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ORIGINAL ARTICLE

The effect of concentrated growth factor (CGF) in the surgical treatment of medication-related osteonecrosis of the jaw (MRONJ) in osteoporosis patients: a randomized controlled study

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Abstract

Objectives The purpose of this present study was to evaluate the efficiency of the growth factors delivered by concentrated growth factor (CGF) on the healing process of osteoporotic patients with medication-related osteonecrosis of the jaws (MRONJ).

Methods This randomized controlled study was composed of osteoporotic female patients who were treated with oral bisphosphonates (BPs) and diagnosed with MRONJ. For the CGF group, each patient was treated with a local application of CGF at the surgical site after removing the necrotic bone, while the surgical area was primarily closed as traditional surgical therapy for the control group. The patients underwent clinical examinations for 6 months postoperatively to check the presence of infection and dehiscence.

Results Complete healing was achieved in 19 patients of 28 patients (mean age: CGF group, 73.57 ± 5.1; control group, 73.64 ± 5.49) diagnosed with MRONJ. There was no significant difference in post-op healing data between groups during healing periods ($p > 0.05$). In the CGF group ($n = 14$) in three cases, bone exposure without infection was detected, and one of them showed a recurrent infection. In the control group ($n = 14$) in six cases, bone exposure without infection was detected, and three of them also showed recurrent infection.

Conclusion Although our results were not statistically significant, our findings suggest that the local application of CGF appears to be an effective approach to the surgical treatment of MRONJ in osteoporosis patients by improving tissue regeneration.

Clinical relevance A specific treatment protocol to manage MRONJ is still controversial. This study justifies that CGF can be used in combination with surgical treatment.

Keywords MRONJ · Osteonecrosis · Osteoporosis · Concentrated growth factor

Introduction

Antiresorptive and antiangiogenic therapies are widely used for treating bone metastatic cancers and various bone diseases, such as multiple myeloma, osteoporosis, osteogenesis imperfecta, and Paget's disease [1–4]. They are used to decrease osteoclast-mediated bone loss, particularly in the elderly population, for the treatment or prevention of osteoporosis [2, 4]. However, long-term use of this therapy is associated with a rare but serious adverse event, medication-related osteonecrosis of the jaws (MRONJ). This pathological condition was first reported by Marx as BP-related osteonecrosis of the jaw (BRONJ), when the presence of an avascular area of necrotic bone, with an exposure in the maxillofacial region, lasting for > 8 weeks occurs in a patient who had received BPs and with no history of radiation therapy to the craniofacial region [1, 3, 5, 6]. In 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) modified one of the criteria due to the non-exposed form of MRONJ; they included the cases without bone exposure which can be probed through a fistula intraorally or extraorally. Moreover, they suggested changing the term BRONJ to MRONJ due to the osteonecrosis cases that have been reported after the treatment with other substances [6].

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Several risk factors are associated with the development of MRONJ; in addition to long-term antiresorptive and antiangiogenic therapies, oral infections, mechanical trauma to the jawbone due to ill-fitting dentures, and invasive dental procedures, such as tooth extraction, are thought to be MRONJ-promoting factors [2, 4]. The occurrence of MRONJ impairs the quality of life by causing discomfort, localized pain, paraesthesia, suppuration, and swelling. Moreover, the exposed bone is often associated with food retention, necessitating extra hygiene measures for correcting the oral health profile [5, 7]. The clinical findings of MRONJ may vary in patients, and currently, there is no definitive standard care for MRONJ; the most effective treatment is still controversial [8]. Treatment options are classified into conservative, surgical, and adjuvant non-surgical therapies, and they can be used in combinations. According to the AAOMS position paper in 2014, the first choice of treatment is a conservative approach including local debridement and disinfection with antimicrobial rinses and/or systemic antibiotic therapy [6, 9]. These treatments can be combined with hyperbaric oxygen therapy, low-level laser therapy, and medical ozone applications [10]. These palliative treatments can result in improvement in many patients, but they are not always effective as many patients continue to experience recurrent infections [7]. Surgical therapy, such as bone debridement, sequestrectomy, or resection, is recommended when the extent of osteonecrosis increases and there is no response to conservative treatment [3, 10].

Platelet concentrate products, such as platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and concentrated growth factor (CGF), are autologous preparations obtained from the patient's blood, and they release high quantities of growth factors that can play a major role in the acceleration and stimulation of bone repair and tissue healing [3, 8, 10, 11]. PRP and PRF have been used clinically for various applications, including the treatment of MRONJ, and have been shown to have very successful results in many studies [1, 4, 7, 8, 12]. CGF is the latest generation of platelet concentrate products, which was first developed by Sacco in 2006; it is richer in growth factors than PRF. The different speeds of centrifugation permit CGF to have a wider, denser, and richer fibrin matrix, as reported by Rodella et al. in their immunohistochemical study [12]. CGF has a higher adhesive and tensile strength and a higher viscosity than PRF and PRP [12]. Considering these benefits, CGF would be effective for treating patients with MRONJ by stimulating bone and soft tissue healing.

Thus, the present study was designed to evaluate the effectiveness of CGF in the surgical treatment of MRONJ in osteoporosis patients. We hypothesized that the local application of CGF at the surgical site may be a new alternative method for MRONJ treatment by improving tissue regeneration. The specific aims of the study were to compare the presence of infection and dehiscence by clinical examination at the healing period for the CGF and non-CGF groups after surgical treatment of MRONJ.

