Review Article

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Platelet Rich Fibrin (PRF) in the Management of Osteonecrosis of the Jaw: A Narrative Review

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ABSTRACT

Introduction: Osteonecrosis of the jaw (ONJ) refers to a persistent condition of bone death within the maxillofacial region lasting in excess of eight weeks, frequently linked to therapeutic interventions involving radiation and antiresorptive or anti-angiogenic agents. Regulatory guidelines issued by the American Association of Oral and Maxillofacial Surgeons in 2014 omitted endorsement of standard treatment protocols, underscoring the need for comprehensive review and analysis of current research. This narrative synthesis aims to summarize and evaluate existing empirical evidence on the use of platelet-rich fibrin (PRF) in patients diagnosed with ONJ. **Method**: A search of English-language literature on PRF research on osteonecrosis of the jaw (ONJ) was conducted using the PubMed (Medline) database from 2014 to 2023. The search included randomized controlled trials, clinical trials, observational prospective studies, case reports, retrospective studies, cohort studies, and case series, with review articles excluded. The use of PRF for the management of ONJ was covered in twenty research articles. Follow-up periods ranged from one and half months to 79 months. **Result:** The findings from the selected papers indicate a female predominance. The lower jaw showed site prevalence in this review. In summary, the last ten years' worth of research indicates that PRF may be helpful in the treatment of ONJ, with improvement in wound healing, pain, and infection rates documented. None of the papers included any reports of complications associated with PRF treatment. Nevertheless, methodological errors like small sample sizes and a absence of randomized controlled studies now limit the data. **Conclusion:** To develop evidence-based clinical suggestions and ascertain the effectiveness of PRF in the management of ONJ, more study is required.

KEY WORDS: Platelet rich fibrin (PRF), Osteonecrosis of jaw (ONJ), Leukocyte-Platelet Rich Fibrin (L-PRF), Advanced-Platelet Rich Fibrin (A-PRF), Medication-related osteonecrosis of the jaw (MRONJ).

INTRODUCTION

To define osteonecrosis of the jaw (ONJ), it is visible necrotic bone that lasts longer than eight weeks in the maxillofacial area. Numerous etiologies for ONJ have been identified. High-dose of radiation therapy and antiresorptive and anti-angiogenic medications are the most often related to ONJ. [1] It was first defined as osteoradionecrosis (ORN) in 1922 by Regaud. [2] Marx first reported bisphosphonates related to osteonecrosis of the jaw (BRONJ) in 2003. This observation was made by Marx after he noted that patients with osteoporosis or malignancy who had not previously received treatment with radiation to the jaws also had similar lesions and were using bisphosphonates. [3] The American Association of Oral and Maxillofacial Surgeons (AAOMS) published expert panel recommendations on medication-related osteonecrosis of the jaw (MRONJ) in 2014, with numerous recommendations on risk factors and treatment modalities. However, no specific treatment regimen has been defined as a standard of care. [4-8]

The function of platelet-rich fibrin (PRF) in ONJ treatment has been studied recently. [9] Choukroun *et al.* [10] initially reported PRF as a second-generation platelet concentrates in 2000. Compared to conventionally generate platelet-rich plasma (PRP), PRF had two significant advantages. PRF is an entirely autologous product as; first, just a single centrifugation cycle is required for its creation, which saves time and money. Secondly, no bovine thrombin or anticoagulant is used during the coagulation process. PRF's fibrin network gives it a robust yet flexible framework and releases large amounts of growth factors as well as cytokines throughout the course of at least seven days. These traits seem to be the cause of PRF's

favorable healing characteristics. [9-11] PRF subtypes include pure (P-PRF), leukocyte-PRF (L-PRF), injectable (I-PRF), and advanced (A-PRF). L-PRF has higher leukocyte concentration and releases growth factors and matrix proteins slower. While I-PRF can be utilized in liquid or polymerized form, L-PRF and P-PRF are applied as membranes or clots. [9] A-PRF appears to breakdown more quickly and releases significantly less growth factors (TGFβ1, PDGF-AB, and VEGF) than L-PRF. Thus, the final characteristics of the PRF-clot (its dissolution, cell discharge, growth factors, and cytokines) can be adjusted by utilizing various centrifugation techniques. [12]

As of right now, PRF has been extensively utilized for both therapy and prevention in a variety of oral and maxillofacial surgery applications including surgical extraction, periodontal diseases, sinus lifts, socket preservations and ridge augmentations, oro-antral communication and temporomandibular joint (TMJ) disorder. [9, 11] The purpose of this narrative article review was to provide an overview of the data that currently exists on the use of PRF for the management of ONJ patients.

