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ORIGINAL ARTICLE

Bisphosphonate-related osteonecrosis: laser-assisted surgical treatment or conventional surgery?

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Abstract Bisphosphonates (BSPs) are used for the treatment of multiple myeloma, metastatic breast and lung cancer, Paget's disease, osteoporosis, hypercalcemia due to malignancy, and many other skeletal diseases. BSPs reduce osteoclastic functions, which result in bone resorption. Bisphosphonates-related osteonecrosis of jaws (BRONJ) is a newly developed term that is used to describe the significant complication in patients receiving bisphosphonates. BSPs are known to exhibit an anti-angiogenetic effect that initiates tissue necrosis of the hard tissue. There is currently no consensus on the correct approach to this issue. The aim of this retrospective study is to compare the effects of laser surgery with biostimulation to conventional surgery in the treatment of BSP-induced avascular bone necrosis on 20 patients who have been treated in our clinic. BRONJ was evaluated in patients with lung, prostate, and breast cancer under intravenous BSP treatment. Twenty patients in this study developed mandibular or maxillary avascular necrosis after a minor tooth extraction surgery or spontaneously. Bone turnover rates were evaluated by serum terminal C-telopeptide levels (CTX) using the electrochemiluminescence immunoassay technique and patients were treated with laser or conventional surgical treatments and medical therapy. Ten patients were treated with laser surgery and biostimulation. An Er:YAG laser (Fotona Fidelis Plus II® Combine laser equipment, Slovenia) very long pulse (VLP) mode (200 mJ, 20 Hz) using a fiber tip 1.3 mm in diameter and 12 mm in length was used to remove the necrotic and granulation tissues from the area of avascular necrosis. Biostimulation was applied postoperatively using an Nd:YAG laser. Low-level laser therapy (LLLT) was applied to the tissues for 1 min from 4 cm distance using an Nd:YAG laser (Fotona-Slovenia) with a R24 950-μm fiber handpiece long-pulse (LP) mode, 0.25-W, 10 Hz power/cm^2 from the mentioned distance the spot size was 0.4 cm^2, and power output was 2.5 J. Energy density from the mentioned distance was calculated to be 6.25 J/cm^2. The other ten patients were treated with conventional surgery. Treatment outcomes were noted as either complete healing or incomplete healing. There were no statistically significant differences between laser surgery and conventional surgery ($p>0.05$). CTX values also did not affect the prognosis of the patients. Treatment outcomes were significantly better in patients with stage II osteonecrosis than in patients with stage I osteonecrosis. Our findings suggest that dental evaluation of the patients prior to medication is an important factor in the prevention of BRONJ. Laser surgery is a beneficial alternative in the treatment of patients with this situation. Further randomized studies with larger patient numbers may also improve our understanding of treatment protocols for this situation.

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Introduction

First synthesized in 1865, bisphosphonates (BSPs) are used for the treatment of conditions related to bone metabolism such as, Paget's disease, osteoporosis, multiple myeloma, and bone metastasis of breast and prostate cancers. Bisphosphonate-related osteonecrosis of jaws (BRONJ) is a newly emerged term that is used to describe the significant complication in patients receiving bisphosphonates. The term significantly states an adverse effect that occurs as a result of reduced bone resorption and bone turnover.

According to the AAOMS position paper, there are three groups of stages for the evaluation of BRONJ [1]:

Stage I. Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection
Stage II. Exposed/necrotic bone in patients with pain and clinical evidence of infection
Stage III. Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border

It is important for the oncologist, the oral and maxillofacial surgeon, and the dentist to work in perfect collaboration. An emphasis on the guidelines published by the American Dental Association is particularly laid on the requirement of oral hygiene and completion of dental treatments prior to bisphosphonate treatments [2, 3].

Several authors have reported the limitations of surgical treatment of BRONJ, and emphasized that conservative therapy is the treatment of choice for these patients whenever possible [4–9]. It is only recommended in the cases which do not respond to conservative treatment to perform local debridement, bone contouring procedures, and segmental osteotomies [6, 8, 10–13].

