ORIGINAL ARTICLE

EFFECTIVENESS OF LEUKOCYTE- AND PLATELET-RICH FIBRIN IN THE TREATMENT OF STAGE 2 AND STAGE 3 MEDICATION-RELATED OSTEONECROSIS OF THE JAW IN GERIATRIC PATIENTS: A RETROSPECTIVE STUDY

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Abstract

Introduction: Medication-related osteonecrosis of the jaw is a challenging complication associated with the use of anti-resorptive and anti-angiogenic medications, often impairing bone healing and quality of life. Recent regenerative approaches, such as leukocyte- and platelet-rich fibrin, have attracted interest because of their potential to improve treatment outcomes by supporting angiogenesis, soft tissue healing, and bone regeneration. The aim of this study was to evaluate the effectiveness of leukocyte-and platelet-rich fibrin in promoting healing in patients with stage 2 and 3 osteonecrosis.

Materials and Method: This retrospective clinical study included 21 patients (8 males, 13 females; mean age: 66.9 years) diagnosed with stage 2 or 3 osteonecrosis and treated at a single-center oral and maxillofacial surgery clinic. Patients were grouped on the basis of the application of platelet-rich fibrin during surgery. Clinical healing was assessed postoperatively and classified as primarily healed or primarily not healed.

Results: In the platelet-rich fibrin group (n = 9), 88.9% of patients achieved primary healing, whereas 66.7% of patients in the non- platelet-rich fibrin group achieved primary healing (n = 12) (p = 0.338). Healing was achieved in 100% of stage 2 patients and 83.3% of stage 3 patients treated with platelet-rich fibrin. Drug type, usage duration, and etiology were not significantly associated with healing outcomes.

Conclusion: Platelet-rich fibrin tended to improve postoperative healing in osteonecrosis patients, especially in stage 2 patients, but the difference was not statistically significant. These findings support the potential use of platelet-rich fibrin as an adjunctive treatment and highlight the need for further studies with larger sample sizes.

Keywords: Platelet-Rich Fibrin; Bisphosphonate-Associated Osteonecrosis of the Jaw; Denosumab; Geriatrics.

INTRODUCTION

Osteonecrosis of the jaw associated with the use of bisphosphonate drugs was first reported by Marx in 2003 and was initially termed bisphosphonate-related osteonecrosis of the jaw (BRONJ) (1). In addition to bisphosphonates, other anti-resorptive drugs, such as denosumab and anti-angiogenic drugs, affect bone mechanisms in ways similar to those of BRONJ (2,3). Consequently, in 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) recommended changing the terminology from BRONJ to medication-related osteonecrosis of the jaw (MRONJ) to encompass all drugs implicated in the condition (4).

Tooth extraction is recognized as the most common predisposing factor in the development of MRONJ, accounting for approximately 45–61% of cases (5,6). Additional dental risk factors include implants, periodontal and periapical disorders, removable prostheses, and intraoral trauma. Interestingly, spontaneously occurring MRONJ constitutes the second most frequently reported category in the literature, with prevalence estimates ranging from 17% to 70% (7,8). The AAOMS and the American Society for Bone and Mineral Research recommend conservative management approaches for MRONJ. These include the use of antibiotics, oral antimicrobial mouthwash, and minimal lesion debridement when necessary (9). However, surgical debridement remains a controversial treatment option (10,11).

Leukocyte-and platelet-rich fibrin (L-PRF) was introduced as a biocompatible material that facilitates sustained release of growth factors, accelerates healing, and minimizes risks of contamination, edema, and postoperative pain. Surgically, L-PRF aids in achieving hemostasis in the surgical field, promotes primary wound healing, and supports the remodeling of both soft and hard tissues (12). Leukocytes within L-PRF contribute to its anti-infective properties, immune regulation, and production of VEGF. Despite these biological advantages, research on the application of L-PRF in MRONJ treatment is limited (10).

In this context, our study retrospectively evaluated the outcomes of L-PRF combined with surgical intervention for the treatment of stage 2 and stage 3 MRONJ cases managed at the oral and maxillofacial surgery clinic.