SEARCH STRATEGY

An electronic search of the English-language literature on PRF research on ONJ was conducted in the last ten years using the PubMed (Medline) database, covering the period from January 2014 to December 2023. The author employed the terms "treatment of osteonecrosis of the jaw (ONJ)" and "platelet rich fibrin (PRF)" to search the online archive. Randomized controlled trials (RCTs), controlled clinical trials, observational studies, case reports, retrospective studies, case studies, cohort studies, and case series were among the inclusions. Review articles, conference abstracts, in vitro research, and experimental studies were among the publications that were excluded. When it was not possible to download the entire text of the articles or when there was insufficient data, these were excluded.

RESULTS

Using PubMed (MEDLINE), the first search technique listed 58 research papers. There were 19 papers omitted due to review articles. A total of 23 papers were downloaded and scrutinized. Finally, the specified inclusion and exclusion criteria allowed for the review of 20 papers. [13-32] There were three articles [33–35] excluded because these papers focused on the prevention of ONJ by using PRF. The findings from the selected papers indicate a female predominance. The lower jaw showed site prevalence in this review. Follow-up periods ranged from one and half months to 79 months. The L-PRF was used mostly. The extracted data from the selected papers is shown in Table 1.

DISCUSSION

PRF in the management of ONJ presents a significant clinical challenge, often arising from the long-term use of antiresorptive or anti-angiogenic drugs. Recent literature over the past ten years has increasingly focused on the use of PRF as an adjunctive treatment in the management of ONJ, with studies reporting varying degrees of success. PRF, a second-generation platelet concentrate, has been shown to release growth factors and chemotactic agents that are crucial for tissue repair mechanisms.[9-12, 36] In accordance with the size and extent of the surgical defect that needs to be filled; 10–20 ml of peripheral blood should be drawn for preparing the L-PRF at the irrigation time. After that, a sample of blood is taken into an 8.5-ml tube without anticoagulant, and it is centrifuged for 10 minutes at 3000 rpm properly.[9] This procedure is completed quickly in order to stop the coagulation cascades from starting before centrifugation and to permit the fibrin matrix to naturally change during centrifugation. An L-PRF is collected from the middle portion of the tube following centrifugation. The A-PRF is made in accordance with the Choukroun A-PRF protocol [17]: 40 ml of autologous venous blood sample is to be drawn into 4 glass tubes (10 ml each, without supplements) and centrifuged at 1300 rpm for 8 minutes in a designated centrifuge. Using the proper surgical tweezers, the yellow platelet concentration is extracted from the tube following centrifugation and from the red bottom red blood cell layer. By compressing the concentrate into the special PRF Box surgical kit (Process for PRF, Nice, France), A-PRF membranes are created, which are thin and stable membranes that are simple in shape and stitches. L-PRF has shown promising results in the treatment and prevention of MRONJ through several mechanisms: growth factors are released, tissue healing and bone regeneration are stimulated, and angiogenesis is promoted by L-PRF. [36] As a barrier membrane between the alveolar bone and oral cavity, it serves to provide gingival healing and protect the underlying bone. [36] L-PRF fibrin matrix contains leukocytes and platelets that secrete growth factors thereby promoting angiogenesis, bone regeneration and soft tissue healing. Faster wound closure and re-epithelialization is achieved by this mechanism. [10, 12, 36, 37]

