that used photosensitizing agents for systemic administration were excluded. At the end of each phases of the study selection process, the Kappa coefficient was calculated to measure the level of inter-examiner agreement. In cases of disagreement, consensus meeting was held between the 2 evaluators where it was decided which studies would be maintained for further evaluation or elimination. Persistent doubts were referred to a third expert evaluator (M.H.C.V.C).

After the identification of studies in scientific bases and eliminating duplicates, 2 previously trained and independent evaluators (J.A.F.N and A.C.V.G) selected studies through screening based on titles and abstracts (Cohen kappa = 0.789 – substantial agreement). Studies that did not meet the established inclusion criteria were excluded from the review. Articles that raised doubts during this phase were kept for a more detailed assessment in the following phase.

In the second step, the same evaluators performed screening based on the full reading of articles, where inclusion and exclusion criteria could be investigated in detail (Cohen kappa = 0.857 – almost perfect or perfect agreement). In addition, a search was carried out on the reference lists of all articles that were fully read in order to identify any studies lost during the search and selection process in databases.

In each selected study, the following information was collected: name of the authors, year of publication, study design, condition / diagnosis, interventions performed (PDT protocol), main results and conclusions. In addition, information regarding light used (source, wavelength, power, dose and energy), photosensitizer, pre-irradiation time and irradiation time per session was also collected.

3. Results

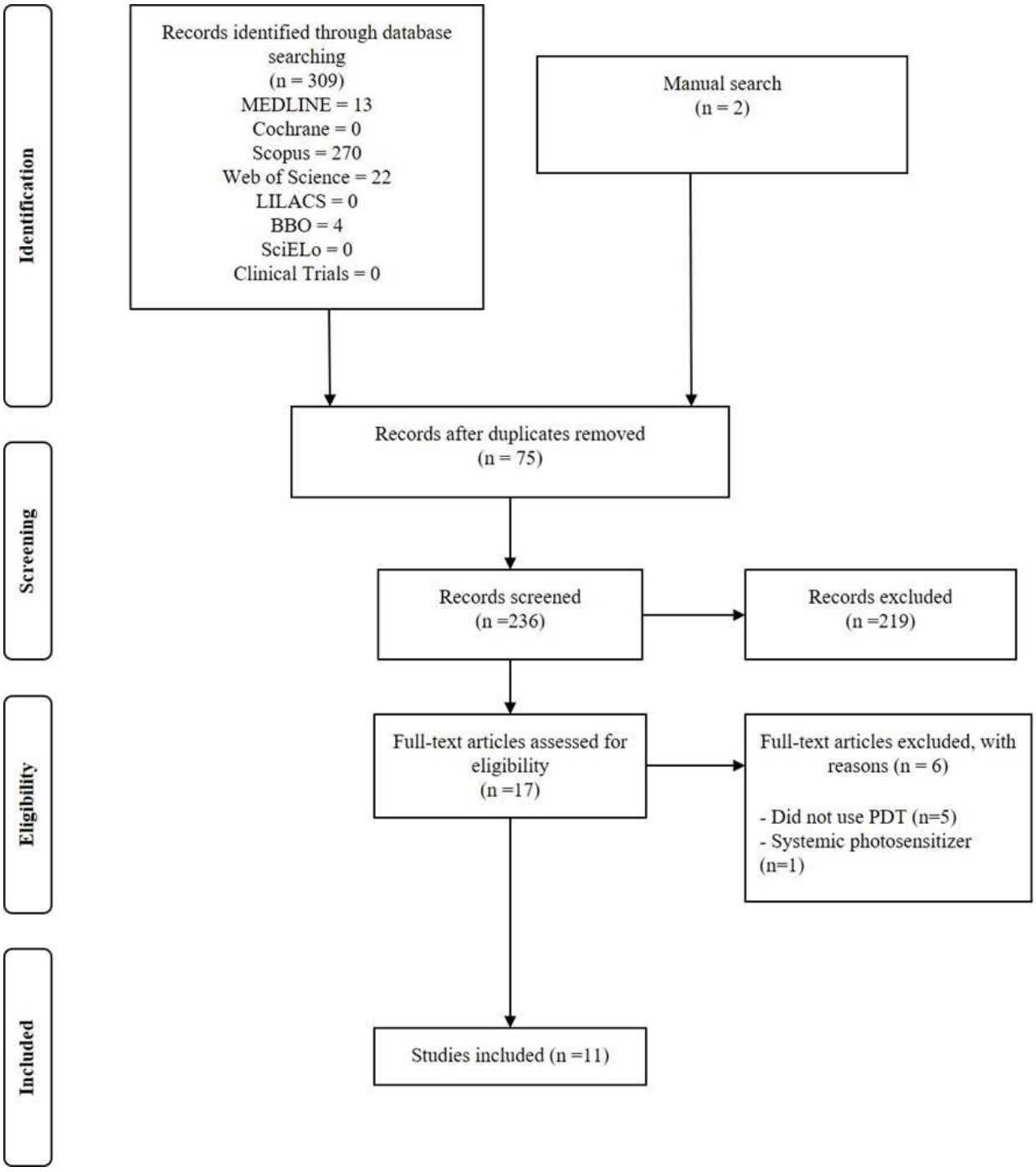
Electronic search strategies identified 309 studies and 2 additional references were manually identified. After excluding duplicates, 236 studies were selected for analysis based on titles and abstracts, and 17 had their texts fully analyzed. After reading full texts, 11 studies met the inclusion criteria (Poli et al., 2019; Tartataroti et al., 2020; Poli, Souza & Maiorana, 2018; Rugani et al., 2013; Ervolino et al., 2019; Tandon et al., 2019; Israel et al., 2016; Hafner et al., 2016; Minamisako et al., 2016; Castro et al., 2016; Sarkarat et al., 2019). The selection process is summarized in Figure 1.