Several precautions should be taken to prevent the occurrence of BRONJ. Kan et al. [2] recommended a treatment protocol for the patients with a high risk of BRONJ development that includes the following steps:

- Interruption of bisphosphonate treatment with a consultation to the patient's oncologist.
- Administration of antibiotics in order to prevent an infection following the surgical approach.
- Performing the extractions with minimal trauma to the adjacent soft tissues and the bone. Special attention should be paid to perform the extractions in an aseptic environment under antibiotic prophylaxis. To hinder the possible infection of open extraction sockets, wound sites are primarily closed, causing minimal trauma to the surrounding tissues.

As a supportive treatment, low-level laser therapy (LLLT) application was performed during and 2 days after the operation, aiming for acceleration in healing of both hard and soft tissues during and after the surgical procedures.

Laser light has several unique properties that make it useful for a variety of applications in medicine. It is capable of ablating and vaporizing residual organic debris, including microbial plaque, and has the potential to disinfect the area.

Contact-free laser ablation has the advantage of cutting bone without friction, which causes additional thermal and mechanical trauma minimizing the risk of cell death and delayed healing. Furthermore, in contrast to conventional procedures, no bony particles are produced. Laser ablation also results in micro-fracturing and micro-explosive removal of the mineral phase of bone. Besides, by laser ablation of mineralized tissue, the vaporization of water subsequently leads to a fast removal of the tissue layers [14]. This leads to uncontaminated and microstructured bone surface free from thermal damage.

In osteogenesis, several in vitro studies using different laser devices have previously demonstrated the beneficial effects of low-level irradiation in promoting new bone formation by including proliferation and differentiation of osteoblasts. LLLT is an innovative approach increasingly used in medicine, which has been shown to have several different effects, including pain relief, wound healing, and nerve regeneration. Low-level lasers are also called soft lasers, therapeutic lasers, low-intensity lasers, or low-power lasers [15–17]. It has the potential for antimicrobial and biostimulating effects with proliferations of macrophages, lymphocytes, fibroblasts, endothelial cells, and keratinocytes when applied to oral tissues by promoting wound healing, enhancing epithelization after periodontal surgery, minimizing edema after third molar surgery, and preventing induced oral mucositis [18–21].

Animal studies have shown that LLLT has a positive effect on bone healing, especially in the first 15 days [22]. In an animal study, Pinheiro et al. [23] have reported a positive effect of LLLT on the repair of bone defects grafted with inorganic bovine bone with increased new bone formation and an amount of collagen fibers around the grafts.

There is currently no consensus on the correct approach to treatment of patients with BRONJ. Various treatment types could be used including laser-assisted treatment [15, 24]. Considering the described benefits of laser-assisted surgical treatment (LAST), it can be postulated that laser biostimulation may be helpful in treating BRONJ [24].

In this study, we have evaluated BRONJ in patients with lung, prostate, and breast cancer under intravenous BSP treatment. The aim of the study is to compare the effects of laser-assisted surgical treatment on bone and wound healing to the effects of conventional surgical methods, and to compare the results with the relevant literature. Also, the effects of serum terminal C-telopeptide (serum CTX) level, which is a biochemical bone turnover marker that is shown to change by antiresorptive treatment [25, 26], on the prognosis of the patients with BRONJ have been evaluated.

Patients and methods

For this study, 20 patients who underwent treatment for BRONJ between 2006 and 2009 at the Istanbul University Faculty of Dentistry Department of Oral and Maxillofacial Surgery were evaluated. We investigated seven male and 13 female patients with nine mandibular and 11 maxillary effected jaw sites (Table 1). All of the patients had a history of minor oral surgical procedures. All patients received i.v. zoledronic acid (Zometa; Novartis® Pharmaceuticals) therapy during the treatment of their primary disease prior to oral surgery.

Serum terminal C-telopeptide levels of the patients were measured prior to surgery using electrochemiluminescence immunoassay (ECLIA) (Roche®, Mannheim, Germany). All of the patients included in this study were selected from patients with stage I and stage II BRONJ, who did not respond to previous antimicrobial therapy with oral rinses and antibiotics (Table 1). Patients were randomly divided into two groups: in the first group (n=10), patients were treated with laser surgery (mandible, five, maxilla, five). In the second group (n=10), patients were treated with conventional surgery (mandible, four, maxilla, six). All surgical procedures were carried out in accordance with the Declaration of Helsinki, as revised in 2000. All patients signed a written informed consent form for the surgical intervention and were thoroughly informed about the surgical procedure.