In a single group study, Kim *et al.*[13] applied L-PRF for the BRONJ treatment. Of a total of 34 patients, 77% had complete resolution, 18% had delayed resolution and had residual disease, and 6% were without resolution. The standard techniques of surgical treatment of jaw osteonecrosis was evaluated by Nørholt *et al.*[14] who reported 93% complete mucosal healing, and potential benefits of PRF membranes in successful outcomes. A 5 year follow up case study demonstrated that PRF is efficacious in treating Stage III MRONJ, with complete wound healing occurring within 25 days of treatment post PRF.[22] A case series noted complete healing in all the latter treated with surgical debridement and PRF with no recurrence of bone exposure or infection.[23] Szentpeteri *et al.*[24] found that PRF membrane significantly improved recovery and stage improvement in MRONJ treatment, indicating its role in enhancing healing and immune response mechanisms. A study on 40 patients with MRONJ underwent necrotic bone resection with PRF found a 85% success rate after 12 months, with higher success (94% when all necrotic bone was removed).[28] These results recommend that PRF can be an efficient treatment modality for MRONJ, promoting speedy soft tissue healing and pain control. However, the effectiveness of PRF in the long-term management of MRONJ is less comprehensible. Giudice *et al.* [17] compared the effectiveness of platelet-rich fibrin (PRF) after bone surgery versus surgery alone in treating MRONJ. 47 patients were divided into two groups: PRF group and non-PRF group. Mucosal integrity, infection absence, and pain evaluation results were significantly different between the two groups. PRF application may improve short term quality of life and reduces pain and post operative infections, suggests the study.[17] Another study on PRF in MRONJ surgical treatment found no noteworthy wound healing improvements in 52 patients with stage I-III MRONJ, suggesting future studies for justification. [29] This points out that the PRF may enhance short-term healing, but its long-term benefits need further study.

Table 1: Extracted data from the reviewed papers

Author, (year)	Country	Study design	Study population (M/F)	Age range (Years)	ONJ (M= MRONJ / R=ORN)	Site (UJ/LJ/UJ +LJ)	Type of PRF	Treatment protocol	Complete resolution (%)	No resolution (%)	Follow up
Kim JW, (2014)[13]	Korea	Prospective study	34 (0/34)	71*	M	UJ= 7 LJ=27	L-PRF	Sequestrectomy and PRF treatment	32 (94%)	2 (6%)	6 months
Nørholt SE, (2016)[14]	Denmark	Prospective study	15 (4/11)	54-83	M	UJ=3 LJ=11 UJ+LJ=1	L-PRF	Sequestrectomy and PRF treatment with BFP reconstruction	14 (93%)	1 (7%)	7-20 months
Gönen ZB, (2016[15]	Turkey	Case report	1 (1/0)	77	M	LJ= 1	L-PRF	Sequestrectomy and PRF treatment	1 (100%)	0 (0%)	18 months
Park JH, (2017)[16]	Korea	Prospective study	55 (4/51) G1= 25 (L-PRF) G2= 30 (L=PRF + BMP-2)	G1= 59-97 (75.24) G2= 60-85 (75.2)	M	UJ=16 LJ=37 UJ+LJ=2	L-PRF	G-1= treated with only L-PRF G-2= treated with L=PRF & BMP-2.	G-1= 22 (88%) G-2= 8 (97%)	G-1= 3 (12%) G-2= 1 (3%)	4 months
Giudice A, (2018)[17]	Italy	RCT	47 (23/24) G1= 24 (PRF) G2= 23 (Non-PRF)	74.7*	M	UJ=12 LJ=49	A-PRF	Sequestrectomy and PRF treatment	G-1= 21 (87.5%) G-2= 14 (60.9%)	G-1= 3 (12.5 %) G-2= 9 (39.1%)	12 months
Chen YT, (2019)[18]	Taiwan	Case report	1 (1/0)	53	R	UJ + LJ=1	L-PRF	Primary closure with BAF and BFP in UJ and debridement with PRF in LJ	1 (100%)	0 (0%)	10 months
Esen A, (2109)[19]	Turkey	Retrospective study	7 (1/6)	50-73	M	UJ =7	L-PRF	Sequestrectomy, bone debridement and reconstruction using a BFP and PRF.	7 (100%)	0 (0%)	12-18 months
Valente NA, (2019)[20]	Italy	Retrospective study	15 (6/9)	56-71	M	UJ=6 LJ=9	L-PRF	Sequestrectomy, debridement and PRF treatment	11 (73.33 %)	4 (26.67%)	6-74 months
Şahin O, (2019)[21]	Turkey	Case report	1 (0/1)	63	M	UJ=1	L-PRF	Sequestrectomy and PRF with BPF treatment	1 (100%)	0 (0%)	12 months
Antonelli A, (2020)[22]	Italy	Case report	1 (1/0)	69	M	LJ= 1	A-PRF and I-PRF	Sequestrectomy and PRF treatment	1 (100%)	0 (0%)	60 months
Fernando de Almeida Barros Mourão C, (2020)[23]	Brazil	Case series	11 (2/9)	38-84	M	UJ=4 LJ=7	L-PRF	Sequestrectomy and PRF treatment	11 (100%)	0	12-36 months
Szentpeteri S, (2020)[24]	Hungary	Retrospective study	101 (27/74) G1 (surgery alone)= 73, G2 (surgery with PRF)= 28	G1= 64*, G2= 68*	M	UJ=27 LJ=68 UJ+LJ=6	A-PRF	Sequestrectomy, debridement and PRF treatment	G1= 48 (65.75), G2= 18 (78.26%)	G2= 25 (34.25%), G2= 5 (21.74%)	12 months
Tenore G, (2020)[25]	Italy	Retrospective study	34 (8/26) G1= 13 (L-PRF + PBM G2= 8	58*	M	UJ=14 LJ=20	L-PRF	Sequestrectomy, debridement and PRF with or without PBM treatment	G1=13 (100%), G2= 5 (62.5%), G3= 11	G1= 0 (0%), G2= 3 (37.5%), G3= 2	6 months