MATERIALS AND METHOD

Study design/sample

This retrospective study analyzed the records of 24 patients who were diagnosed with MRONJ and admitted to the Oral and Maxillofacial Surgery Clinic. The study received approval from the Medical Research Ethics Committee (IRB 23-9.1T/54). Additionally, the study was conducted in accordance with the Declaration of Helsinki.

Patients who had used anti-resorptive drugs, developed stage 2 or stage 3 MRONJ, had the entire treatment procedure completed by the same investigator adhering to the MRONJ treatment protocols established by the AAOMS, and had complete treatment and follow-up documentation were included in the study. Exclusion criteria included patients who underwent radiotherapy to the head and neck region and patients who had previously undergone surgery in the same region. On the basis of these criteria, the records of 24 patients were reviewed. However, three files were excluded from the study because of incomplete clinical follow-up data.

One-year routine clinical control data, demographic information, and perioperative details of the patients were retrospectively reviewed and recorded. Among the 21 patients classified as having stage 2 or stage 3 MRONJ, data from 9 patients who underwent L-PRF following surgery and 12 patients who did not receive L-PRF were analyzed. Postoperative follow-up data, obtained from clinical records, were used to evaluate soft tissue healing and signs of infection.



Variables

In this study, the independent variable was the application of L-PRF during the surgical treatment of MRONJ. The dependent variable was postoperative healing, which was evaluated through clinical follow-up. The healing status was determined on the basis of observational findings during clinical control, and patients were classified as "primary healed" or "primary not healed" according to these criteria. To evaluate the factors influencing healing, patient and clinical characteristics such as age, gender, MRONJ stage, drug type, therapy duration, etiology, and lesion location were analyzed. These variables were extracted and categorized from clinical data in line with the study's retrospective design.

Surgical Management

Prior to surgery, the necessary consultations were conducted with the physician who had prescribed the anti-resorptive or anti-angiogenic medication (e.g., the oncology or endocrinology department, depending on the underlying indication). Surgical intervention was performed only for patients whose blood test results (complete blood count, PTH, Ca^{+2}, vitamin D, HbA1C, sedimentation) were within normal limits, whose consultations indicated no contraindications for surgery, and where no infection was present at the operation site. For patients showing signs of infection at the surgical site prior to the procedure, a regimen including amoxicillin, NSAIDs, antimicrobial mouthwash, and diluted hydrogen peroxide mouthwash was prescribed. Surgical treatment was carried out once the signs of infection resolved.

Under local anesthesia, following the elevation of the mucoperiosteal flap, the sequestrum was removed, the site was curetted using high-speed surgical rotary instruments, and sharp bony edges were smoothed. The area was irrigated with saline. L-PRF, prepared by centrifuging the patient's venous blood (12 min at 2700 rpm using the EBA 200®, Hettich, Tuttlingen, Germany), was shaped into a membrane and placed at the surgical site. The wound was then closed with primary closure (Figure 1 and Figure 2). Resected tissues were sent for pathological examination. Patients were given