Regarding study design, it was observed that among the 11 selected articles, 8 are case reports or case series (Poli et al., 2019; Tartataroti et al., 2020; Poli, Souza & Maiorana, 2018; Rugani et al., 2013; Israel et al., 2016; Hafner et al., 2016; Minamisako et al., 2016.,; Castro et al., 2016), 2 *in vivo* animal studies (Ervolino et al., 2019, Sarkarat et al., 2019) and 1 *in vitro* study (Hafner et al., 2016) (Table 1).

Although all studies used the laser device as light source for PDT, it was observed that the power of devices, energy density, energy, pre-irradiation time and irradiation time varied considerably among studies. As for the most used photosensitizer, it was found that methylene blue was the most prevalent. The detailed information of selected articles, including the results of studies as reported, is shown in Tables 1 and Table 2.

Despite the diversity of protocols found, studies pointed out that PDT can be considered a useful therapy both for prevention and treatment of osteonecrosis of the jaw. All studies with humans used PDT in combination with other treatments, according to the osteonecrosis degree (Table 1).

Figure 1 - Flowchart with identificaton of studies, inclusions and deletions in the different steps.



Source: Authors.

Table 1 - Main characteristics of the selected studies.

Study/ Year/ Study design	Condition / diagnosis	Treatment performed	Main results	Main conclusions
Rugani et al. 2013 Case series	Treatment of 5 cases of BRONJ stage 0 and 7 cases of BRONJ stage 2.	Stage 0: The fistulas were washed with antiseptic fluids + PDT. Stage 2: Surgery + PDT. The photosensitizer was applied topically on the surface of all affected tissue and no incubation time was awaited. A diode laser at 2 mm distance was used to PDT. PDT was applied twice a week for the first 2 weeks.	Stage 0: After 2 weeks all fistulas healed and correlating clinical symptoms vanished. Stage 2: 5 of 7 lesions are healed by secondary granulation. In 2 cases the lesion did not heal. 1 patient was scheduled for another, more invasive surgical intervention indicated by the appearance of a further sequester. In the second patient, suffering from breast cancer, general health worsened significantly and therefore conservative maintenance therapy was applied.	PDT can be a supportive tool in BRONJ treatment. It may be used as an adjuvant before or after BRONJ surgery or as the primary therapy option in cases of very early BRONJ or if surgery is not indicated.
Israel et al. 2016 Case report	Treatment of 1 case of MRONJ.	Topical chlorhexidine 3 times/day + Clavulin 875 mg 12/12 hours for 7 days + PDT + laser therapy. PDT consisted of applying the photosensitizer to the lesion area and pre-irradiation time was awaited. The red laser was used to irradiation. The photosensitizer was removed with sterile saline irrigation.	8 months after, panoramic examination showed kidnapping bony. There was good healing, without signs of infection and the presence of overlying mucosa under sequestration. 11 months after, spontaneous sequestration occurred with subsequent mucosal healing with patient clinically stable, free of signs and symptoms.	Promising results have been reached by using PDT and posterior laser exposure.