All of the patients were questioned for a detailed history about the frequency and dosage of BSP treatment, duration of the BSP therapy, BSP drug holiday, any other systemic diseases, presence of pain and halitosis, any dental surgery during the BSP therapy, steroid treatment, smoking habit, diabetes mellitus, and oral hygiene. None of the patients had recently received corticosteroids. Each patient was scheduled for 1 ml of blood drawn for serum C-terminal telopeptide (CTX), which is a bone turnover marker when they were first admitted to the clinic. CTX levels were re-evaluated the day before starting the treatment. Patients who had CTX values under 150 pg/ml were given a drug holiday for a minimum of 3 months before any kind of surgical treatment. CTX levels were evaluated every 3 months after each kind of surgical treatment. Risk for bisphosphonate-related osteonecrosis of the jaws (BRONJ) depending on CTX values were determined according to Marx et al. [11] (Table 2). One patient at high risk (90 pg/ml) and two patients at moderate risk for BRONJ (149 pg/ml and 129 pg/ml) were also operated on after waiting for the drug holiday. Patients were examined for wound healing every other day for the first 10 days and monthly thereafter for the next 6 months. All patients were given a drug holiday at least for 6 months after all surgeries. After 6 months of follow-up, CTX values were re-evaluated and healing of the surgical wounds and osteonecrosis were diagnosed.

Evaluation of the surgical wound and osteonecrosis

Diagnosis of the osteonecrosis of the jaw was based on radiological and clinical examinations. Radiological examinations were visualized with computed tomography (CT) and panoramic radiographs (Fig. 1). In clinical examination, non healing of the exposed or necrotic bone of the mandible, maxilla, or both for more than 10 weeks was considered as osteonecrosis of the jaw [1] (Fig. 2). Patients who received radiotherapy from the head and neck area or patients with the infection of the soft tissues were excluded from the study. All of the patients included in this study were selected from patients with stage I and stage II BRONJ who did not respond to previous antimicrobial therapy with oral rinses and antibiotics.

Basic surgical procedures

All surgical procedures were performed under local anesthesia. Following the appropriate minimal conservative incisions, all mucoperiosteal flaps were elevated around the BSP-induced osteonecrosis (Fig. 3). Fibrous and inflammatory lesions were thoroughly removed from the sites. The mobilized avascular bone necrosis tissues were removed from the wound with bone forceps. Immobile necrotic tissues were removed either by laser-assisted surgical or conventional surgical procedures followed by prescription of postoperative antibiotics (amoxicillin+ clavulanic acid 1,000 mg × two/day and metronidazole 500 mg × two/day) and non-steroid antiinflammatory drugs (naproxen Na 550 mg × two/day). Mouth rinse with 0.2% chlorhexidine gluconate 2 × 1 for 10 days was also prescribed to all patients.

Conventional surgical procedures

The affected bony tissues were curetted from the surface of the bone using bone curettes and round tungsten carbide burs (44–47 mm in length and 3.5, 4, and 5 mm in diameter) under aggressive irrigation with saline. In most

Table 1 List of patients included in this study. *Ptnt* patient, *PD* primary disease, *PT* period of the therapy with BSP, *CTX Lvl F* blood serum CTX level in first admission, *BRONJ Etgy* bisphosphonate-related osteonecrosis of jaw etiology, *BRONJ Site* bisphosphonate-related osteonecrosis of jaw site, *DHBS* drug holiday before surgery, *CTX Lvl S* blood serum CTX level in surgery, *BRONJ risk* bisphosphonate-related osteonecrosis risk, *BRONJ Stg* bisphosphonate-related osteonecrosis stage, *TT* type of treatment, *FU* follow-up, *OTC* outcome, *CH* complete healing, *IH* incomplete healing, *MM* multiple myeloma, *Brst* breast cancer, *Neur* neuroendocrine tumor, *Prst* prostate cancer, *Mnd* mandible, *Max* maxilla, *MOSP* minor oral surgery procedures