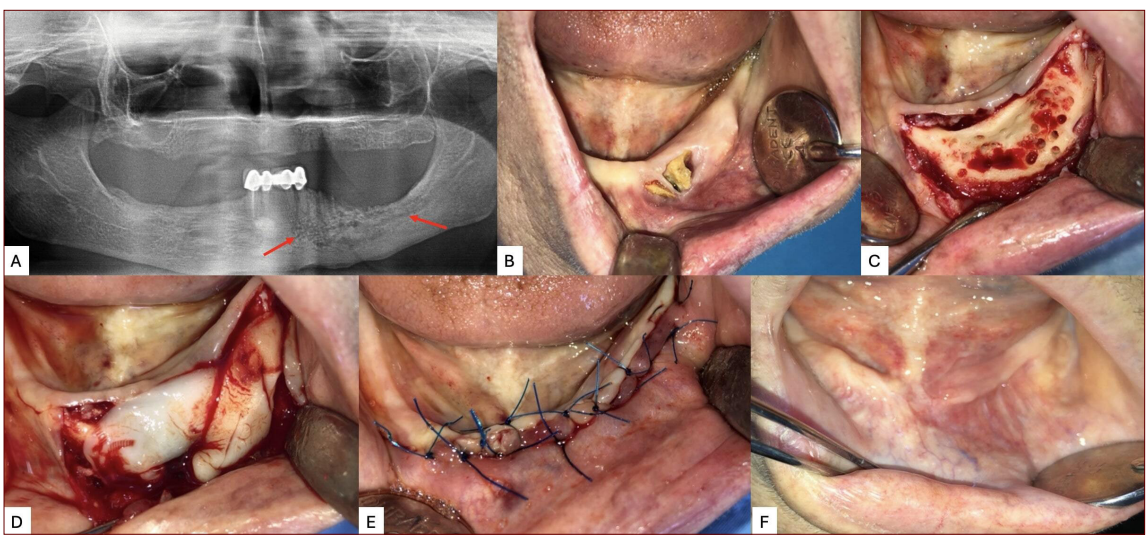


Figure 1. Presentation of a stage 2 MRONJ case. A) Radiographic appearance of necrotic bone in the left mandibular posterior region (indicated by the red arrow), B) clinical intraoral view showing osteonecrosis, C) appearance following sequestrectomy and perforations made in healthy bone, D) application of L-PRF obtained from the patient to the surgical site, E) tension-free primary closure of the area using 4/0 polypropylene sutures, and F) successful healing observed at the surgical site during the 2nd postoperative week.