Materials and methods

Patient selection

This randomized controlled study comprised 28 elderly female osteoporotic patients diagnosed with MRONJ at the department of oral and maxillofacial surgery of a university hospital in İzmir/Turkey between May 2016 and April 2018. The study was in accordance with the Declaration of Helsinki, and the study protocol was approved by the institutional ethics committee before patient selection. This present study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines and registered on ClinicalTrials.gov (NCT04531800).

The inclusion criteria were (1) treatment with oral bisphosphonates (BPs) for osteoporosis, (2) MRONJ diagnosis with exposed bone in the jaws that had persisted for longer than 8 weeks according to 2014 recommendations of the Association of Oral and Maxillofacial Surgeons (AAOMS) [7], (3) MRONJ stage 2 or 3 with bone destruction and sequestrum confirmed by clinical and radiographic examination, and (4) insufficient improvement with conservative treatment. The exclusion criteria were (1) a history of head and neck radiation therapy, (2) metastatic bone disease of the jaws, and (3) platelet values under than 150,000 mm^3 in a complete blood count.

All the selected patients signed the consent forms that included details regarding the surgery and possible risk of treatment complications.

Randomization

The sequentially numbered sealed envelopes were used by the examiner (G.I.) to randomly assign patients to the study groups. Before the surgery, these sealed envelopes were opened by the same examiner, and each patient was assigned to one of the study groups:

CGF group (14 patients treated with CGF clots + primarily closure)

Control group (14 patients treated without CGF placement + primarily closure)

Surgical procedure

Before the surgery, all patients underwent periodontal and dental examinations to achieve clinically acceptable oral hygiene and an oral antibiotic prescribed to all patients (amoxicillin/clavulanic acid 2 g/day) for 2 weeks.

According to a systematic review and meta-analysis on drug suspension protocol, the authors reported that drug holiday can be suggested in convenience with the condition of each patient [13]. Even though there is no consensus in the literature about the surgical treatment of the patients who received bisphosphonate which bonded irreversibly with the bone hydroxyapatite crystals, there were higher rates of complete healing for osteoporosis patients after interruption protocol of bisphosphonate treatment [14–16]. Based on these published data, each patient referred to their physician to ask for a drug holiday preoperatively.

For the CGF group, CGF clots were prepared several minutes before starting the surgery, as described by Sacco et al. [11]. Venous blood samples (4 × 9 cc) were obtained from each patient's forearm in two disposable, non-anticoagulant, silica-coated tubes (Vacuette®, Greiner Bio-One, GmbH, Kremsmünster, Austria). The blood in the test tubes was immediately centrifuged (Medifuge, Silfradent srl, Sofia, Italy) using the following CGF-specific program: 30-s acceleration, 2700 rpm for 2 min, 2400 rpm for 4 min, 2700 rpm for 4 min, 3000 rpm for 3 min, and 36-s deceleration and stop. At the end of the centrifugation, there were three layers in the test tubes: (1) the topmost serum layer, representing the liquid phase of plasma; (2) the second layer, representing CGFs white cell lines, stem cells, and the buffy coat; and (3) the bottom red blood cell layer (Fig. 1). CGF (the buffy coat and liquid phase layers) was separated from the red blood cell layer.

All procedures were performed under local anesthesia (Ultracaine DS Forte, Sanofi-Aventis, articaine hydrochloride 4%, epinephrine 1:100,000) by the same surgeon (M.Ö.Y). Before the surgical procedure, the examiner (G.I.) informed the surgeon about the patients' group assignment. After removal of superficial bone sequestrum, the necrotic bone was removed with rotating burs, curettage was performed, and the surface of the bone was smoothened (Fig. 2). CGF was then applied to the surgical area in the CGF group ($n = 14$), and the area was primarily closed after additional releasing incisions were made to the periosteum to assure tension-free soft tissue closure (Fig. 3). In the control group ($n = 14$), the surgical area was only primarily closed without any mobilization of the flap following sequestrectomy and bone curettage as a traditional surgical therapy (Fig. 4, Fig. 5a, b). A soft diet and daily

