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Adjunctive application of antimicrobial photodynamic therapy in the prevention of medication-related osteonecrosis of the jaw following dentoalveolar surgery: A case series

Pier Paolo Poli[a,*], Francisley Ávila Souza[b], Susanna Ferrario[c], Carlo Maiorana[a]

[a] Implant Center for Edentulism and Jawbone Atrophies, Maxillofacial Surgery and Odontostomatology Unit, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, University of Milan, Via Commenda 10, 20122, Milan, Italy

[b] Department of Surgery and Integrated Clinic, Araçatuba Dental School, São Paulo State University "Júlio de Mesquita Filho", UNESP, Rua José Bonifácio, 1193 - Vila Mendonca, Araçatuba, SP, 16015-050, Brazil

[c] School of Dentistry, Department of Biomedical, Surgical, and Dental Sciences, University of Milan, Via della Commenda 10, 20122, Milan, Italy

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ABSTRACT

Background: Medication-related osteonecrosis of the jaw (MRONJ) is a debilitating complication strongly associated to antiresorptive agents. The present study aimed to describe the use of antimicrobial photodynamic therapy (aPDT) in the prevention of MRONJ.

Methods: The sample consisted of 11 non-oncologic osteoporotic subjects in therapy with non-intravenous antiresorptive agents, requiring tooth extractions and/or implant removal. After minimally invasive surgical extractions, each alveolar socket was debrided and bony edges were smoothened. At this point, aPDT was performed using methylene blue-based phenothiazine chloride dye irradiated with a hand-held 100 mW diode laser with a wavelength of 660 ± 10 nm. Flaps were sutured to achieve first intention closure. Soft tissue healing was promoted with weekly applications of low-level laser therapy for 6 weeks. Recall visits were scheduled weekly for the first two months and monthly thereafter up to 6 months. At the 6-month appointment, healing was assessed clinically and radiographically.

Results: A total of 62 surgical extractions were performed in both jaws, including 51 natural elements and 11 dental implants. 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.

Conclusions: aPDT might constitute a promising preventive treatment to reduce the risk of MRONJ in non-oncologic osteoporotic patients treated with non-intravenous antiresorptive agents that underwent dentoalveolar surgery.

1. Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration in bone tissue, leading to enhanced bone fragility and increased fracture risk. Existing drugs for the prevention or treatment of osteoporosis include, amongst others, bisphosphonates and denosumab, a human monoclonal antibody to the receptor activator of nuclear factor-κB ligand [1]. Osteoporosis treatment with such antiresorptive agents has been strictly associated to medication-related osteonecrosis of the jaw (MRONJ) [2,3]. MRONJ has been defined as an area of exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than 8 weeks, with no history of radiation therapy to the jaws or obvious metastatic disease to the jaws [4]. In the osteoporosis patient population, the incidence of MRONJ in subjects prescribed antiresorptive agents is estimated at 0.001% to 0.01% [5]. In patients receiving bisphosphonates or denosumab therapy, dental extractions with concomitant underlying infection are associated with an increased risk of developing MRONJ [6]. Hence, dentists play a pivotal role in the prevention of MRONJ. Several recommendations have been

* Corresponding author.
E-mail addresses: pierpaolo_poli@fastwebnet.it (P.P. Poli), f.avilasouza@foa.unesp.br (F.Á. Souza), ferrariosusanna@gmail.com (S. Ferrario), carlo.maiorana@unimi.it (C. Maiorana).