			(antibiotic + surgery) G3 = 13 (antibiotic + PBM)						(84.7%)	(15.3%)	
Bouland C, (2021)[26]	Belgium	Case report	2 (0/2)	76-77	M	UJ= 1 LJ=1	L-PRF	Stromal vascular fraction with L-PRF	2 (100%)	0 (0%)	18 months
Özalp Ö, (2021)[27]	Turkey	Retrospective study	13 (6/7)	54-84	M	UJ=2 LJ=11	L-PRF	Marginal resection/sequestrectomy/ curettage and PRF treatment	9 (69%)	4 (31%)	12-79 months
Zelinka J, (2021)[28]	Czech Republic	Prospective study	40 (16/24)	37-85	M	UJ=15 LJ=25	L-PRF	Sequestrectomy and PRF treatment	34 (85%)	6 (15%)	12 months
Blatt S, (2022)[29]	Germany	Prospective observational	52 (25/27)	71.5*	M	NR	A-PRF	Group A (n=22)- Necrotic bone removal Group B (n=30)- Necrotic bone removal with PRF membrane	Group-A, n=12 (60%), Group B, n= 17 (68%)	Group-A, n=8 (40%), Group B, n= 8 (32%)	6 weeks
Parise GK, (2022)[30]	Brazil	Case control study	20 (8/12) G-1= 7 (control) G-2= 8 (prevention with L=PRF) G-3= 5 (treatment with L=PRF)	41-91 (61.9)	M	UJ=9 LJ=11	L-PRF	G-1= extraction without L-PRF G-2= extraction with L-PRF G-3= sequestrectomy/ curettage and PRF treatment	G-1= 5 (57%) G-2= 8 (100%) G-3= 4 (80%)	G-1= 2 (43%) G-2= 0 (0%) G-3= 1 (20%)	6 months
Şahin O, (2022)[31]	Turkey	Retrospective cohort study	21 (7/14)	49-85 (68.04)	M	UJ=8 LJ=13	L-PRF	Sequestrectomy, debridement and PRF treatment	21 (100%)	0 (0%)	9-28 months
Asfour MAR, (2023)[32]	Syria	Case report	1 (0/1)	43	M	UJ=1	A-PRF	Sequestrectomy, debridement and PRF treatment	1 (100%)	0 (0%)	6 months