Fig. 1 CGF layers

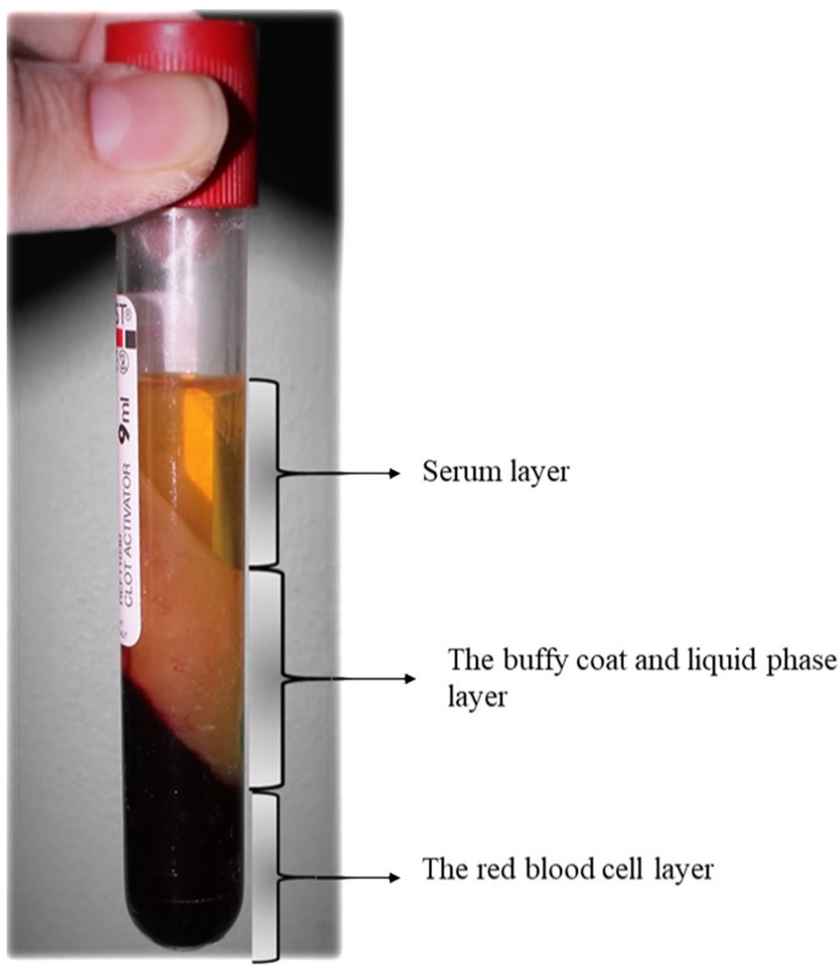

Fig. 2 The appearance of superficial bone sequestrum of a test group patient

irrigation with 0.12% chlorhexidine were prescribed for 2 weeks postoperatively. The sutures were removed 14 days postoperatively.

Study variables

The primary outcome variable of this study was soft tissue healing 6 months postoperatively. Preoperative and postoperative data were recorded by the blinded examiner (E.A.), who did not participate in randomization or surgical procedures.

Healing was defined as the previously described by Ristow et al. [17] and Park et al. [18]. The patients underwent weekly clinical examinations for the 1st month and then monthly clinical examinations for 6 months postoperatively. At the time of the evaluation, soft tissue coverage in the surgical site was assessed without signs of infection and/or necrotic bone (Fig. 6a, b). The presence of infection was assessed as follows: erythema, swelling, bleeding on probing, and purulent exudate. The differences between the study groups were recorded and considered to indicate postoperative healing. BP treatment status and ONJ classification of each patient were recorded, and these differences were also assessed in soft tissue healing.

In addition, anamnestic and therapeutic data as patients' age, the type of BPs, timing of medication, location of the exposed necrotic bone, and MRONJ-promoting factors were recorded for each patient.

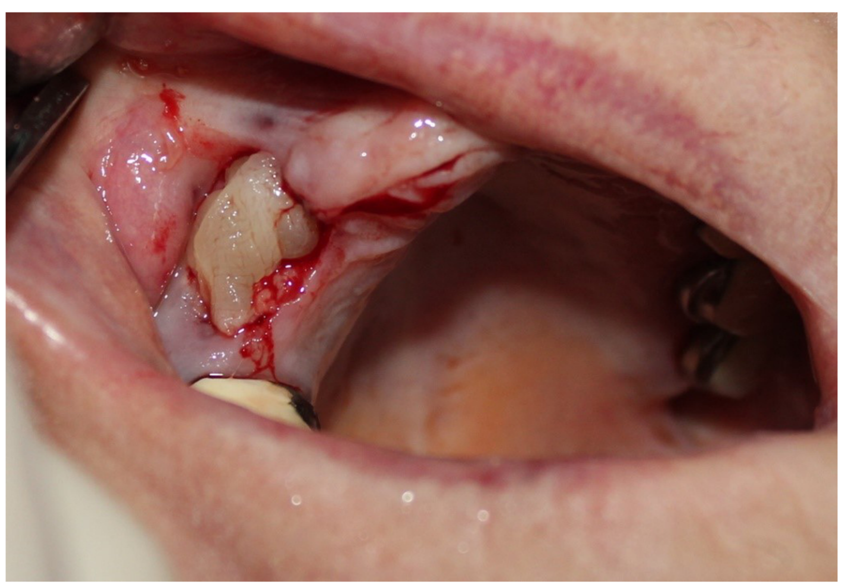

Fig. 3 CGF application to the surgical area

Fig. 4 The appearance of superficial bone sequestrum of a control group patient

Statistical analysis

Sample size calculation

The sample size of the study was determined considering the study of Ustaoglu et al. [19]. The data of the study were analyzed with a power analysis program (G * Power: Statistical Power Analyzes for Windows, Dusseldorf, Germany). The sample-size calculation determined that 8 patients per treatment group would provide 80% power to detect a true difference between test and control groups using tissue healing rate values as the primary outcome variable. Accordingly, a sample of 14 patients per group (28 observations in total) was included to compensate for possible dropout during the study period.

Statistical software (SPSS Inc. version 21 IBM, Chicago, IL) was used to analyze the data. Descriptive statistics such as the mean and frequency were calculated for each variable. First, scale variables were tested for normality using the Shapiro-Wilk test. Comparisons were performed using the two independent sample t test in scale variables. Categorical variables were analyzed using the Pearson chi-square test. Univariate logistic regression analysis was used to examine the association between the healing at 6 months and each variable. Variables with $p \leq 0.1$ were then involved in multivariate logistic regression analysis to examine the joint effects of these factors on the healing at 6 months. Statistical significance was set at $p < 0.05$ for all statistical analyses.