Ptnt	Age	Sex	PD	PT Mth	CTX lvl F. pg/ml	BRONJ Etgy	BRONJ site	DHBS Mth	CTX lvl S pg/ml	BRONJ risk	BRONJ Stg	TT	FU Mth	OTC
1	62	M	Prst	14	240	MOSP	Mnd	2	204	Low	Stg2	LS	17	IH
2	53	F	Brst	38	120	MOSP	Mnd	10	261	Low	Stg2	LS	18	CH
3	68	F	Brst	18	240	MOSP	Mnd	1	240	Low	Stg2	LS	21	CH
4	50	F	MM	7	228	MOSP	Max	5	228	Low	Stg1	LS	28	CH
5	59	F	Brst	13	196	MOSP	Mnd	5	276	Low	Stg2	LS	11	CH
6	56	M	MM	52	489	MOSP	Max	1	489	Low	Stg2	LS	12	CH
7	51	F	Brst	67	261	MOSP	Max	2	261	Low	Stg2	LS	9	IH
8	55	F	Brst	132	220	MOSP	Max	9	250	Low	Stg2	LS	26	CH
9	58	F	MM	22	131	MOSP	Mnd	6	235	Low	Stg2	LS	15	CH
10	53	F	Brst	96	470	MOSP	Max	6	470	Low	Stg2	LS	9	IH
11	54	F	Brst	31	230	MOSP	Mnd	20	230	Low	Stg2	S	10	IH
12	54	M	MM	6	380	MOSP	Max	0	675	Low	Stg1	S	18	IH
13	52	M	MM	22	101	MOSP	Max	1	149	Mod	Stg1	S	14	IH
14	48	M	MM	30	70	MOSP	Max	3	90	Hgh	Stg1	S	18	IH
15	52	F	Brst	20	86	MOSP	Max	3	157	Low	Stg1	S	3	IH
16	54	M	MM	18	92	MOSP	Mnd	3	129	Mod	Stg2	S	15	CH
17	39	F	Brst	9	130	MOSP	Max	3	265	Low	Stg2	S	12	CH
18	65	F	Brst	24	1220	MOSP	Mnd	6	1,220	Low	Stg2	S	4	CH
19	67	F	Brst	8	276	MOSP	Max	1	276	Low	Stg2	S	3	CH
20	58	M	Neur	20	55	MOSP	Mnd	3	225	Low	Stg1	S	3	IH

sites the necrotic bone was completely removed until the vital bone tissues and vessel spots appeared. Close attention was paid in order to perform an atraumatic operation. The operation site was irrigated by saline solution several times and mucoperiosteal flaps were closed with 4/0 silk or polyglactin 910 (Vicryl rapide) sutures tension-free. Post-operative controls were made 1 week after surgery.

Laser-assisted surgical procedures

Before the use of laser, the necrotic tissues were removed with the aid of a bone forceps in order to shorten the duration of the procedure. In the laser-assisted surgery group, in addition to removal of the necrotic and infected tissues, laser ablation and decontamination followed by biostimulation were applied. Both soft and hard tissue laser treatments were made with Fotona Fidelis Plus II® Combine laser equipment (Fotona-Slovenia). Fotona Fidelis Plus II® laser equipment had two wavelengths; Er:YAG (2,940 nm) and Nd:YAG (1,064 nm). Fibrous and inflammatory granulation tissues were removed from the wound by using Er:YAG laser very long pulse (VLP) mode (200 mJ, 20 Hz) using a fiber tip 1.3 mm in diameter and 12 mm in length. The avascular necrotic bone tissues were vaporized from

Table 2 Risk classification for patients under BSP treatment

Serum CTX values and risk for BRONJ:	
High risk	≤100 pg/ml
Moderate risk	≤ 150 pg/ml
Low or no risk	= 150 pg/ml
Normal values	= 350 pg/ml