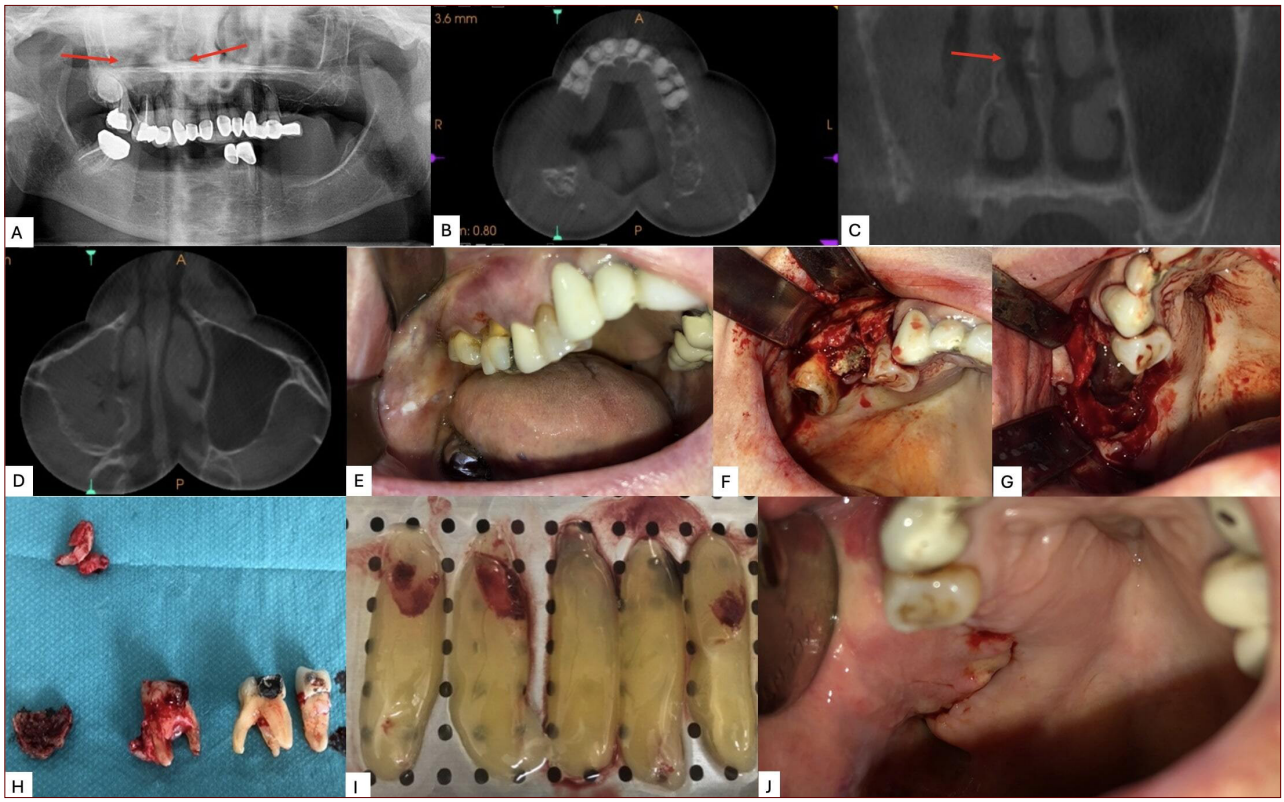


Figure 2. Radiological findings and surgical treatment of a stage 3 MRONJ patient. A) OPG image showing the necrotic area in the right maxillary posterior region (indicated by the red arrows), B) CBCT axial analysis revealing perforation in the palatal bone (indicated by red arrow), C) frontal section showing perforation in the right nasal lateral wall (indicated by red arrow), D) the right maxillary sinus observed as radiopaque, E) preoperative intraoral condition, F) necrotic bone exposed following the extraction of teeth 15 and 16 in the affected region, G) view of the maxillary sinus after sequestrectomy, H) necrotic bone removed along with extracted teeth 15, 16, and 17, I) L-PRF obtained from the patient, and J) intraoral view of the surgical site after suture removal on postoperative Day 10.

postoperative instructions and advised to attend regular follow-up appointments. Sutures were removed after one week, and wound healing was evaluated. Healing outcomes were assessed using clinical follow-up notes recorded by the treating physician. All extracted data were entered into a structured table for analysis.

Data Analysis

Data analysis was performed using SPSS 25.0 (IBM Corp., Armonk, NY, USA). The results of the Kolmogorov–Smirnov test indicated that the data did not follow a normal distribution ($p>0.05$). Therefore, the Mann–Whitney U test was applied to compare quantitative data between groups, whereas the chi-square test of independence was used to analyze categorical data ($\alpha=.05$). Owing to the limited sample size and the small expected cell counts, exact significance values were computed for all categorical comparisons. Test statistics are reported together with their corresponding p values (χ^2 and degrees of freedom for categorical analyses; the Mann–Whitney U and standardized test statistic Z for quantitative comparisons).

RESULTS

In this study, data from 21 patients, including 8 males (38.1%) and 13 females (61.9%), were



Table 1. Demographic and clinical characteristics and postoperative healing outcomes of the 21 patients included in the analysis. Three of the 24 reviewed patients were excluded owing to incomplete follow-up data.

Patient No	Age/ Gender	Disease	Drug	Drug Usage Duration	Preop Drug-Free Period	Etiology	MRONJ Stage	L-PRF	Post-Op Evaluation
1	75/F	Osteoporosis	Bonviva	1 Year	1 Year	Implant placement	2	No	Primary Not Healed
2	75/F	Breast CA/ Metastasis	Zometa	2 Years	1 Year	Spontaneously	3	Yes	Primary Healed
3	75/M	Prostate CA	Zometa	5 Years	6 Months	Spontaneously	2	No	Primary Healed
4	46/F	Breast CA	Zometa	2 Years	4 Months	Spontaneously	3	No	Primary Healed
5	70/M	Prostate CA	Zometa	2 Years	1 Year	Tooth Extraction	2	No	Primary Healed
6	65/M	Prostate CA/ Metastasis	Zometa	1 Year	1 Year	Tooth Extraction	3	Yes	Primary Healed
7	62/M	Prostate CA	Zometa	2 Years	4 Months	Spontaneously	2	No	Primary Not Healed
8	57/F	Cervix CA/ Metastasis	Zometa	1 Year	4 Months	Spontaneously	3	No	Primary Healed
9	66/F	Osteoporosis	Fosamax	4 Years	3 Months	Tooth Extraction	2	No	Primary Healed
10	72/M	Prostate CA/ Metastasis	Zometa	5 Years	6 Months	Spontaneously	3	No	Primary Healed
11	73/M	Prostate CA	Zometa	2 Years	2 Years	Tooth Extraction	3	No	Primary Healed
12	65/F	Breast CA/ Metastasis	Zometa	1 Year	1 Year	Spontaneously	2	No	Primary Healed
13	69/F	Breast CA	Zometa	2 Years	1 Year	Spontaneously	2	No	Primary Not Healed
14	73/F	Breast CA/ Metastasis	Denosumab	3 Years	2 Years	Spontaneously	3	Yes	Primary Healed
15	62/F	Breast CA/ Metastasis	Zometa	4 Years	1 Year	Spontaneously	2	Yes	Primary Healed
16	62/F	Breast CA/ Metastasis	Zometa	4 Years	1 Year	Spontaneously	3	Yes	Primary Healed
17	52/F	Breast CA	Zometa	2 Years	1 Year	Tooth Extraction	3	Yes	Primary Healed
18	84/F	Osteoporosis	Fosamax	10+ Years	Continues to Use Medication	Spontaneously	2	Yes	Primary Healed
19	63/M	Prostate CA	Zometa	3 Years	1 Year	Spontaneously	3	No	Primary Not Healed
20	59/F	Breast CA	Zometa	3 Years	4 Months	Tooth Extraction	3	Yes	Primary Not Healed
21	83/M	Prostate CA/ Metastasis	Zometa	3 Years	3 Months	Spontaneously	2	Yes	Primary Healed