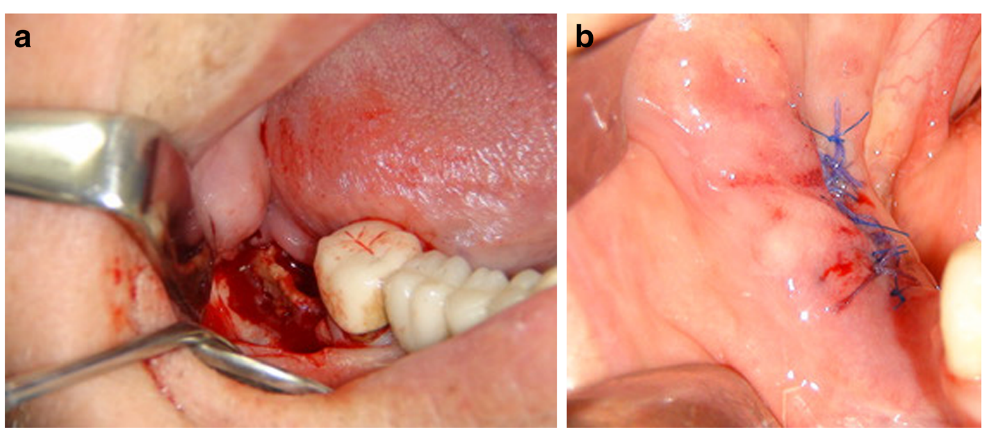

Fig. 5 **a** The appearance of surgical area of a control group patient. **b** Tension-free soft tissue closure of the flap following sequestrectomy and bone curettage

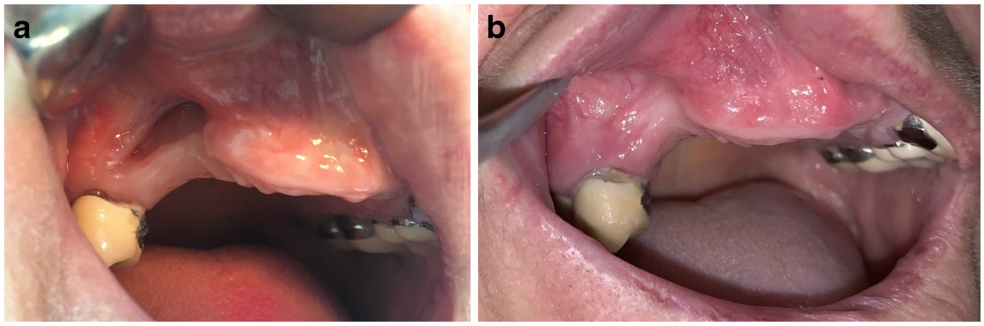

Fig. 6 **a** Postoperatively one-month clinical control of a patient from test group. **b** Six months after surgery, clinical control of a patient from test group

Results

This study comprised 28 elderly patients; all of the selected patients were women (65–81 years old) and were being treated with oral BPs for osteoporosis. The study was completed with 14 patients (13 patients with alendronate, 1 patient with risedronate) aged between 65 and 81 years (mean age 73.57 ± 5.1) in CGF group and 14 patients (12 patients with alendronate, 2 patient with risedronate) aged between 65 and 81 years (73.64 ± 5.49) in the control group (Fig. 7). The study groups were similar in mean ages ($p > 0.05$) (Table 1). The patients' medication use timings, ONJ classifications, BP treatment status, locations of necrotic bone, and promoting factor distributions were similar in the CGF and control groups ($p > 0.05$) (Table 1). In addition to osteoporosis, in the CGF group ($n = 14$), one patient underwent corticosteroid treatment due to an underlying autoimmune disease; two patients had diabetes mellitus; and four patients had hypertension. In the control group, only one patient had additional comorbidities, both diabetes mellitus and hypertension. There was found no significant difference in both groups on comparison of comorbidities ($p > 0.05$) (Table 1).

No significant difference was found when we compared post-op healing data between CGF and control groups at 2 weeks and 1, 2, 3, 4, 5, and 6 months ($p > 0.05$). In univariate logistic regression analyses, healing at 6 months was about 2.75 times more observed in CGF group than the control group, but also this association is not statistically

