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Original Research

Management of bisphosphonate related osteonecrosis of the jaw (BRONJ) with platelet rich fibrin (PRF) as an adjunct to surgical therapy

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ABSTRACT:

Introduction: BRONJ is potentially a challenging complication that usually result from the long-term usage of bisphosphonates. Platelet-rich fibrin (PRF) represents a relatively new biotechnology for the stimulation and acceleration of tissue healing and bone regeneration. The aim of this study is to assess the management of bisphosphonate related osteonecrosis of the jaw (BRONJ) with platelet rich fibrin (PRF) as an adjunct to surgical debridement. **Materials and Methodology:** The study was conducted in the Deptt of oral and Maxillofacial surgery, Government Dental College, Srinagar from June 2019 to April 2022. Blood samples were collected from each patient with a 21G needle, in 10-mL glass collection tubes, without the addition of anticoagulants. After its collection, the blood was immediately allowed to be centrifuged, with a force applied of approximately 400g for 12 min, at 2700 rpm. The amount of PRF membranes used was left to the surgeon's decision and it was personalised for each case as needed, depending on the extension of the surgical bone defect. **Results:** After treatment with L-PRF, 28 patients (77%) showed complete resolution, 7 (18%) had delayed resolution, and 2 (6%) did not resolve at all. Both of these two were being managed with bisphosphonates. The results have reportedly showed excellent soft tissue healing, minimised post-operative pain and also improved bone healing after the addition of L-PRF.There was a significant association between the response to treatment and the stage of BRONJ (p=0.002). **Conclusion:** PRF technique is considered as an effective alternative treatment modality that could prove beneficial for the closure of bone exposure and tissue healing associated with BRONJ patients.

Keywords: bisphosphonates, PRF, osteoradionecrosis, BRONJ

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INTRODUCTION

Bisphosphonate-related osteonecrosis of the jaw (BRONJ)was first introduced in the year 2003 which is reportedly a potential adverse effect of bisphosphonates and is expressed as the exposed bone in the oral cavity which has been present more than eight weeks with the earlier history of bisphosphonate administration and no previous radiation therapy to the jaws.[1] Bisphosphonates are the most commonly prescribed anti-resorptive drug for the effective management of those patients affected with osteoporosis, Paget's disease, multiple myeloma, metastatic carcinoma and symptomatic fibrous dysplasia.[2]

Platelet concentrates are second generation autologous products that have high concentrations of several protein growth factors that include platelet-derived growth factor, transforming growth factor - β,vascular endothelial growth factor (VEGF), and endothelial growth factor and all these are secreted by platelets.[3] This platelet-enriched preparation is reported to stimulate and accelerate the healing of tissue and bony regeneration and is being used as an effective adjunct in various research fields.[4,5]Recently, several researches have shown many promising results from the use of platelet-rich plasma for BRONJ,[6] and this has become a popular application for the platelet concentrates.

Over the past decades, other classes of non-BP drugs (mainly antiresorptive or antiangiogenic medications) have been associated to clinical features of bone exposure in the jaws.[7]And from the year 2009, the term BRONJ was swiftly modified to medication-related osteonecrosis of the jaw (MRONJ). The first

stage is the "at risk" category, in which there is no apparent necrotic bone in asymptomatic patients who have been managed with intravenous or oral antiresorptive or antiangiogenic therapy. The last one, the stage 3, with the exposed necrotic bone in patients with pain, infection, results in pathologic fracture, extraoral fistula, oral/ antral-oral/ nasal communication.[8] Hence the aim of this study is to assess the management of bisphosphonate related osteonecrosis of the jaw (BRONJ) with platelet rich fibrin (PRF) as an adjunct to surgical debridement.

MATERIALS AND METHODOLOGY

After obtaining the ethical clearance, the patients who reported to the Department of Oral and Maxillofacial Surgery, Government Dental College, Srinagar within the study period from June 2019 to April 2022,were examined. The inclusion of the participants was based on their screening. The diagnosis of bisphosphonate related osteonecrosis of Jaw (BRONJ) of all the patients was made clearly after careful clinical examination and radiographic examination. The inclusion criteria that were followed in this study include diagnosis of BRONJ and need for surgical management under local anaesthesia; patients able to undergo surgical treatment (ASA-1 or ASA-2); patients able to sign an informed consent form. During the period of study a total of 37 patients who were diagnosed with bisphosphonate related osteonecrosis of the jaw were included in the study.

Blood samples were collected from each patient with a 21G needle (BD, Brazil), in 10-mL glass collection tubes (BD, São Paulo, Brazil), without the addition of anticoagulants. After its collection, the blood was immediately allowed to be centrifuged (Intra-Spin® EBA 200, Intra-Lock System, FL, The United States of America), with a force applied of approximately 400g for 12 min, at 2700 rpm. After adequate centrifugation, the tubes were placed vertically in a shelf that allowing the blood to clot for not more than 15-20 minutes. At the end of the procedure, the clot (PRF) was removed from the collection tubes and implanted directly into the operated site.

All patients medially interrupted the use of anti-resorptive medication three months before surgical procedure. Local anaesthesia was inducted with 2% lidocaine with 1:100.000 epinephrine. In order to get an access to the surgical site, a mucoperiosteal flap was elevated and mobilised to ensure the tension-free closure. Necrotic bone was allocated to be removed with rotating burs and the bone surface underwent surgical debridement of the necrotic bone. Any sharp edge was intended to be removed. The extent of the resection was based on the preoperative computed tomography findings and intra-operative appearance of the bone vitality (bleeding) at the resected surface of the bone.