F: Female. M: Male

Table 2. Distribution of patients according to MRONJ stage and L-PRF application

MRONJ Stage	L-PRF (+)	L-PRF (-)	Total
Stage 2	3 (14.3%)	7 (33.3%)	10 (47.6%)
Stage 3	6 (28.6%)	5 (23.8%)	11 (52.4%)
Total	9 (42.9%)	12 (57.1%)	21 (100%)

evaluated. The patients' ages ranged from 46 to 84 years, with a mean age of 66.9 years (standard deviation [SD]=9.65). Detailed patient information is summarized in Table 1. Among the patients who received L-PRF, 6 were classified as stage 3 and 3 as stage 2, whereas among those who did not receive L-PRF, 5 were classified as stage 3 and 7 as stage 2 (Table 2).

Although the gender distribution among patients who underwent L-PRF was not significantly different ($\chi^2 = 1.68$, df = 1, p = 0.367), the majority of patients were female (2 males/7 females). Similarly, the relationship between age and L-PRF application, in patients aged between 46 and 84 years, was not statistically significant (U = 47.0, Z = −0.50, p = 0.651).

The distribution of L-PRF application in the maxilla and mandible was also examined. L-PRF was applied to 60% of patients who developed MRONJ in the maxilla, whereas it was used in 23.1% of patients with MRONJ in the mandible. Additionally, L-PRF was applied to all three patients who developed MRONJ in both the maxilla and the mandible. Statistical analysis revealed that the distribution of L-PRF according to location (maxilla vs. mandible) was statistically significant ($\chi^2 = 6.68$, df = 2, p = 0.026). L-PRF was applied significantly more frequently in the maxilla than in the mandible. However, when evaluating whether the location of MRONJ affected postoperative healing, it was determined that the location did not have a statistically significant effect ($\chi^2 = 1.66$, df = 2, p = 0.499).

When the various etiological factors causing MRONJ were evaluated, it was observed that the condition occurred spontaneously without irritation in 14 patients, following tooth extraction in 6 patients, and after dental implant placement in 1 patient. The analysis revealed no statistically significant effect of these different etiologic factors on healing outcomes ($\chi^2 = 3.41$, df = 2, p = 0.249).

Drug groups associated with MRONJ were also analyzed in this study (Table 1). Postoperative wound healing was not primary in the patient who received ibandronic acid. In the patient treated with denosumab, no adverse healing outcomes were observed. Similarly, both patients on alendronic acid experienced normal healing, whereas 4 of the 17 patients on zoledronic acid did not achieve primary postoperative wound healing. When the influence of these different drugs on postoperative healing was analyzed, the effect was found to be statistically insignificant ($\chi^2 = 4.14$, df = 3, p = 0.462).