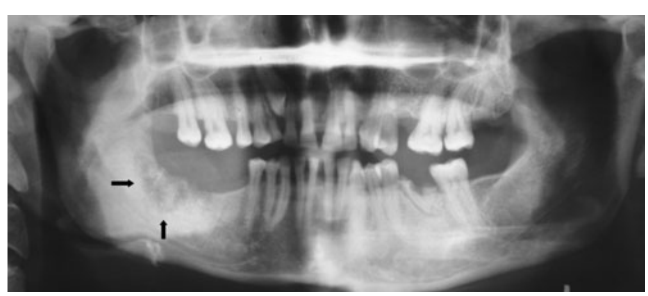

Fig. 1 Panoramic view of the osteonecrosis site shown by the *arrows* on the right side of the mandible

Fig. 2 Intraoral view of the BRONJ patient at stage 2. Puss at the necrosis site can be seen

the surface with the Er:YAG laser, with R14 hand piece very short pulse (VSP) mode (200 mJ, 20 Hz) using a fiber tip 1.3 mm in diameter and 12 mm in length. This procedure was carried out until the vital sites of the bone were reached and intra-bony bleeding was observed (Fig. 4). Thereafter, mucoperiosteal flaps were closed with 4/0 silk sutures tension-free. Low-level laser therapy (LLLT) was applied to the tissues for 1 min from 4 cm distance using an Nd:YAG laser (Fotona-Slovenia) with a R24 950-μm fiber handpiece long-pulse (LP) mode, 0.25-W, 10-Hz power/cm^2 from the mentioned distance. The spot

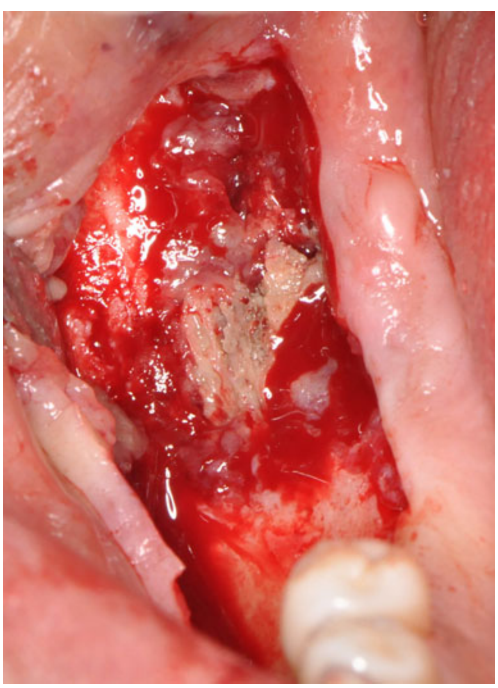

Fig. 3 Osteonecrotic site exposed after elevating mucoperiosteal flap during surgery

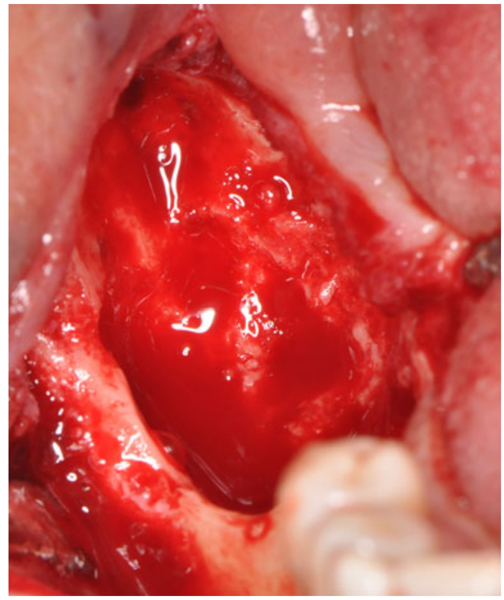

Fig. 4 Intraoral view of the operation site after all the necrotic tissues are vaporized from the surface

size was 0.4 cm^2 and the power output was 2.5 J. Energy density from the mentioned distance was calculated to be 6.25 J/cm^2. Biostimulation of the surgical wounds were made every other day with the Nd:YAG laser Fidelis Plus® for a total of five sessions for 10 days.

Statistical evaluation

A software package (SPSS 11.0, SPSS, Chicago, IL) was used for the statistical analysis. Chi-square and Fisher's exact tests were used for the evaluation of the differences. Significance was assigned at the $p<0.05$ level.