Hafner et al. 2016 *In vitro* study	*Actinomyces naeslundii* strain isolated from a patient with MRONJ was used to determine the bactericidal activity of aPDT against *A. naeslundii*.	*In vitro* activity of 3 different agents against slowly growing *Actinomyces naeslundii* isolated from a patient with osteonecrosis was evaluated. Polyhexanide 0.04% solution, chlorhexidine 0.12% solution, and PDT were compared. In the group treated with PDT, a sterile, isotonic, deep blue, and odorless aqueous solution photosensitizer was used. Low-power continuous-wave diode laser in combination with the spot probes as optical fibers were used as the light source All measurements were performed independently in triplicate.	The most efficient decrease of bacterial load was achieved by the combination of laser light and photosensitizer. Colony-forming units (CFUs) were decreased by more than 4 orders of magnitude.	The most effective means of decreasing colony forming units was achieved by a combination of laser light and dye, which also can be used clinically.
Minamisako et al. 2016 Case report	Treatment of 1 case of MRONJ stage 2.	Clindamycin 600mg/day + oral hygiene guidance + topical application of chlorhexidine gluconate gel 0.12% at bone exposure + superficial bone debridement + PDT + laser therapy. PDT consisted of staining the bone exposure with photosensitizer and irradiation with laser. Patient was included in a follow-up regimen twice a month during 6 months after wound healing.	There was remission of the fistula, absence of bone necrosis, infection and/or suppuration control, pain relief and total repair of the oral mucosa. It was found that PDT applied directly to exposed bone with suppuration can bring beneficial effects to control the infected MRONJ lesion.	The findings of this case suggest that both laser therapy and PDT brought important benefits to patient, assisting in clinical management of the MRONJ.
Castro et al. 2016 Case reports	Treatment of 2 cases of BRONJ stage 3 and 2.	Stage 3: Amoxicillin 875 mg + Potassium Clavulanate 125 mg + Metronidazole 400 mg (3 times a day for 15 days) + surgical debridement + PDT + platelet-rich fibrin (PRF) to fill the bone defect and recoat the exposed bone area. Stage 2: Clindamycin 300 mg (3 times a day for 7 days) + debridement of necrotic bone + PDT + PRF. The PDT protocol adopted consisted of topically placing photosensitizer in the surgically exposed bone, which was followed by vigorous washing with saline solution and then continuous low-level laser irradiation, punctually and in contact mode.	Stage 3: 14 days of follow-up showed full coverage of bone tissue by mucosa and absence of infection and 10 months later a complete healing of the operated area, with the presence of bone neoformation and absence of symptoms was detected. Stage 2: A 14 months follow-up of indicated complete recovery of the operated area, significant bone neoformation, full coverage of bone tissue by healthy mucosa and absence of symptoms.	PDT and PRF significantly improved the bone healing. Results suggest the association of PDT and PRF, complementarily to antibiotic therapy and surgical debridement for patients bearing BRONJ, and especially for cases that do not respond to the classical treatment.