The duration of medication use among the MRONJ patients included in the study ranged from 1 year to more than 10 years. When the effects of different durations of drug use on postoperative recovery were evaluated using the Mann–Whitney U test, the results were statistically insignificant (U = 28.0, Z = −1.01, p = 0.310). Additionally, the time interval between the last dose of medication and the date of surgery was examined. It was observed that some patients continued using the medication on the basis of consultation advice, while others discontinued use for varying periods, including 3, 4, 6, 12 or 24 months. The effect of this preoperative medication-free interval on recovery was also not statistically significant (U = 39.5, Z = −0.04, p = 0.965).

The potential differences in postoperative recovery among patients at different stages were also investigated. For this purpose, the healing outcomes of 10 patients in the stage 2 group and 11 patients in the stage 3 group were evaluated. Primary wound healing was not achieved in 3



patients in the stage 2 group and in 2 patients in the stage 3 group, while the remaining patients in both groups experienced uneventful healing. Statistical analysis revealed no significant relationship between postoperative healing outcomes in stage 2 and stage 3 patients ($\chi^2 = 0.40$, df = 1, p = 0.635).

The impact of L-PRF application on postoperative healing was also analyzed. Among 12 patients who did not receive L-PRF, 4 experienced postoperative healing disorders, whereas only 1 patient (11.1%) out of 9 who received L-PRF experienced a similar issue. However, a chi-square test indicated that L-PRF application did not significantly influence postoperative healing outcomes. Thus, the incidence of complications was statistically comparable with or without L-PRF application ($\chi^2 = 1.40$, df = 1, p = 0.338). The effectiveness of L-PRF application across different stages was analyzed. Chi-square analysis revealed that L-PRF application did not result in a statistically significant difference across the stages ($\chi^2 = 1.29$, df = 1, p = 0.387).

The 7 patients in the stage 2 group who did not receive L-PRF had a postoperative healing impairment rate of 42.9%. In contrast, the impairment rate in the stage 3 group without L-PRF, comprising 5 patients, was 20.0%. Among patients who received L-PRF, none in stage 2 group experienced postoperative healing impairment, whereas 1 out of 6 patients (16.7%) in stage 3 developed a healing disorder. A chi-square test was conducted to determine significant differences among the four groups. The analysis revealed no significant differences between the groups ($\chi^2 = 2.546$, df = 3, p = 0.5).

DISCUSSION

Medication-related osteonecrosis of the jaw (MRONJ) is a severe complication of the jawbone associated with the use of anti-resorptive and anti-angiogenic drugs. This condition is particularly prevalent in patients receiving long-term treatment with medications such as bisphosphonates and denosumab.

These studies indicate that MRONJ is more prevalent in women, primarily because of the frequent use of bisphosphonates for osteoporosis treatment. Additionally, researchers have reported that advanced age increases the risk of MRONJ (4,5). The results of our study are consistent with the literature. However, our study revealed no statistically significant difference in MRONJ occurrence between male and female patients. These findings suggest that risk factors for MRONJ extend beyond age and gender and that other factors potentially play a significant role.

Various etiologic factors play significant roles in the development of MRONJ. Studies have suggested that procedures may trigger MRONJ development, but this risk involves a complex interplay of local and systemic factors (3,4,13). In our study, different etiologic factors did not significantly affect postoperative healing (p=0.2). This may be due to the overlapping influence of systemic conditions, medication history, and patient-related variables, making it difficult to isolate the effects of etiologic factors.

The effect of lesion localization on MRONJ treatment outcomes has been a subject of debate in the literature. Some studies have reported that conservative MRONJ treatment at various stages yields similar outcomes for both the mandible and the maxilla (14,15). Conversely, other studies have indicated that mandibular MRONJ cases are more prevalent than maxillary cases and that lesions in the mandible tend to follow a more resistant course (4,7). In our study, however, the analysis revealed no statistically significant difference in postoperative healing based on whether MRONJ was present in the mandible or maxilla (p=0.5). These findings may reflect the relatively small sample size and heterogeneity of cases and support the view that lesion localization alone is not a decisive factor in healing.

Bisphosphonates and denosumab, in particular, impact bone metabolism and significantly increase the risk of osteonecrosis in jawbones (2,4). Although previous findings in the literature (4,8) indicate that zoledronic acid is associated with a higher risk for MRONJ and impaired healing, our study did not find a statistically significant effect of drug type on postoperative recovery (p=0.5). The relationship between drug duration and MRONJ healing has also been widely examined. Several studies have indicated that the development of MRONJ is not solely dependent on the duration of drug use but is also influenced by systemic health, dental condition, and individual variability (4–6,14). Our findings are consistent with this view, as no statistically significant association was found between drug duration and postoperative healing.