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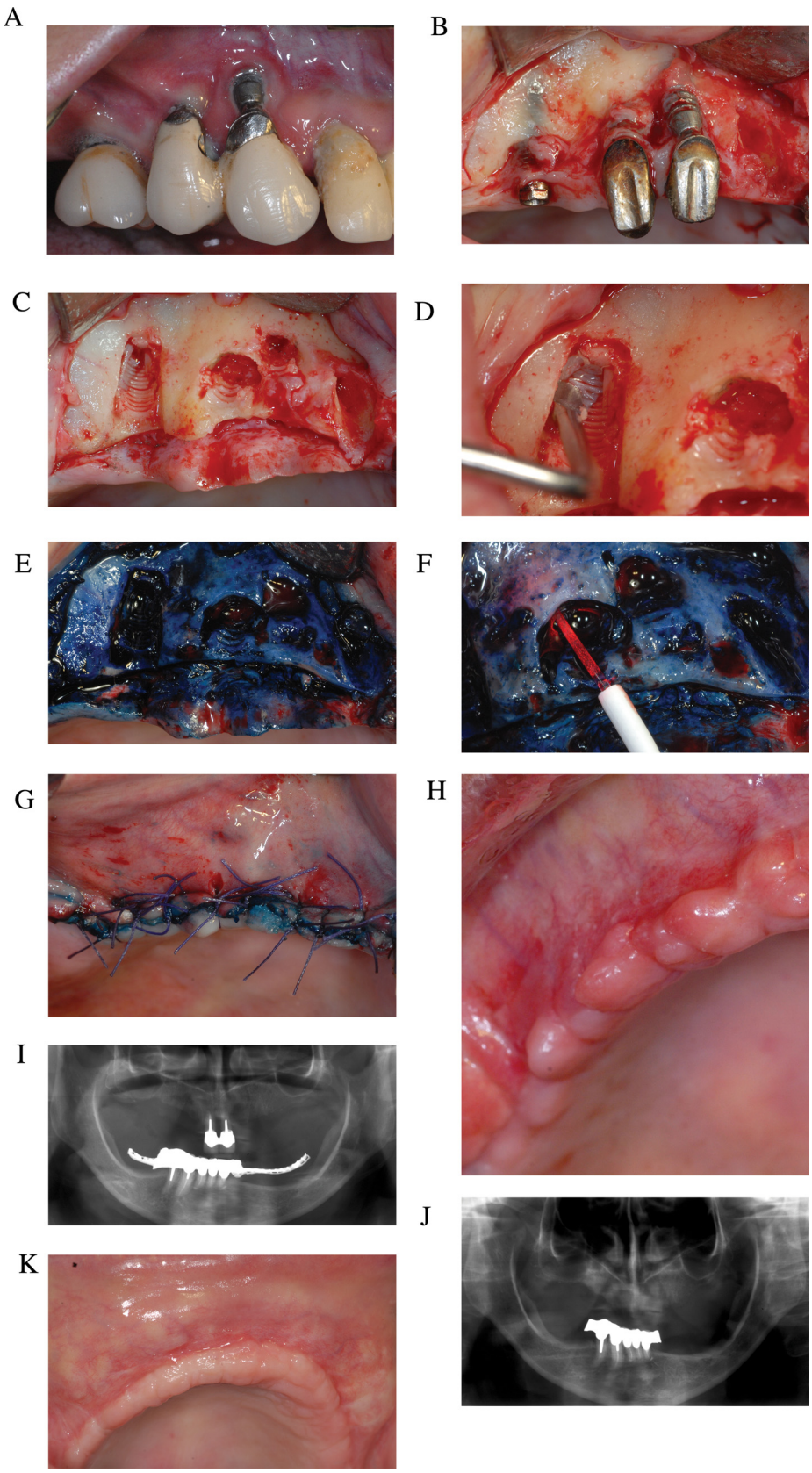

Fig. 1. A – Pre-operative clinical view of implant-supported crowns affected by peri-implantitis; **B –** Clinical view of the implants surrounded by inflamed granulation tissue and bone loss; **C –** Bone sockets following removal of the implants and extraction of the lateral incisor; **D –** Detail of the distal extraction socket in close proximity to the maxillary sinus at the most apical region; **E –** Phenothiazine chloride dye applied in the surgical area; **F –** Irradiation of each socket and adjacent bone with a 3D probe; **G –** Suture of the surgical wound with resorbable suture; **H –** Uneventful healing of the soft tissues at 6 post-operative months; **I –** Follow-up orthopantomograph performed after 6 months from the surgical procedure.