Poli, Souza & Maiorana 2018 Case report	Treatment of 1 case of MRONJ stage 1.	Sequestrectomy of the exposed bone + open-flap debridement + PDT + laser therapy. PDT was performed with a specific setup: photosensitizer was applied over the affected region. Subsequently, the area was rinsed for 1 min with sterile saline to remove the excess photosensitizer. Laser was used to activate the previously dyed surface with circular movements. After irradiation, the entire region was rinsed with sterile saline.	The healing proceeded uneventfully. A complete resolution was observed in terms of the maintenance of mucosal closure without any signs of residual infection, fistulae, or exposed necrotic bone at the surgical site. Clinical healing was corroborated by a radiological evaluation showing no radiographic signs of MRONJ and smooth margins at the 6-month follow-up.	The outcome reinforces the use of PDT and laser therapy for the successful treatment of MRONJ. Successful results were obtained and maintained from both clinical and radiological aspects.
Sarkarat et al. 2019 *In vivo* study in rats	PDT in preventing BRONJ after extraction of molars in rats subjected to bisphosphonate therapy.	PDT was performed in the experimental group: the photosensitizer was placed on top of the exposed bone, and then laser beam was emitted from a tip of 7 mm in diameter from the buccal and lingual surfaces and from a tip of 1 mm in diameter from within the socket in the same day of tooth extraction and the weeks 1, 2, 3, 4, 5, 6, and 7 post-surgery.	Bone exposure was reduced in the PDT group and it reduced inflammation considerably in terms of gingival eosinophils and lymphocytes and bone neutrophils, eosinophils, and lymphocytes. A higher percentage of live bone and a lower percentage of necrotic bone, empty lacunae, and neovascularization were observed in the PDT group. PDT also maintained bone remodeling, indicated by a high number of osteoclasts.	PDT was found to be considerably effective clinically and histopathologically in reducing or preventing BRONJ in rats. Future human studies are needed to verify our results.
Ervolino et al. 2019 *In vivo* study in senile rats	PDT in the alveolar repair of rats with major risk factors for BRONJ.	Antisepsis of the buccal cavity with 10% povidone-iodine + first molar extraction + 3 sessions of PDT at the tooth extraction site at 0, 2 and 4 post-operative days. For PDT, photosensitizer was deposited and kept on the tooth extraction site. Subsequently, the laser tip was positioned at a single point in the center of the tooth extraction site, parallel with the long axis of the tooth socket and in contact with the treated area.	Group that did not receive PDT showed tissue repair impairment, lower percentage of newly formed bone tissue, higher percentage of non-vital bone tissue, fewer mature collagen fibers and increased immunolabeling for tumor necrosis factor (TNFα), interleukin (IL)-1β and IL-6.	PDT in the dental extraction site improves tissue repair process and prevents the occurrence of BRONJ-like lesions after tooth extraction.
Tandon et al. 2019 Case report	Treatment of 1 case of BRONJ stage 3.	Intra-oral debridement + biopsy + PDT + oral hygiene instructions + use of Povidone-Iodine mouth rinse in a1:20(ml) dilution every 3–4h (7.5%w/v) during treatment. PDT consisted of staining the intra-oral bone exposure and the extra-oral fistula with photosensitizer followed by rinsing with saline in multifunction syringe to remove excess dye and any dye deposits. The irradiation was performed with a diode laser. The patient was treated with 2 sessions per week for first 2 weeks, followed by 1 session per week over next 6 weeks. The 11th and 12th sessions were provided after one month of their previous sessions.	After the first 4 sessions the lesion started to improve. Complete healing of the extra-oral fistula was seen after 8 weeks in 10 treatment sessions. The intra-oral lesion was asymptomatic after 12 sessions, however complete soft tissue coverage of the exposed bone was achieved over a year. During the follow up of 2 years there was no recurrence of the fistula, no bone necrosis or sequestration and no superimposed infection or suppuration.	PDT can be a viable treatment of advanced stages of BRONJ.
Poli et al. 2019 Case series	Use of PDT in the prevention of MRONJ of 11 osteoporotic subjects in therapy with non-intravenous antiresorptive agents, requiring tooth extractions and/or implant removal.	0.2% chlorhexidine digluconate solution twice daily for 1 month (2 weeks before the surgical procedures) + professional oral hygiene procedures (1 week prior surgery) + oral amoxicillin 1g every 8h for 20 days (3 days before the extractions) + minimally invasive surgical extractions + PDT + ibuprofen 600mg every 8h for 3 days + topical application of ice packs for 48h + soft cold diet for 72h after surgery + laser therapy. PDT was performed with a specific setup: photosensitizer was applied in the surgical area. Subsequently, the area was rinsed for 1 min with sterile saline to remove the excess photosensitizer. Laser was used to activate the previously dyed surface with circular movements. After	A total of 62 surgical extractions were performed in both jaws. No intraoperative complications were observed. Immediate post-operative period was generally uneventful except for mild pain and ecchymosis that occurred rarely and resolved spontaneously. Healing proceeded uneventfully, with no clinical or radiological prodromal manifestations of MRONJ up to the latest follow-up visit.	PDT might constitute a promising preventive solution to reduce the risk of MRONJ in non-oncologic osteoporotic patients treated with non-intravenous antiresorptive agents that underwent dentoalveolar surgery.