Results

BSP-induced necrosis sites were evaluated clinically and radiographically in the post-operative period in order to follow up the healing process. Healing was recorded as

Fig. 5 Intraoral view of the operation site after 4 months of healing

Fig. 6 Panoramic view of the operation site after 4 months of healing

either complete healing (Figs. 5 and 6) or incomplete healing for all of the groups where complete healing is described as full epithelization of the exposed bone and no signs of infection.

Treatment type

When the patients were compared for treatment type, there was no significant difference between the laser and conventional surgery groups for healing (Table 3).

CTX

Regarding the CTX values, the patients were divided into two groups as CTX<150 pg/ml and CTX>150 pg/ml. There was no statistical difference between the low and high CTX value groups for healing (Table 4). According to serum CTX guideline, we operated on one patient from the right mandible with a high risk of BRONJ, two patients with a moderate risk of BRONJ and 19 patients with no or low risk.

BRONJ stage

When the patients were evaluated for staging, the patients with BRONJ stage II had significantly better healing than the patients with BRONJ stage I osteonecrosis (Table 5).

Discussion

In this study, the effects of serum CTX levels, treatment method, and stage of osteonecrosis on the treatment outcome of BRONJ were evaluated. In the treatment of BRONJ, complete closure of the wound is aimed for to increase the patient's quality of life, even though cancer patients who have bone metastasis do not have a high expectancy of life. Pain may not be a symptom in stage I of the disease, however, exposed bone bears the risk of infection or disease progression. In our study, the treatment outcomes were classified as complete healing and incomplete healing, in which the complete epithelization of the wound was considered to be complete healing. The stage of BRONJ is an important factor on treatment planning and patients in stage I and II are more prone to heal by only antimicrobial treatment [6, 27]. However, the patients who did not heal with antibiotherapy were managed by surgical treatment. Conservative treatment in the second and third stages is shown to be less successful [18, 38, 39, 43] when compared to surgical management [28–31].

Our findings state that patients with stage II BRONJ presented better healing following the surgical procedures. Considering that stage II is a more advanced form of the disease, this finding can either be due to a low number of patients or due to the fact that the lesion is more in the spongious bone in stage II patients whereas the lesion mostly effects the compact bone in stage I patients. Better vascularization of the spongious bone might be the reason for the stated result.

The effects of laser use on the nutrition of skin and mucosa, the speed of the reparative process, the increase in the organic matrix of the bone, and the mitotic osteoblastic activity, both in vivo and in vitro, have been reported by several authors [32] and these studies have supported the use of laser biostimulation in the treatment of BRONJ of the jaws [33].

Successful application of the Er:YAG laser has been reported in both hard tissue procedures and soft tissue management, without major thermal side-effects [34]. The high level Er:YAG laser has been increasingly used in various procedures due to effective soft tissue and bone tissue ablation and potential biostimulation. Because of this, the Er:YAG laser has recently been described as one of the most promising laser systems for bone surgery [35–37]. The results of a recent study by Leucht et al. [38] analyzing bone repair after plasma laser corticotomies revealed an excellent bone regeneration with circumvention of thermal denaturation of the collagen-rich matrix. Their results

Table 3 Statistical comparison of treatment types

			Treatment		Total	*p* value
			Laser	Conventional		
Outcome	1	Complete healing	70.0%	40.0%	55.0%	p=0.370
	2	Incomplete healing	30.0%	60.0%	45.0%	
Total			100.0%	100.0%	100.0%	

Table 4 Statistical comparison of CTX values and healing

			ctx150		Total	*p* value
			<150	>150		
Outcome	1	Complete healing	33.3%	58.8%	55.0%	p=0.566
	2	Incomplete healing	66.7%	41.2%	45.0%	
Total			100.0%	100.0%	100.0%	

showed an accelerated osteochondroprogenitor cell migration, attachment, and differentiation followed by an enhancement of alkaline phosphatase activity, indicating and providing an environment conductive to skeletal tissue regeneration. Successful results with a various square-pulsed Er:YAG laser are reported as the results of preliminary studies [39]. The ablation effect is the result of the high absorption of the irradiation in the targeted tissues. This should now be an incentive for clinicians and scientists to further analyze the chemical, physical, and pharmacological aspects of laser application in the field of bone and mineralized tissue research to understand the biological interactions and to eventually come to a safe and reliable treatment option for bisphosphonate-related osteonecrosis of the jaw. Causing a reduced initial inflammatory response, laser treatment of bone might be a promising alternative to conventional mechanical instruments. These advantageous effects of laser irradiation on bone support the hypothesis that the laser will not only be an innovative and highly beneficial tool for cutting vital bone but also could be used in the treatment of several pathological conditions involving the bone.