suggested to reduce the risk of MRONJ, including the use of antibiotics before and/or after the procedure, antimicrobial mouth rinsing, appropriate closure of the wound following tooth extraction, and maintenance of good oral hygiene [5]. Photobiomodulation using low-level laser therapy (LLLT) may constitute an additional preventive measure to avoid MRONJ following tooth extractions [7–9] even in patients previously affected by MRONJ [10]. The rationale is to exploit the biostimulation of the mitochondrial cells induced by the irradiation,

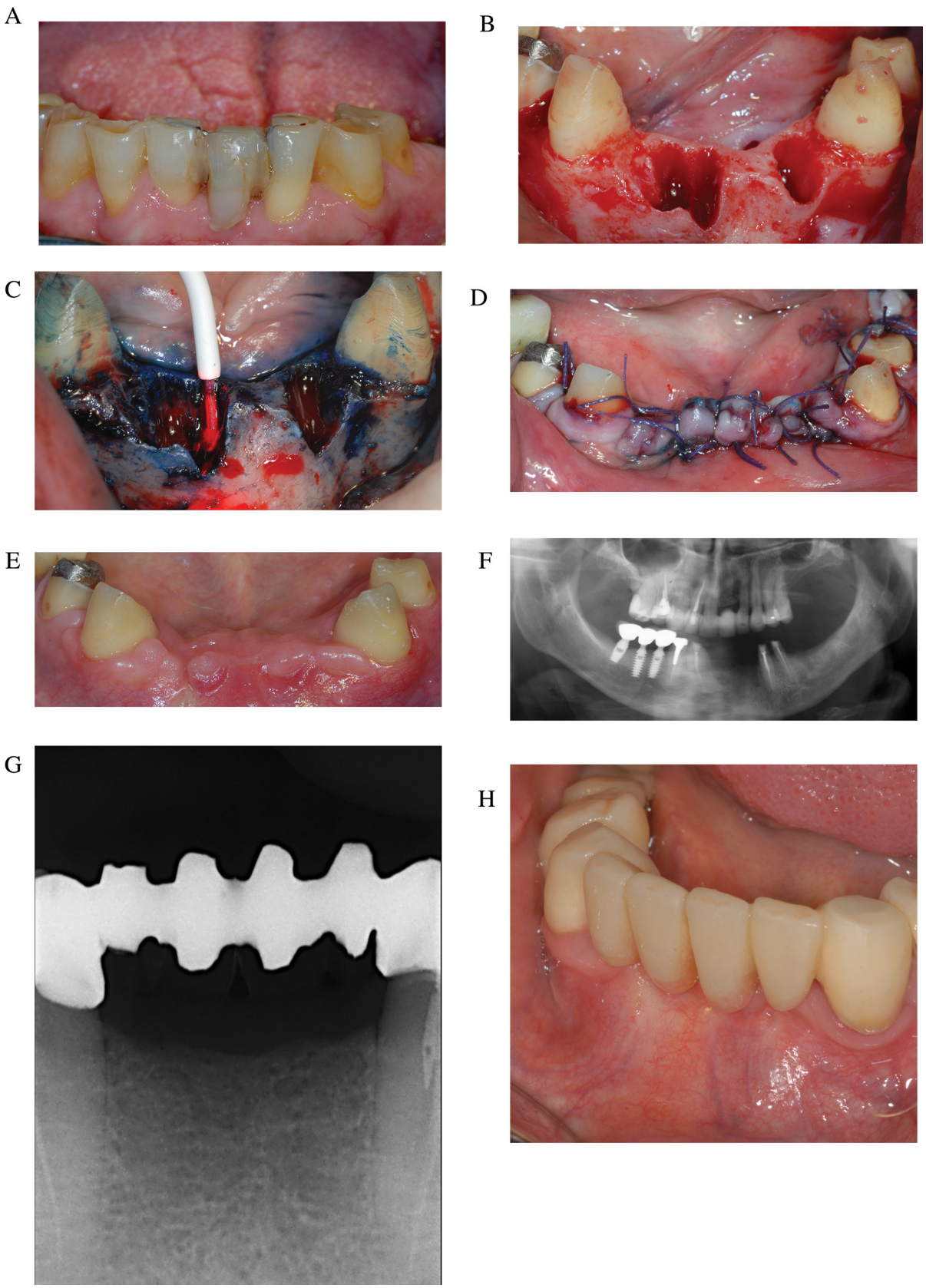

Fig. 2. A – Pre-operative clinical view of periodontally compromised lower incisors supporting a resin-bonded fixed partial denture; **B –** Post-extraction alveolar sockets following removal of the incisors; **C –** Antimicrobial photodynamic therapy performed in the surgical area; **D –** First intention closure of the surgical wound with resorbable suture; **E –** Clinical healing of the soft tissues at the 6-month follow-up recall visit; **F –** Follow-up orthopantomograph performed after 6 months from the surgical procedure.

resulting in improved healing of both hard and soft tissues. After tooth extraction however, bone directly exposed to the oral environment is vulnerable to colonization by organized microbial biofilms. Such polymicrobial communities composed of bacteria and occasionally yeast, fungi, and viruses embedded in extracellular polymeric substance, have been found in bone specimens from sites affected by MRONJ [11]. This complex microbial environment prompted the clinicians to adopt more sophisticated therapies to combat the multi-organism MRONJ-associated biofilm. In this sense, antimicrobial photodynamic therapy (aPDT) is considered an effective method against many Gram-positive and Gram-negative bacterial pathogens, as well as parasites, fungi and viruses [12]. The bactericidal effect is achieved through the use of a photosensitizer, which upon illumination with non-thermal light source of a specific wavelength (630–880 nm), releases reactive oxygen species responsible of microbial cells death. These properties supported the use of aPDT to treat patients who developed MRONJ following tooth extractions with successful results [13–15]. However, to the best of authors' knowledge, the use of aPDT to reduce the risk of MRONJ in patients scheduled for dentoalveolar surgery and treated with antiresorptive agents has not been documented so far.