		irradiation, the entire region was rinsed with sterile saline.		
Tartaroti et al. 2020 Case Series	Prevention of MRONJ of patients who had been exposed to one of the drugs associated with MRONJ or have been referred to the clinic for treatment of MRONJ at any clinical stage.	Prevention protocol: 24h preoperative course of antibiotic (500mg Amoxicillin or 400mg ampicillin or 300mg Clindamycin orally) + dental extractions under minimum trauma + PDT preventive protocol + daily mouth rinsing with 0.12 % chlorhexidine digluconate + laser therapy. Treatment protocol: PDT + 500mg Amoxicillin or 300mg Clindamycin orally 8/8h + sequestrectomies + daily mouth rinsing with 0.12 % chlorhexidine digluconate + laser therapy. For MRONJ prevention, PDT was applied immediately after tooth extraction. Photosensitizer was applied inside socket followed by irradiation with a diode laser (laser probe was placed at central, and two equidistant points). MRONJ treatment included preoperative PDT sessions until signs and symptoms of infection had reduced. Then, after necrotic bone removal, PDT was applied inside surgical wounds and reapplied weekly until healing.	18 patients underwent preventive protocol, and none presented signs of MRONJ after a follow-up of at least 6 months. 17 patients presented with MRONJ underwent aPDT protocol and 16 of them showed total regression of lesions.	PDT and laser therapy appear to be effective as adjuvant approach not only for preventing MRONJ development due to tooth extraction but for treating MRONJ lesions at early stages with no adverse effects.

Source: Authors.

Table 2 - Parameters related to light sources and photosensitizers used in the studies.

Study	Wavelength	Power	Energy Density	Energy	Photosensitizer	Pre-irradiation time	Irradiation time
Rugani et al. (2013)	680nm	75mW	112.5 J/ cm^2	6.75J (total)	Methylene blue (50 mg/5 ml)	0	90s
Israel et al. (2016)	660nm	100mW	320 J/cm^2	9J	Methylene blue 0.005%	5 minutes	90s
Hafner et al. (2016)	660nm	100mW	-	-	Methylene blue 1%	-	-
Minamisako et al. (2016)	660nm	100mW	142J/cm^2 per point	4J/point	Methylene blue 0.01%	3 minutes	40s/point
Castro et al. (2016)	660nm	40mW	100J/cm^2 per point	4J/point	Toluidine blue (37.5 mg/L)	5 minutes	100s/point
Poli, Souza & Maiorana (2018)	660 ± 10nm	100mW	3.6J/cm^2	10.8 J	10 mg/mL phenothiazine chloride dye consisting of Methylenthioniniumchlorid based on methylene blue compound	3 minutos	60s per 1cm^2
Sarkarat et al. (2019)	808nm	250mW	39.04 J/cm^2	15J	Indocyanine green	-	-
Ervolino et al. (2019)	660nm	35mW	74.2 J/cm^2 per point	2.1J/point	Methylene blue (100µg/ml)	60 s	60s/point
Tandon et al. (2019)	-	-	-	-	Thiazin-Derivat dye	60 s	60s per cm^2
Poli et al. (2019)	660 ± 10nm	100mW	3.6J/cm^2	-	10 mg/mL phenothiazine chloride dye consisting of Methylenthioniniumchlorid based on methylene blue compound	3 minutes	60s per 1cm^2
Tartaroti et al. (2020)	660nm	100mW	321J/cm^2 per point	9J/point	Methylene blue 0.01 %	5 minutes	90s/point

"-" means that the article did not provide the information. Source: Authors.

4. Discussion

MRONJ is currently a well-reported complication associated with antiresorptive and antiangiogenic therapies for diseases that affect an increasing number of patients (Ruggiero, 2015). Despite the strong association between jaw necrosis and these drugs, MRONJ pathophysiology is not yet fully understood. Therefore, effective and appropriate therapy for the disease has yet to be decided and it is crucial to have a collaborative approach involving dentists, doctors and pharmacists to prevent the development of the disease (AlDhalaan et al., 2020).