The amount of PRF membranes used was left to the surgeon's decision and it was personalised for each case as needed, depending on the extension of the surgical bone defect **(Table 1).** The suturing was performed with a silk suture black threads with the needle (4-0 size). A soft diet was prescribed for two weeks, and topic 0.2% chlorhexidine (Perioxidin®, Lacer, Brazil) was used for two weeks after the surgical procedure. The patients were strictly followed until soft tissue closed and any symptom disappeared, and then they were scheduled for follow-up control visits. The outcomes were promptly determined by the success of the surgical treatment (hard and soft tissue healing at the treated site, disappearance of any symptoms) and the occurrence of post procedural complications.

RESULTS

The study was conducted between June 2019 to April 2022.A total of 37participants of which 24 were reported to be females and 13 males. Study participants included those who fulfilled the inclusion criterion that has been intended to be followed in the study. The mean age was observed to be 69 ± 11 years. **Table – 1** shows the baseline characteristics of the participants and the observed treatment responses are included in **Table – 2.**

After treatment with L-PRF, 28 patients (77%) showed complete resolution, 7 (18%) had delayed resolution, and 2 (6%) did not resolve at all. Both of these two were being managed with bisphosphonates. Their lesions were almost in similar findings even after the intervention with L-PRF and their exposed necrotic bone and the post operative pain persisted even after the 4 months of follow – up. There were no allergic or immune reactions reported with L – PRF. There have been results that have reportedly showed excellent soft tissue healing, minimised post-operative pain and also improved bone healing after the addition of L-PRF. There was a significant association between the response to treatment and the stage of BRONJ (p=0.002). The associations between site of BRONJ, sCTX concentration and the presence of Actinomycosis with response to treatment did not differ significantly.

Table – 1: Baseline characteristics

Parameters	N
Mean age	69 ± 11
Gender	
Male	13
Female	24
Bisphosphonate therapy – reasons	
Osteoporosis	33

Bony metastasis	4
Route of administration	
Intravenous	33
Orally	4
Type of bisphosphonates	
Alendronate	22
Risedronate	9
Pamidronate	4
Zolendronate	2
Co-morbidity	
Chemotherapy	4
Steroids intake	6
Diabetes	9
Obesity	5
Renal failure	1
Dental etiological risk factors associated	
Tooth extraction	25
Implantation	6
Ill-fitting prostheses	3
Spontaneous occurrence of BRONJ	3

Table – 2: Treatment outcomes

Parameters	Complete	Delayed	None	P – value
Overall response	B	7	1	-
Site:				
Maxilla	5	3	1	0.23
Mandible	23	4	1	
AAOMS stage				
I	8	0	0	**0.004***
II	19	4	0	
III	1	4	1	

P value = * Statistically significant

DISCUSSION

Platelet concentrate mostly refers to an autologous concentration of human platelets that is extracted by centrifuging blood and it eventually produces a high concentration of various protein growth factors that are secreted actively by platelets.[9] The technique has been suggested for various purposes, including stimulation of production of collagen, promotion of vascular ingrowth, relief of local inflammation, and improvement in wound healing.[10] BRONJ is known to be associated with over-suppression of bony remodelling, anti-angiogenic effects, reduced immune responses and toxicity to soft tissues by bisphosphonates.[3,4] There have been various choices in order to use PRP for BRONJ on the assumption that concentrated growth factors will enhance the healing of tissue, control the progression of disease and stimulate angiogenesis.[11] PRP has been proved to be effective in the management of BRONJ.

L-PRF on the other hand, which was developed by *Choukroun* et al,[12] is a new addition to the use of platelet concentrates. L-PRF does not require any gelling agent, because natural blood is centrifuged without the usage of any added chemicals.[13]When the results have been compared with PRP, its slow and natural polymerisation produces physiologically favourable fibrinous architecture with equilateral junctions[13] and permits incorporation of platelets, leucocytes, cytokines and circulating stem cells into the fibrin network.[14] This serves as a biological healing matrix.[15] The biological properties are the most prospective aspects of L-PRF in monitoring its therapeutic potential when compared with PRP which is relatively unstable and has reportedly a short lifespan. The low cost and comparative cost - effectiveness of the procedure also make L-PRF the most suitable of platelet concentrates for its widespread use. Collectively, this states that the enmeshed BMP in fibrin matrix (L-PRF) might contribute to the induction of bony healing. Various studies have also suggested possible roles for leucocytes in platelet concentrates like antimicrobial activity, immune regulation[13] and the capacity to produce large amounts of VEGF.[16]

Blood-derived growth factors have been used in the recent years to promote tissue healing in many oral surgery procedures.[17,18] The present study used PRF, which is prepared without the addition of chemicals (blood anticoagulants and platelet activators), as opposed to platelet-rich plasma or platelet-rich in growth factors.[19] PRF can be prepared in the form of membranes with physical properties that permit it to be handled and layered in order to cover the bone[9] and helping the healing process of the oral mucosa.[19] This

by-product that has been seen from the patient's own blood has a high concentration of platelets and leukocytes that are rich in growth factors and other substances that have an important influence on wound healing, such as Platelet-derived growth factor, epidermal growth factor, transforming growth factor-beta, vascular endothelial growth factor, procoagulant factor, cytokines and antimicrobial proteins.[20,21] A recent systematic review greatly nudged that the current evidence on the antimicrobial effect of platelet-rich preparations based on a number of in vitro studies and animal models of infection.[22]And this review had concluded that although the specific action mechanisms of the interaction with microbial pathogens deserve further investigation, platelet-rich preparations showed to have antimicrobial properties, and could therefore represent a beneficial tool for controlling the postoperative infections at the surgical site.

CONCLUSION

PRF technique is considered as an effective alternative treatment modality that could be proved effective for the closure of bone exposure and tissue healing associated with BRONJ patients. More comprehensive studies with much more study samples are necessary to determine the applicability and the effectiveness of this treatment protocol in order to understand the exact mechanism of PRF.

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