In view of the above, the aim of the present case series was to report the use of aPDT as adjunctive treatment to prevent the onset of MRONJ in a population of osteoporotic patients treated with antiresorptive agents and requiring surgical extractions of teeth and implants.

2. Materials and methods

From September 2016 to August 2017, a sample of 11 non-oncologic subjects affected by type I, and type II primary osteoporosis, was referred for evaluation of the residual dentition. All patients were treated with either bisphosphonates or human monoclonal antibodies. During anamnesis, data on the antiresorptive agents were collected in relation to the type, dosage, frequency of administration, and therapy duration. The rest of the medical history was non-contributory, with no contraindications to oral surgery procedures. All patients were non-smoking and reported no allergies to drugs.

During the first appointment, thorough clinical evaluation of the oral cavity and radiological assessment by means of orthopantomographs were conducted to plan the extraction of hopeless teeth and/or dental implants. During the evaluation of the residual dentition, the indications for extraction listed in the American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-Related Osteonecrosis of the Jaw [4] were adopted. These included tooth mobility, periodontal disease, presence of root fragments, caries, periapical pathology, periradicular lesions, and recurrent odontogenic abscesses. Removal of dental implants was planned in case of implant mobility or presence of peri-implant disease. Clinical stability was assessed by mechanical testing with hand instruments. In case of implants supporting a clinically stable bridge, the supra-construction was removed to check for individual stability of each implant. Peri-implant disease defined as peri-implantitis, was diagnosed in case of implants presenting with radiographic evidence of bone loss $\geq$ 3 mm and/or probing depths $\geq$ 6 mm in conjunction with profuse bleeding on probing [16]. All patients were provided with detailed information about the possible sequelae related to dentoalveolar surgery and simultaneous treatment with antiresorptive agents. Prior extractive surgery, the treatment plan was discussed and accepted by all patients, and a signed informed consent was obtained.