In the present search, it was observed that some of the studies did not provide some important characteristics regarding light sources or protocols used, which prevents the comparison of results and the reproducibility of these parameters in future studies.

Among photosensitizers used, methylene blue stands out, which was the most used by the authors. This dye is a good component for the clinical application of PDT because its maximum absorption length is in the red range (affinity with red lasers), presenting good relative penetration in the skin, proven action against pathogenic microorganisms, absence of side effects and low toxicity (Tardivo et al., 2005).

Currently, methylene blue has been used or proposed as photosensitizing agent in PDT during the treatment of several other oral diseases, such as herpes labialis (Lotufo et al., 2020), endodontic treatments (Coelho et al., 2019), mucositis (Simões et al., 2017), halitosis (Mota et al., 2016), periodontitis and peri-implantitis (Chambrone et al., 2018).

According to Tartaroti et al. (2020), PDT should not be performed when there is purulent secretion in the lesion area or when there is large amount of bleeding inside the alveolus, which could impair the interaction of the dye with the surface of interest. In addition, in this situation, the photosensitizing agent, as well as blood, will act as an optical barrier during irradiation.

It is noteworthy that in selected studies, PDT was used both for prevention and treatment of osteonecrosis. For Rugani et al. (2013), the performance of PDT immediately after surgical intervention can increase the success rates, since complications related to impaired wound healing can be effectively resolved through this therapy.

It was observed that in all studies with human beings, PDT was used together with other treatments, being therefore proposed as an adjunctive therapy. Minamisako et al. (2016) observed that a new therapeutic approach (antibiotics, conservative debridement, low-level laser therapy and PDT) decreased the stage of osteonecrosis injury, bringing beneficial effects to disease control and improving the patient's quality of life. The authors also point out that as the injury healing can be very slow, a combined therapeutic approach is necessary.

Some studies (Poli et al., 2019; Tartataroti et al., 2020; Poli et al.; Israel et al., 2016; Minamisako et al., 2016) used laser therapy after performing PDT. One of the great advantages, in addition to the analgesic effects, inflammation modulators and healing promoted by laser therapy, is that in most cases the same laser device used to perform PDT can be used, adjusting dosimetry.

The two *in vivo* animal studies (Ervolino et al., 2019; Sarkarat et al., 2019) that evaluated the use of PDT in the management of osteonecrosis of the jaw were able to histologically evaluate treated regions and observed positive findings in groups treated with this therapy. Despite the limitations inherent in the study design, these surveys reveal trends, help in understanding how tissues microscopically respond to the therapy and encourage more in-depth and clinical studies.

The only *in vitro* study carried out on the subject (Hafner et al., 2016) observed that PDT was effective in eliminating *Actinomyces naeslundii* isolated from a patient with osteonecrosis. *Actinomyces* are species known as primary colonizers within the oral cavity and are among the main contributors to the formation of biofilm and plaques. The study also demonstrated that the association of red laser and methylene blue is much more effective than when they are used in isolation.

Fliefel et al. (2015) reinforce, through a systematic review on available BRONJ treatments, that the application of adjuvant treatments remains an opinion-based approach, not an evidence-based one. Controlled studies or clinical trials should be performed to evaluate these adjuvant treatments.

It is noteworthy that most studies found (report and series case), due to their methodological characteristics, do not provide a high degree of scientific evidence. These studies occupy hierarchically inferior positions in relation to the level of evidence of a study when compared, for example, with clinical trials. The main disadvantages of these studies are: absence of control or comparative group, conclusions based on a single or a few cases and absence of standardization regarding diagnostic methodologies.

5. Conclusion

After analyzing the studies found, it could be concluded that there are few studies that evaluated the use of PDT in the management of osteonecrosis of the jaw. Despite this fact and the diversity of protocols found, studies have shown that this therapy can be useful as an adjuvant for both prevention and treatment of the disease, even in more advanced stages. In the absence of randomized clinical trials on the subject, these studies should be carried out in order to have stronger scientific evidence and to more safely support the use of PDT in the treatment of osteonecrosis of the jaw.

Acknowledgments

The authors acknowledge the Coordination for the Improvement of Higher Education Personnel (CAPES) for granting a postgraduate scholarship.

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