BAF, Buccal advancement flap; BFP, Buccal fat pad flap; BMP-2, bone morphogenetic protein-2; F, female; G1, group-1; G2, group-2; G3, group-3; M, male; MRONJ, Medication related Osteonecrosis of the Jaw; n, number; NR, not reported; ORN, Osteoradionecrosis; PBM, photobiomodulation; PRF, Platelet Rich Fibrin; UJ, Upper Jaw; LJ, Lower Jaw; L-PRF, Leukocyte-Platelet Rich Fibrin; A-PRF, Advanced-Platelet Rich Fibrin; a only average age available.
*mean age,

Park *et al.*[16] compared the healing outcomes of MRONJ treated with combined BMP-2 and L-PRF and L-PRF alone. Results showed that both treatments led to complete resolution of lesions, significantly better than L-PRF alone. The presence of bacterial colony in the biopsy specimen negatively affected disease resolution. The combined regimen may benefit patients needing antiresorptive therapy.[16] In conjunction with surgical therapy, PRF and PBM provides optimal wound healing and bone regeneration in MRONJ lesions, [25] which supports the potential advantages of combined therapeutic approaches that improve the efficaciousness of PRF in MRONJ treatment. In addition, the literature describes PRF utilizes for other surgical procedures besides MRONJ, including exodontia, where it has been effective in soft tissue healing and bone regeneration. [9,11,37]

There was a single paper[18] that covered the use of PRF in ORN. It was a case report of a 53-year-old man suffering from ORN of both jaws. Debridement of necrotic bone and granulation tissue was followed by PRF treatment of the surgical defect with a buccal fat pad flap and a buccal advancement flap. A subsequent radiographic test conducted ten months after surgery showed that the bone healing was going well.[18] The notion that ORN arises from a radiation-induced fibro-atrophic process, which could be addressed with oral antioxidant therapy, may serve as a framework for understanding the limited research supporting PRF treatment in ORN management.[38, 39] However, due to the scarcity of evidence available, it is not feasible to make assessments regarding the efficacy of PRF in treating ORN.

The use of PRF in the management of ONJ has shown promising results, particularly in the short-term postoperative period. The long-term advantages of PRF are still unclear, despite the data supporting its function in improving tissue healing and lowering pain. To make PRF a common supplementary treatment for ONJ, more studies with bigger sample sizes and longer follow-up times are required. The integration of PRF into treatment protocols could potentially improve

patient outcomes and quality of life for those suffering from this debilitating condition. Further research will require large, high quality RCTs to evaluate efficacy and safety of PRF in different ONJ stages and in a variety of patient populations. The optimal combination therapies involving PRF, including PBM or BMP-2 or antibiotics are also still worth further investigation. Because the evaluation of long term effects of PRF and determining its cost effectiveness relative to other treatment modalities requires longitudinal studies.

SUMMARY

This narrative literature review set out to compile the information that was currently accessible on the use of PRF in the medical management of ONJ patients. We found that the scientific proof regarding the effectiveness of PRF in the treatment of ONJ is inadequate and mostly observational. This review demonstrates that PRF may be a beneficial adjunct in the management of ONJ, particularly when combined with surgical intervention. Studies have shown that PRF can enhance soft tissue healing, reduce postoperative infections, and improve patient quality of life in the short term. The application of PRF, both in solid and liquid forms, has been associated with positive outcomes such as the resolution of oro-cutaneous fistulas and complete wound healing within specific time frames. However, the long-term benefits of PRF application beyond initial follow-up periods appear to be less clear, with some studies reporting no significant differences in outcomes between PRF and non-PRF groups at later stages. In summary, while the use of PRF shows promise in the management of ONJ, particularly in the short-term postoperative period, there is a need for further research to establish its efficacy over longer-term follow-ups. The current evidence suggests that PRF may improve early healing outcomes, but its role in sustained management and prevention of ONJ requires more robust, randomized controlled trials to determine its definitive effectiveness.

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