A 2-month drug holiday period before the surgery up to the complete clinical healing of the surgical wound was planned for those patients receiving higher cumulative doses of bisphosphonates ($>$ 3 years). Patients in treatment with denosumab were treated after 4 weeks from the last administration and no later than the 6 weeks before the next administration, so as to ensure an adequate healing period.

Two weeks before the surgical procedures, patients were instructed to rinse for 1 min with 15 mL 0.2% chlorhexidine digluconate solution twice daily for one month. One week prior surgery, professional oral hygiene procedures were performed to remove plaque and calculus. Three days before the extractions, oral administration of amoxicillin 1 g every 8 h for 20 days was prescribed.

A surgical protocol published recently [14] and adapted to the prevention of MRONJ after extractive surgery was adopted and illustrated in Figs. 1 and 2. Local anaesthesia was induced with infiltrations of mepivacaine hydrochloride 30 mg/mL avoiding intraligamentous injections to prevent periodontal and gingival ischemia. A full-thickness flap was reflected and minimally-invasive extractions were carried out to preserve the cortical plates by means of thin luxators, elevators, and extraction forceps. Following extraction, each alveolar socket was debrided meticulously to remove all granulation and infected tissues, and rinsed with 0.9% sodium chloride solution. Then, bony edges were strictly smoothened by use of a surgical bur mounted on a straight handpiece under copious irrigation with sterile saline. At this point, aPDT was performed to minimize the local infection and to biostimulate the soft tissues with a specific setup (HELBO®, Bredent Medical, Senden, Germany). A 0.5-mL solution of 10 mg/mL phenothiazine chloride dye consisting of Methylenthioniniumchlorid (HELBO® Blue Photosensitizer, Bredent Medical, Senden, Germany) based on methylene blue compound, was applied in the surgical region and left in place for 3 min. Subsequently, the area was rinsed vigorously for 1 min with sterile saline to remove the excess photosensitizer. A hand-held 100 mW diode laser with a wavelength of 660 $\pm$ 10 nm (HELBO® TheraLite Laser, Bredent Medical, Senden, Germany) equipped with a dedicated probe (HELBO® 3D Pocket Probe, Bredent Medical, Senden, Germany) providing a power density of 60 mW/cm^2 was used to activate the previously dyed surface of approximately 3 cm^2 for 60 s per cm^2 with circular movements. The resulting fluence was 3.6 J/cm^2, while the total energy applied varied depending on the extension of the surgical area. After irradiation, the surgical region was rinsed with sterile saline. Finally, periosteal releasing incisions were performed to mobilize the flap coronally and a passive suture was achieved with horizontal mattress sutures and single stitches using absorbable suture material (4-0 and 5-0 Vicryl, Ethicon Inc., Somerville, NJ, USA).

In addition to chlorhexidine digluconate mouthwash rinses, post-operative domiciliary recommendations included ibuprofen 600 mg every 8 h for 3 days for pain relief, topical application of ice packs for 48 h, and a soft cold diet for 72 h.

Soft tissue healing was promoted with weekly applications of low-level laser therapy (LLLT) with the same apparatus for 6 weeks. The sutures were removed after 2 weeks. Recall visits were scheduled weekly for the first two months and monthly thereafter up to 6 months from the surgical procedure. At the 6-month appointment, a new orthopantomograph was performed to evaluate the radiological healing. Clinical and radiological follow-ups were scheduled every 6 months thereafter.

Patients were not allowed to wear removable prostheses until complete mucosal healing of the extraction sockets assessed clinically from the first post-operative month. Afterwards, pre-existing or new partial or complete removable dentures were relined with a resilient material (Soft Liner; GC Corporation, Tokyo, Japan). During the subsequent recall visits, dentures were relined when needed to avoid excessive compression to the underlying bone.