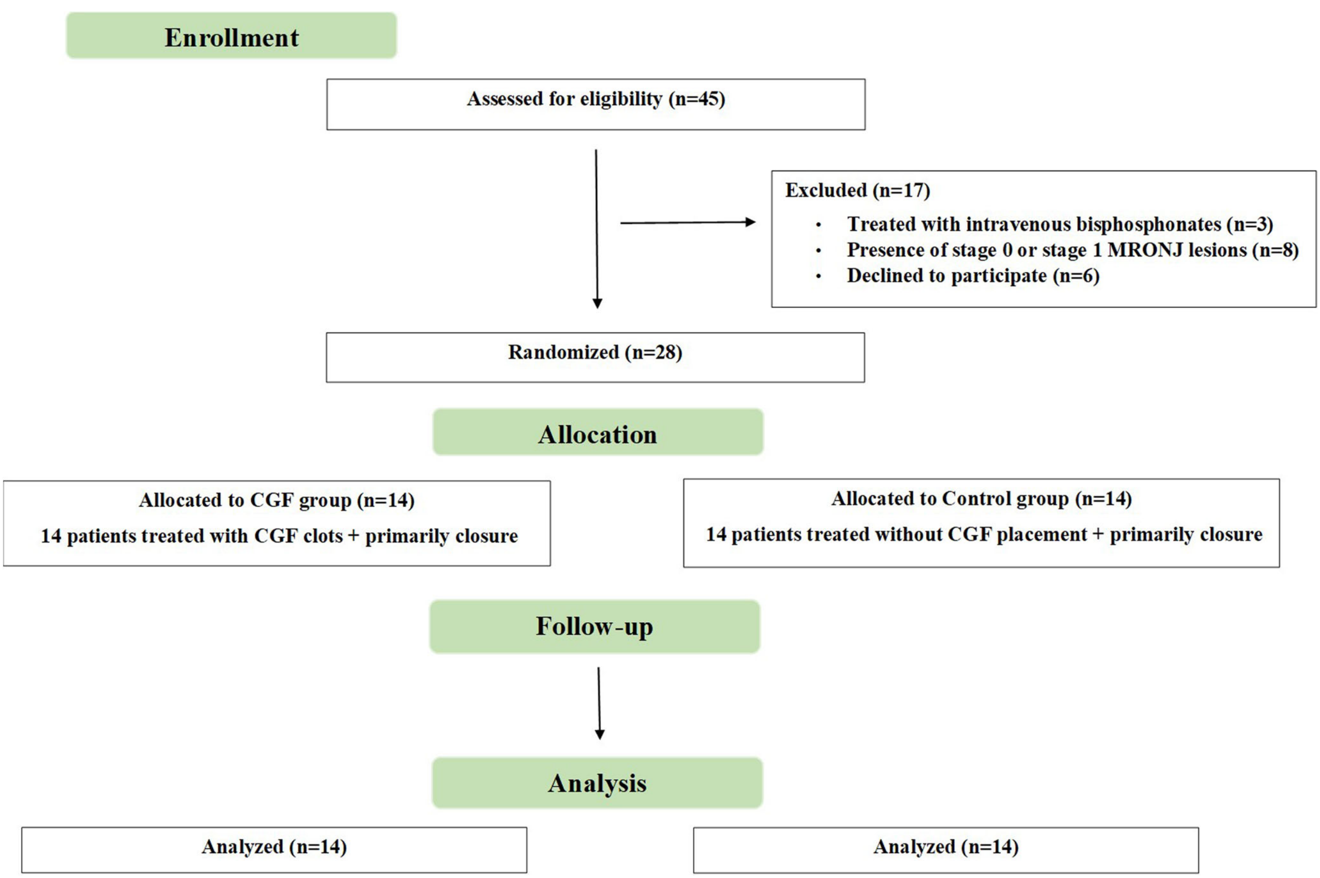

Fig. 7 A CONSORT flow diagram

Table 1 Demographic findings in the study groups

Analyzed anamnestic and therapeutic data	CGF group *N* (%) (*n* = 14)	Control group *N* (%) (*n* = 14)	Statistical probe	Value	df	*p* value
Age (mean ± SD)	73.57 ± 5.1	73.64 ± 5.49	Independent sample *t* test	− 0.036	26	0.972
Type of BPs						
Alendronate	13 (92.9)	12 (85.7)	Pearson chi-square	0.373	1	0.541
Risedronate	1 (7.1)	2 (14.3)				
Medication use timing (year) (mean ± SD)	9.07 ± 2.20	8.86 ± 1.96	Independent sample *t* test	0.272	26	0.787
Comorbidities						
No comorbidities	7 (50.0)	7 (50.0)	Pearson chi-square	2.000	4	0.736
Hypertension	4 (28.6)	5 (35.7)				
Diabetes Mellitus	2 (14.3)	3 (21.4)				
Autoimmune Disease	1 (7.1)	0 (0.0)				
ONJ classification						
2	8 (57.1)	7 (50.0)	Pearson chi-square	0.144	1	0.705
3	6 (42.9)	7 (50.0)				
BP treatment discontinued						
Yes	9 (64.3)	8 (57.1)	Pearson chi-square	0.150	1	0.699
No	5 (35.7)	6 (42.9)				
Location of necrotic bone						
Posterior maxilla	5 (35.7)	4 (28.6)	Pearson chi-square	0.164	1	0.686
Posterior mandibula	9 (64.3)	10 (71.4)				
Promoting factors						
Tooth extraction	7 (50.0)	5 (35.7)	Pearson chi-square	0.676	3	0.879
Periodontal infection	3 (21.4)	4 (28.6)				
İll-fitting dentures	2 (14.3)	3 (21.4)				
Spontaneous	2 (14.3)	2 (14.3)				