The role of temporarily discontinuing drug holiday has also been debated. Although the AAOMS and some studies recommend a three-month drug holiday for high-risk patients, no conclusive evidence supports this practice (2,4). In our study, the duration of drug discontinuation had no significant effect on healing. Our results support the controversial situation of drug holidays.

Several studies have reported favorable outcomes with L-PRF in MRONJ treatment (10,16–21). In a study by Yalcin-Ulker et al., L-PRF combined with surgical debridement led to 80% healing in stage 2 and 3 MRONJ cases, supporting its potential role as an adjunctive treatment (21). Coropciuc et al. used L-PRF along with sequestrectomy in their study, and their results indicated that combining L-PRF with surgery led to complete resolution of the disease, resulting in more effective outcomes than those of sequestrectomy alone (14). On the other hand, in a clinical study published in 2022, the outcomes of surgery alone were compared with those of surgery plus PRF in 52 patients with MRONJ stages 1 and 2. This study revealed no significant advantage of adding PRF to surgery in terms of wound healing, postoperative pain, or quality of life (22). In a randomized controlled clinical trial involving 47 patients with stage 2 and stage 3 MRONJ, one group received only surgical treatment, while the other group received both surgery and PRF. Faster wound healing was observed in the PRF group at 1 month, but at 6 and 12 months, the advantage of PRF was not significant (23).

Furthermore, when systematic reviews by investigators such as Lopez-Jornet (13), Fortunato (24), and Rusilas (25) are evaluated, it is clear that there are studies suggesting that platelet concentrates do not show a significant advantage in MRONJ treatments, as also indicated by our retrospective clinical study.

A further point that warrants discussion is the uneven distribution of disease stage between the two groups. A greater proportion of stage 3 (more advanced) cases received L-PRF (6/9, 66.7%), whereas stage 2 cases predominated in the non-L-PRF group (7/12, 58.3%). This pattern most likely reflects a clinical tendency to add the adjunctive regenerative material in more severe cases, rather than a randomized allocation. Importantly, despite this skew toward more advanced disease, the L-PRF group still achieved a numerically higher primary healing rate. Although this difference did not reach statistical significance, it suggests that the favorable trend in the L-PRF group cannot be attributed to preferential treatment of less severe cases. Conversely, this non-random, indication-driven allocation represents a source of confounding that precludes causal interpretation and reinforces the need for prospective randomized studies.

This study has several limitations. First, its retrospective, single-center design and the relatively small sample size (n = 21) limit statistical power and increase the risk of type II error; this is the most likely explanation for the absence of statistically significant differences despite



the favorable healing trend in the L-PRF group. Second, no a priori sample-size calculation was performed, as the analysis was based on available clinical records. Third, L-PRF allocation was not randomized but determined by clinical judgement, introducing potential confounding by indication. Finally, healing was assessed clinically by the treating surgeon without a standardized or blinded radiographic outcome measure. The principal strengths include a standardized surgical protocol performed by a single experienced operator, which minimized inter-operator variability; complete one-year clinical follow-up of all patients; and a focus on advanced (stage 2 and 3) MRONJ, for which high-quality evidence on adjunctive L-PRF remains scarce.

Conclusion

Considering the limited and variable evidence in the current literature, our study provides additional insight into the potential use of platelet concentrates as a treatment option for MRONJ. While the use of platelet concentrates such as L-PRF has been widely explored in early-stage disease, their role in advanced stages remains unclear. Although a statistically significant difference was not observed, the favorable healing trend in the L-PRF group may indicate clinical relevance. This is important in a clinical context where treatment options for advanced-stage MRONJ remain limited and unpredictable. Well-designed prospective randomized controlled trials with larger sample sizes and longer follow-up periods are needed to better define the role of L-PRF and guide future treatment protocols.

Conflict of Interest: The authors declare that they have no conflict of interest related to this study.

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