3. Results

Overall, 8 female and 3 male subjects affected by primary osteoporosis treated with antiresorptive agents were treated in a private practice setting by the same operator. Demographic data and patient details were reported in Table 1. The average age of the patients was 72.5 $\pm$ 4.2 years (age range: 65–79 years). The mean duration of antiresorptive treatment was 39.2 $\pm$ 15.4 months (range: 24–72 months). Routes of administration varied from oral to subcutaneous to intramuscular. None of the patients received intravenous

Table 1
Patients' characteristics and demographic data.

Patient ID	Age	Sex	Molecule	Dosage	Route	Duration of treatment	History of MRONJ[a]	Drug holiday	Type of extraction	Number of elements	Surgical site	Follow-up
1-AR	72	F	Alendronate	70 mg/week	Oral	6 years	No	Yes	Multiple teeth	1 canine, 2 premolars	Mandible	6 months
2-CP	69	M	Denosumab	60 mg/6 months	Subcutaneous	2 years	No	No	Multiple teeth	4 incisors, 2 canines, 1 premolar	Mandible	6 months
3-LE	68	F	Clodronate	100 mg/week	Intramuscular	4 years	No	Yes	Teeth/implants	1 incisor, 1 canine[b], 1 premolar[b], 1 molar[b], 2 premolars[c]	Maxilla	1 year
4-ML	65	F	Clodronate	200 mg/2 weeks	Intramuscular	2 years	No	No	Multiple teeth	3 incisors, 1 premolar[c]	Mandible	1 year
5-NS	71	F	Clodronate	100 mg/week	Intramuscular	3 years	No	No	Teeth/implants	1 canine[c], 3 incisors[c], 2 premolars[c], 1 molar[c] 1 molar[b], 4 premolars[b], 1 canine[b], 2 incisors[b]	Maxilla Mandible	1 year
6-CA	77	M	Denosumab	60 mg/6 months	Subcutaneous	2 years	No	No	Multiple teeth	4 incisors, 1 canine, 1 premolar	Mandible	6 months
7-FP	76	F	Denosumab	60 mg/6 months	Subcutaneous	3 years	No	No	Multiple teeth	2 molars[c], 3 premolars[c], 1 canine[c]	Maxilla	6 months
8-MAD	73	F	Alendronate	70 mg/week	Oral	5 years	No	Yes	Multiple teeth	1 canine 2 premolars, 1 molar	Maxilla Mandible	6 months
9-MAN	70	F	Clodronate	200 mg/2 weeks	Intramuscular	2 years	No	No	Multiple teeth	4 incisors[c], 1 canine[c]	Maxilla	1 year
10-PF	79	F	Alendronate	70 mg/week	Oral	4 years	No	Yes	Multiple teeth	2 premolars[c]	Maxilla	1 year
11-TA	78	M	Denosumab	60 mg/6 months	Subcutaneous	3 years	No	No	Multiple teeth	1 incisor[c], 2 canines[c], 1 premolar[c]	Mandible	6 months

[a] Medication-related osteonecrosis of the jaw.
[b] Dental implant.
[c] Residual root.

administrations. All subjects reported no history of previous manifestations of osteonecrosis of the jaw caused by tooth extractions performed elsewhere.

Before intervention, a drug holiday period was planned for four patients treated with antiresorptive agents for a cumulative period > 3 years. A total of 62 surgical extractions were performed, including 51 natural elements and 11 dental implants. A total of 7 surgical sites were located in the mandible, while 6 surgical sites were located in the maxilla.

All surgeries were completed according to the above-mentioned protocol with no intraoperative complications. Immediate post-operative period was uneventful in most of the patients. Four subjects complained of mild pain during the first three days after surgery that was controlled with pain relievers. Three patients developed ecchymosis adjacent to the surgical area that resolved spontaneously within 2 weeks without specific additional treatments.

The follow-up ranged from 6 months to 1 year. During the follow-up period, no patients showed prodromal manifestations of MRONJ according to Ruggiero et al. [4]. Clinical findings included tooth-unrelated odontalgia, bone pain in the jaw, maxillary sinus pain, altered neurosensory function, loosing of adjacent teeth unaffected by chronic periodontitis, intraoral fistulae, and exposed necrotic bone. Radiographic features included abnormal alveolar bone loss or resorption, changes to trabecular pattern, region of osteosclerosis, and thickening or obscuring of the periodontal ligament of the remaining dentition. No case of MRONJ was recorded up to the latest follow-up visit.