Laser biostimulation of the tissues is still a controversial issue. Authors have various opinions on the physical and biological variables like the type of laser, frequency of the light pulse, output power, time of application, fluence, and distance of source from the irradiated tissue [40]. The Er:YAG laser was also used in this study in combination with LLLT using the Nd:YAG laser. Even though Scoletta et al. [15] have reported promising results with LLLT, our results did not show any significant differences supporting the benefit of laser surgery in patients with BRONJ when compared to conventional surgical methods. However, the outcome of the LLLT depends not only on the total dose of irradiation but also the duration and mode of the radiation may affect healing [22]. In this study, we used an energy level of 6.25 J/cm^2, which is a dose within the accepted therapeutic window [41].

CTX values of the patients were measured both preoperatively and post-operatively and even though we have observed that the patients with higher CTX values revealed better wound healing, edema and pain are not among the parameters of the present study, so it should be stressed that these observations were not built upon specific measurements but our subjective observations. Our findings of complete or incomplete healing show no significant correlation between serum CTX levels and healing.

The patients receiving BSP treatment were classified according to their serum CTX levels by Marx et al. [26] as high, moderate, and low or no risk of patients. However, our results did not show any effect of CTX on bone healing.

In their study, Marx et al. [6] reported that 37.8% of their BRONJ cases occurred as a result of tooth extractions. Our findings also support this statement. All of the patients included in this study developed BRONJ following tooth extractions.

Although the treatment of BRONJ is still controversial and no efficacy has been shown for either medical or surgical treatment, studies for the use of lasers in the management of BRONJ of the jaws have promising results [32, 33].

Preventive dental procedures are currently accepted as the gold standard in treatment of BRONJ together with bisphosphonate treatment modification [42, 43]. Early diagnosis of BRONJ is extremely important for the success of the treatment. Treatment outcomes have better results in the earlier stages of BRONJ [26, 44]. Surgical debridement of the necrotic bone is considered as a relatively conservative treatment of BRONJ in the stages II and III, because as the disease progresses, resections which decrease the patient's quality of life may be required [12, 45]. However, surgical debridement is not an easy procedure because of

Table 5 Statistical comparison of healing and BRONJ stage of the disease

			BRONJ stage		Total	*p* value
			I	II		
Outcome	1	Complete healing	16.7%	71.4%	55.0%	p=0.050
	2	Incomplete healing	83.3%	28.6%	45.0%	
Total			100.0%	100.0%	100.0%	

the insufficiency of imaging techniques in visualizing the borders of the necrosis [46, 47]. Fluorescence-guided bone resection seems to be a promising technique in the surgical treatment of BRONJ [47–49]. It has been previously stated by other authors that evaluating the treatment outcomes of BRONJ was difficult for particularly two reasons. The first reason is that there is no universally accepted definition of success in the treatment of BRONJ, and the second reason is the lack of controlled clinical trials regarding the subject [29, 48].

According to our results, local and general medical treatments such as a combination of antibiotherapy, chlorhexidine rinses, and antiinflammatory drugs only produces a temporary reduction of pain and local symptoms of infection but does not determine any kind of improvement in a long-term follow-up.

Conclusions

Considering that all of the cases were the results of tooth extractions, all of the bisphosphonate treatment candidates should have a complete dental evaluation prior to medication. Once the patient develops BRONJ, it may be very difficult for the surgeon to deal with the situation since the treatment of this situation is still controversial. Laser surgery is a beneficial alternative in the treatment of patients with BRONJ. Larger and randomly controlled trials from various clinics are required in order to understand the outcomes of different treatment types in the management of BRONJ.

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