All data is presented as actual numbers and percentages in brackets unless otherwise noted

significant (Exp(B): 2.75, 95% CI: 0.52–14.44, $p = 0.232$) (Table 2). In comparison to post-op healing data according to ONJ classification, it was found that more dehiscence (necrotic bone) was observed in 3rd-degree ONJ patients especially at post-op 1, 2, 4, 5, and 6 months ($p < 0.05$). Consistent with this significant difference, ONJ classification showed statistically significant association with post-op 6-month healing in univariate logistic regression. Accordingly, 7.8 times more healing was observed in 2nd-degree ONJ patients than 3rd-degree ONJ patients at post-op 6 months (Exp(B): 7.58, 95% CI: .1.12–48.0, $p = 0.031$) (Table 2). When we compared post-op healing data between BP status, a significant difference between groups was observed at all times ($p < 0.05$). In this process, it was determined that more dehiscence (necrotic bone) and dehiscence (necrotic bone) + infections were observed in patients with ongoing BP treatment. Also, according to univariate logistic regression, there was a statistically significant association between BP status and post-op 6-month healing; 5.6 times more healing was found in BP treatment discontinued patients than patients with ongoing BP treatment (Exp(B): 5.6, 95% CI: 1.0–31.32, $p = 0.049$) (Table 2). When the post-op healing data of different treated areas were compared, no difference was found between the posterior maxilla and mandibula at all times ($p > 0.05$).

Tooth extraction in twelve (seven in CGF group, five in control group), ill-fitting dentures in seven (three in CGF group, four in control group), and periodontal infection in five (two in CGF group, three in control group) of the patients were the promoting factors for MRONJ development, whereas MRONJ occurred spontaneously in four patients (two in CGF group, two in control group). When we compared post-op healing data between the promoting factors, no significant difference was found between the groups at 2 week and 1-, 2-, 3-, 4-, 5-, and 6-month data ($p > 0.05$). In univariate logistic regression analyses, age, medication use timing, promoting factors, comorbidities, location of necrotic bone, and type of BPs showed no statistically significant associations with post-op 6-month healing ($p > 0.05$) (Table 2). Multiple logistic regression analysis was applied to variables with p value ≤ 0.1 in univariate logistic regression (medication use timing, comorbidities, ONJ classification, and BP status). There was no statistically significant difference association between the selected variables and post-op 6-month healing ($p > 0.05$) (Table 2).

Table 2 Univariate logistic analysis of variables associated with post-op 6-month healing and multiple logistic regression analysis of variables with p value ≤ 0.1 in univariate logistic regression

				Univariate logistic analysis		Multiple logistic analysis	
Patient characteristics	*N* (%) ($n = 28$)	Healed *N* (%)	Not healed *N* (%)	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Age	28 (100)	19 (67.9)	9 (32.1)	(0.75–1.05)	0.177		
Groups							
CGF	14 (50)	11 (78.6)	3 (21.4)	2.75 (0.52–14.44)	0.232		
Control	14 (50)	8 (57.1)	6 (42.9)	1.0			
Comorbidities							
No	14 (50)	11 (78.6)	3 (21.4)	4.8 (0.78–29.6)	0.090	3.92 (0.47–32.95)	0.208
Yes	14 (50)	8 (57.1)	6 (62.9)	1.0		1.0	
ONJ classification							
2	15 (53.6)	13 (86.7)	2 (13.3)	7.58 (1.12–48)	0.031	2.82 (0.31–25.36)	0.354
3	13 (46.4)	6	7	1.0		1.0	
BP treatment discontinued							
Yes	17 (60.7)	14 (82.4)	3 (17.6)	5.6 (1.0–31.32)	0.049	2.72 (0.34–22.02)	0.346
No	11 (39.3)	5 (45.5)	6 (54.5)	1.0		1.0	
Location of necrotic bone							
Posterior maxilla	9 (32.14)	8 (88.9)	1 (11.1)	5.82 (0.60–56.29)	0.128		
Posterior mandibula	19 (67.86)	11 (57.9)	8 (42.1)	1.0			
Promoting factors							
Tooth extraction	12 (42.86)	5 (41.7)	7 (58.3)	1.0	0.463		
Periodontal infection	7 (25)	7 (100)	0 (0)	N/A	N/A		
İll-fitting dentures	5 (17.86)	4 (80)	1 (20)	5.60 (0.472–66.4)	0.172		
Spontaneous	4 (14.28)	3 (75)	1(25)	4.20 (0.33–53.12)	0.268		
Medication use timing	28 (100)	19 (67.9)	9 (32.1)	(0.39–1.05)	0.077	0.69 (0.41–1.17)	0.167

N/A not applicable

In comparison to different ONJ degree's post-op healing status between CGF and control groups, it was found no significant difference at all times ($p > 0.05$). When we compared post-op healing status according to the presence of comorbidity between CGF and control groups, there was no difference in both groups ($p > 0.05$). Also, it was found no difference between CGF and control groups in comparison of post-op healing status according to BP treatment status ($p > 0.05$).

Eleven of the 14 MRONJ sites healed uneventfully in the CGF group, without flap dehiscence or infection. Bone exposure without infection was detected in three of the MRONJ sites, one of them at 14 days postoperatively, one of them at post-op 1 month, and the other one at post-op 3 months. One of these patients was under corticosteroid therapy, and two of them had diabetes mellitus. These three patients underwent routine dental check-ups every month, and daily irrigation with 0.12% chlorhexidine was recommended. One of these sites in which bone exposure was detected at post-op 14 days had a recurrent infection 3 months postoperatively. Penicillin-based antibiotic treatment and disinfectant mouthwash were prescribed for this patient. Six of the MRONJ sites healed uneventfully in the control group, and two of them at post-op 14 days and one of them at post-op 3 months showed a recurrent infection. Five of these patients had diabetes mellitus and/or hypertension, and the remaining tone had no additional disease. Similarly, the remaining six patients underwent routine dental check-ups every month, and daily irrigation with 0.12% chlorhexidine and penicillin-based antibiotic treatment was recommended for the patients with infection.