4. Discussion

The purpose of the present case series was to strengthen the current evidence concerning the use of aPDT as adjunctive treatment modality to prevent MRONJ. The sample consisted of non-oncologic osteoporotic patients treated with non-intravenous antiresorptive agents, and requiring multiple tooth and/or implant extractions. Antiresorptive agents including bisphosphonates and denosumab have been considered as drugs involved in the etiopathogenesis of MRONJ [2,3]. More precisely, the incidence of MRONJ ranges from 1.04 to 69 per 100.000 patients/year in osteoporotic subjects prescribed oral bisphosphonates, and from 0 to 30.2 per 100.000 patients/year in osteoporotic subjects prescribed denosumab [5].

The prevention of MRONJ has been indicated as a crucial factor in those patients receiving antiresorptive agents. In the present study, preventive measures consisted of preoperative professional oral hygiene, antimicrobial mouthwashes, systemic antibiotic, minimally invasive procedure, removal of sharp bony edges, and primary wound closure. Such preventive modalities have been clearly recommended to optimize the prevention of MRONJ, but may not be enough against complex microbial biofilms extremely difficult to eradicate once established [5,17–20].

Indeed, it is worthy of note that oral infections might play a leading part in the pathogenesis of MRONJ. Several aggressive anaerobic bacteria commonly found in periodontal and peri-implant lesions have been found in necrotic bone from MRONJ samples, such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*. Other dominating pathogens have been observed, including, *Lactobacillus* spp., *Prevotella* spp., *Actinomyces* spp., *Streptococcus* spp., and *Fusobacterium spp* [21]. In this respect, aPDT showed successful results when used to eliminate microorganisms associated with biofilms implicated in the etiology of periodontitis and peri-implantitis [22–24]. All these findings taken together suggest that the use of aPDT in the prevention and management of MRONJ may provide beneficial results in addition to the conventional treatments. In this sense, aPDT has been used in clinical cases presenting with already established MRONJ lesions with promising results. de Castro et al. reported two cases of MRONJ treated complementarily with aPDT [13]. All were osteoporotic patients treated with oral administrations of bisphosphonates.

Following aPDT, a complete healing of the surgical site with bone neoformation and absence of symptoms was observed in both subjects. Similarly, Poli et al. applied aPDT to treat a MRONJ lesion developed following tooth extractions in an osteoporotic patient in therapy with intramuscular bisphosphonates [14]. Even in this case, a complete resolution of the disease was observed in terms of maintenance of mucosal closure without any signs of residual infection, fistulae, or exposed necrotic bone at the surgical site. Another clinical report by Minamisako et al. described the management of MRONJ with aPDT in a patient treated with oral bisphosphonates for 8 years who underwent tooth extractions in the same region [15]. The patient showed clinical improvement following treatment, with no recurrence of the disease, absence of bone necrosis, control of infection and suppuration, pain relief, and total healing of the soft tissues.

On the other hand, to the best of the authors' knowledge, the adjunctive use of aPDT in the prevention of MRONJ in humans has not been previously reported so far. Thus, in the present study, aPDT was used as an additional strategy to minimize the occurrence of adverse events in patients at risk of MRONJ. The dye was a phenothiazine chloride-based photosensitizer consisting of 1% methylene blue (3.7-bis-(dimethylamino)-phenothiazin-5-ium chloride), glucose, methylhydroxypropylcellulose, and citrate, irradiated with a 660 nm wavelength 100 mW low-power continuous-wave diode laser. The system used herein was available on the commercial market with sterile dye, and sterile bi-dimensional and three-dimensional spot probes as optical fibers, which allowed maintaining the surgical asepsis. All of the patients healed uneventfully from both clinical and radiological aspects over a minimum follow-up of 6 months. It is noteworthy that the same aPDT system turned out to be the most effective means of decreasing *Actinomyces naeslundii* colony forming units isolated from a patient with MRONJ [24]. The fact that *Actinomyces* spp. has been designated as the leading bacterial pathogen isolated from MRONJ lesions [4,25] might justify the use of aPDT in the prevention of such adverse event. The use of aPDT with methylene blue dye is also encouraged by the effective inactivation of *Staphylococcus aureus* biofilms in compact and cancellous bone [26], as well as in bone infections [27].