Discussion

Our objective was to evaluate the effect of CGF in the surgical treatment of MRONJ in patients with osteoporosis. We hypothesized that the local application of CGF in MRONJ patients at the surgical site could improve tissue regeneration and accelerate healing. According to the results revealed from the study, the use of CGF has a possible benefit in the surgical site for wound healing and repair. However, there was no statistically significant difference in post-op healing data between groups during healing periods ($p > 0.05$), and our hypothesis was not accepted. Considering the less recurrence rate in the CGF group, the small sample size for the present study may be regarded as a limitation; therefore, further studies are needed to generalize the findings.

The use of antiresorptive and antiangiogenic therapies is increasing with the increase in the number of patients with cancer and osteoporosis. These medications save the life of patients with osteoporosis by preventing hip fractures and that of patients with cancer by preventing bone metastases and stabilizing their skeleton [20]. Consequently, they reduce the symptoms and complications of bone diseases. Besides these positive effects, these therapies have anti-angiogenic effects, and this affects bones with high vascularity, such as jaw bones. However, these therapies affect not only the jaws but also the entire skeleton, with low levels of osteoclastic activity and bone remodeling getting evident [3, 20]. MRONJ is as an adverse effect of antiresorptive and antiangiogenic therapy that has a severe impact on the quality of life of the affected patients. Studies have shown that longer therapy with these drugs increases the incidence of developing MRONJ [21]. In accordance with the literature, all patients included in our study had a history of long-term oral BP therapy.

According to the literature, the incidence of MRONJ is greater in patients receiving intravenous BPs than in those receiving oral BPs [5]. Mavrokokki et al. reported this difference as 0.01–0.04% in patients receiving oral BPs and 0.88–1.15% in patients receiving intravenous BPs [22]. The risk is greater in patients with cancer receiving intravenous BPs; moreover, the risk increases 50–100 times in patients treated with zoledronic acid [23]. Alendronate was reported as the most commonly prescribed oral BP for osteoporosis, and at the same time, it is the most frequently related oral BP associated with the development of MRONJ [24]. In agreement with the other studies, in the present study, 25 of the patients were receiving alendronate for the treatment and prevention of osteoporosis.

Removable dentures exerting inadvertent pressure, dentoalveolar surgery, and periodontitis are the most common promoting factors that lead to MRONJ development [20, 25]. Twelve of the patients had a history of tooth extraction, seven had a history of periodontal infection, and five had an old removable denture. Additionally, some medications and diseases could be also a risk factor such as corticosteroid therapy and diabetes mellitus [1, 6]. Our findings support the published data; the patient who was under corticosteroid therapy and the three patients who had diabetes mellitus had insufficient wound healing, and recurrence occurred in these cases.

Because of the large number of cases of osteoporosis and breast cancer, MRONJ was found to be more common in women [23]. This therapy can effectively control bone resorption; therefore, the incidence of patients receiving BPs is increasing, particularly in women with osteoporosis. As a nature of osteoporosis, the disease is more prevalent in elderly postmenopausal women with an age of 65 and more [5, 23, 25]. In accordance with the literature, in the present study, all patients were female and were under oral BP therapy for osteoporosis with the following mean age: in CGF group, 73.57±5.1, and in control group, 73.64±5.49.

Because there is no universally accepted treatment protocol for managing MRONJ, different approaches have been proposed and are still being researched [1, 25]. All therapeutic protocols for managing MRONJ aim at eliminating pain and preventing the progression of bone infection and necrosis [3]. In the short term, the conservative approach, which includes penicillin-based systemic antibiotics and disinfectant mouthwashes, has many benefits. The response to surgical therapy has a risk of worsening bone exposure [1, 25]. The surgical approach includes bone debridement, sequestrectomy, or resection. Some of the reports highlight that all the margins surrounding the MRONJ area are affected when BPs are administered systemically [26]. For this reason, these affected areas should be resected until a margin of "normally bleeding" bone is obtained. Radical intervention is only recommended in patients with stage 3 MRONJ, i.e., when there is a large MRONJ area affecting the inferior border of the mandible or floor of the sinus, with extra-oral fistula and with or without a pathological jaw fracture [1, 25, 27]. In the present study, we only performed surgery with minimal disturbance to the surrounding soft tissues by removing the necrotic bone and sharp edges of the MRONJ area in combination with the local application of growth factors using CGF in the CGF group. Similar to the conservative approach, penicillin-based antibiotics and mouthwashes were prescribed.