It remains unclear however, whether biofilms may hamper the effectiveness of aPDT by limiting the penetration of the dye into individual cells. In this regard, it must be noted that aPDT was the last phase of the surgical protocol described earlier. Before the application of the dye, mechanical disruption of the biofilm was performed with manual instruments during the curettage of the alveolar sockets, and with mechanical instruments during the osteoplastic procedure by means of pear-shaped burs mounted on surgical handpiece under copious irrigation with saline solution. This sequence may have improved the efficacy of aPDT in these terms.

Although no human studies are currently available on the use of aPDT in the prevention of MRONJ, the results of the present study corroborate recent findings obtained in animal models. In the experimental study by Ervolino et al., senile female rats receiving zolendronate underwent single-tooth extraction in the presence of induced periodontitis [28]. Three sessions of aPDT were performed at the tooth extraction site at 0, 2 and 4 postoperative days with methylene blue as photosensitizer. The authors found that aPDT improved the alveolar repair process and prevented the occurrence of MRONJ-like lesions. Furthermore, the authors noted that sockets not treated with aPDT had areas of necrotic bone surrounded by colonies of bacteria. The same was not observed in sockets treated with aPDT, demonstrating an antimicrobial action. Roughly the same study design was adopted by Sarkarat et al. to assess the efficacy of aPDT in decreasing or preventing MRONJ [29]. Single-tooth extraction was performed in rats treated with zoledronic acid. After extraction, aPDT was performed in the experimental group after surgery and at weeks 1, 2, 3, 4, 5, 6, and 7 after surgery. The results showed that aPDT treatment effectively decreased inflammation, bone exposure, and MRONJ stage, and considerably improve the extent of live bone.

Interestingly, both Ervolino, Sarkarat, and co-workers claimed they were the first to propose and characterize aPDT as a preventive strategy to avoid MRONJ. The aim of the present preliminary case series was to give a further insight into the preventive application of aPDT in humans. Our results, however, must be interpreted cautiously due to some limitations that need to be addressed. First of all, there is a lack of external validity when interpreting the results. Accordingly, only non-oncologic osteoporotic patients assuming non-intravenous agents were treated. In this patient population, the risk of developing MRONJ remains very low [4]. In contrast, on the basis of epidemiological data regarding the onset of MRONJ, the risk is greater for cancer patients [30], and for patients prescribed long-term high dose intravenous agents [5]. Even the molecule itself may be considered a cofounding factor. In the present study, patients were treated with two different types of bisphosphonates, namely clodronate that is a non–nitrogen-containing alkylbisphosphonate, and alendronate, which is a nitrogen-containing aminobisphosphonate. Generally, non–nitrogen-containing bisphosphonates are less potent and bind more weakly to hydroxyapatite. This might explain why alendronate is 100-fold more potent than clodronate and has been more frequently associated to MRONJ [31]. The fact that only three patients in the present study were treated with alendronate may lead to an overestimation of the efficacy of aPDT. Therefore, the effectiveness of aPDT should not be generalized to more challenging clinical situations with increased risk of developing MRONJ. Furthermore, even when aPDT was not applied, the use of other conventional preventive measures showed good results in terms of prevention of MRONJ. Thus, it is difficult to isolate and estimate the real effect of aPDT in the present study, where the photodynamic treatment was combined with antibiotics, antimicrobials, surgical debridement, and first intention healing of the wound.

In view of the aforesaid, it can be concluded that aPDT 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.

Declarations of interest

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