Local application of autologous platelet concentrations (APC), such as PRP and PRF, has been used as a combination with surgical therapy for the treatment of MRONJ, and many studies report successful results [1, 7, 10]. Furthermore, previous studies have reported on the analgesic and anti-inflammatory actions of APC [28]. The pH value of APC clots seems to be unfavorable for bacterial growth [4]. Recent studies have reported on their antimicrobial effect, which protects the soft and hard tissues from infection in the early postoperative period [4, 22, 29]. PRP, the first-generation APC, contains multiple growth factors and has various clinical applications. These growth factors promote angiogenesis, facilitate remodeling, and aid in epithelialization [30]. PRF, the second-generation APC, provides a matrix that contains a high concentration of growth factors and leukocytes that have an important role in stimulating oral mucosal wound healing [30]. PRF contains more growth factors, i.e., seven times higher, than PRP. In their study, Mozzati et al. performed tooth extraction in patients under zoledronic acid therapy, and the incidence of MRONJ was found to be lower after tooth extraction with APC than after tooth extraction without APC [31]. In their case series, Coviella et al. treated four patients with MRONJ by standard surgical debridement and applied PRP in three of them and observed clinical improvement in the PRP group [32]. In agreement with these results, Longo et al. compared the surgical approaches with and without PRP to promote MRONJ healing and achieved a successful outcome in patients treated with PRP [33]. Similarly, Kim et al. used PRF for treating MRONJ, with a 77% complete resolution success [34]. As contrary to the above studies, which used PRP and PRF as a treatment approach, the local application of CGF was researched following the surgical treatment of MRONJ, in this present study.

CGF is the latest generation of APC, developed by Sacco in 2006. CGF is a safe, biocompatible, and easy-to-handle product. This product can be used alone or in combination with biomaterials; therefore, it has been widely studied for use during oral implantation and cyst treatments, at extraction sites, and for promoting fracture healing [35, 36]. Several beneficial effects of CGF have been reported, such as mimicking and supporting the physiologic wound healing and tissue reparative process [11, 35–41].

Compared to the biological properties among the CGF, PRP, and PRF, the fibrin matrix of CGF is larger, denser, and richer in growth factors and provokes no immune reaction [37]. This fibrin matrix has a high cohesion because of the agglutination of fibrinogen and factor XIII which prevents plasmin degradation [38], resulting in its higher tensile strength and stability [39, 40]. This particular form facilitates the use of CGF in clinical practice [11, 41, 42]. Moreover, the APCs show differences in their ability to release growth factors. PRP releases more than 95% of presynthesized growth factors in the first hour [43]. PRF continued to release these growth factors during at least 1 week [44]. Unlike, CGF is slowly dissolved and this fibrin matrix could release growth factors up to 13 days [45, 46]. In addition, growth factors are diffused homogenously in the plasma protein layers of CGF; thus, this APC is superior in terms of growth factor retention and release [47]. The growth factors have a significant role to improve the clinical results with control of the process of wound healing [45]. Therefore, these findings suggested that the application of CGF might be more effective to enhance tissue formation in the treatment of MRONJ. Based on these considerations, in the present study, we aimed to investigate the positive effects of the growth factors delivered by CGF on the healing process of patients with MRONJ by clinical examination. A group of 28 patients was surgically treated for MRONJ, and complete healing was observed in 11 patients in the CGF group and 8 patients in the control group. As a limitation of this study, the sample size was small; however, the results of the present study showed that CGF is effective in improving hard and soft tissue healing when combined with surgical therapy for MRONJ. More histological, radiological, and clinical studies are needed with larger sample size and longer follow-up to determine the effects of CGF in the tissue healing process in surgical treatment for MRONJ.

Denosumab, as an antiresorptive medication, acts a role in bone remodeling through inhibit differentiation and function of osteoclasts. Like the patients who are receiving BPs, several cases of denosumab-related ONJ have been reported in the literature [48–50]. Considering the mechanism of these medications, BPs incorporate into the bone mineral matrix and remain united to the bone for years [50]. In contrast to BPs, denosumab has a different mechanism of action, as it does not bind to hydroxyapatite [51]; therefore, the terminal half-life of this medication is approximately 4 to 6 weeks following interruption protocols [48]. According to literature, after the use of denosumab, the bone could be metabolized again [6, 48]. Therefore, some authors stated that surgical treatment of the patients, who received denosumab, might result in more predictable outcomes with a reversible effect on bone mineral density [52, 53]. The results of this present study revealed that CGF combined surgical management of MRONJ appears to be an effective method for tissue formation, while the differences between the groups were not significant. Despite a negative influence of co-medications that have been known [6, 48, 49], the study focused on the patients who had received BPs for the treatment of osteoporosis. This limited the generalization of the study outcomes. Therefore, future research on the application of CGF seems to be necessary to improve the outcome of surgical therapy of MRONJ in patients treated with other antiresorptive medications.

A specific treatment protocol for managing MRONJ is still controversial, and its etiopathogenic mechanism remains unclear. Optimizing dental health is the main directive when managing patients who will receive antiresorptive and antiangiogenic therapy [54]. Any cause of potential infection, including preventive tooth extraction or any other oral surgical procedure, must be identified and treated to reduce the risk of MRONJ [28]. All patients should have their oral condition checked carefully by a dental specialist and should undergo preventive dental treatment before the initiation of antiresorptive and antiangiogenic therapy. If possible, the initiation should be delayed until optimum dental health is achieved [25]. Patients must be informed about the side effects of antiresorptive and antiangiogenic therapy, and while receiving this medication, they must maintain optimal dental health [20, 25]. After starting these medications, routine dental check-ups should be advised to detect any possible signs of MRONJ.

In conclusion, within the limitations of this present study, our results showed that the local application of CGF has a promising success rate for the surgical treatment of MRONJ in osteoporosis patients. The use of CGF as a combination of surgical therapy appears to be an effective approach to improve tissue healing. However, further investigation is needed with a larger population to assess more accurate results.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (15-12.1/10) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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