ORIGINAL RESEARCH

Clinical and Radiographic Evaluation of Role of Platelet-Rich Fibrin in Healing of Impacted Mandibular Third Molar Extraction Sockets: A Prospective Clinical Study

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ABSTRACT

Purpose: The purpose of this prospective, longitudinal, clinical study was to evaluate the role of Platelet-Rich Fibrin in soft tissue and hard tissue healing of impacted mandibular third molar extraction sockets after surgical removal. **Materials And Method**: 20 patients indicated for extraction of an impacted mandibular third molar were included in the study. Patients were equally allotted to study group and control group randomly. After the removal of the tooth, autologous Platelet-Rich Fibrin was prepared by centrifuging freshly collected blood. In the study group autologous platelet rich fibrin was placed and in the control group, no intervention was done. Soft tissue evaluation was done at 7th and 15th day postoperatively. The bone density analysis was done by finding the values on a grey level histogram to evaluate hard tissue regeneration at definite intervals on the immediate postoperative day followed by 1 month, 3 months and 6 months post-operatively. **Results**: Good soft tissue healing was observed in the study group as compared to control group on the 7th day, which was statistically significant. There was statistically significant difference in the grey level histogram values between the control and the study groups at the 3rd month and 6th month postoperatively (p value being 0.003 and 0.001, respectively), signifying definite increment in the bone density in the study group at this time interval. **Conclusion**: Better and quicker soft tissue and hard tissue healing was observed in our case series treated with platelet-rich fibrin than the control group after the third molar surgery.

KEYWORDS: Platelet-Rich Fibrin, Grey Level Histogram, Impacted Mandibular Third Molar

INTRODUCTION

Socket healing is a complex process wherein the initial blood clot is infiltrated with granulation tissue formation which gets gradually converted into soft callus and a mature bone. It involves many sequential biochemical, cellular and molecular sequences along with growth factors, cytokines and other proteins.[1] The development of bioactive surgical additives to enhance healing and regeneration of tissue helps in mitigating the post-operative complications.[2] Various bioactive products like platelet rich plasma, bone morphogenic protein, fibrin glue are being used in surgical wounds, however their regular application in practice is limited owing to the cost or the complexity involved in the procedure.[3]

Recently, the use of platelet concentrates has been proposed as an aid for enhancing regeneration of osseous and epithelial tissues in oral surgery.[4,5] Several in vitro studies, animal experiments and clinical trials suggested that platelet concentrates may effectively trigger stimulation of osseous and soft tissue regeneration, and reduce inflammation and pain.[2,6] Platelets play a predominant role in wound healing process because platelets contain many growth factors (like PDGF, IGF and TGF-β), which when secreted are responsible for increasing cell mitosis, increasing collagen production, initiating vascular in-growth and inducing cell differentiation.[6,7]

Platelet-rich plasma is an autologous concentration of human platelets in a small volume of plasma that has been demonstrated to induce healing. The use of platelet-rich plasma as an adjuvant to bone grafting procedures in Oral and Maxillofacial Surgery has been increasing in popularity since its introduction in 1997 by Whitman et al.[8] Overcoming the restrictions for platelet rich plasma in the French law related to the biochemical handling of blood, Platelet Rich Fibrin was first developed in France by Choukroun et al[2] in 2001. This second generation platelet concentrates also eliminated the risks associated with the use of bovine thrombin. Platelet-rich fibrin is prepared by centrifugation the autologous blood derived from the patient, without an addition of thrombin or

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calcium chloride.[9] This prospective, longitudinal clinical study was undertaken to evaluate the role of Platelet Rich Fibrin in the soft tissue healing and osseous regeneration of bony defects after surgical extraction of the mandibular third molar.

MATERIALS AND METHOD

All the patients who were presenting for surgical extraction of mandibular third molars were explained about the study including the impaction procedure, platelet rich fibrin preparation procedure, its purpose and complications. All the patients who were willing to participate in the study, were included in the study. Patients were randomly divided into the study group (Platelet rich fibrin group) and control group (No intervention). Ethical committee approval was obtained from the institutional review board. Patients with known history local anaesthesia allergy, Immunodeficiency pathology, Uncontrolled systemic diseases, estrogen replacement therapy, bisphosphate therapy, bone metabolic disorders, psychiatric illness, chain smoking, chemotherapy, immunosuppressive therapy, platelet disorders or hematological disorders were excluded from the study.

Case history was taken with a standard questionnaire besides radiographic and clinical assessment of the impacted tooth. The patient was prepared and draped, and the impacted third molar was removed under local anesthesia with the standard surgical procedure. The extraction socket was inspected for bony spicules, fine edges, irrigated with normal saline solution and hemostasis was achieved. 4 ml of blood was drawn from the patient in a pre-sterilized test tube and centrifuged immediately in a centrifuging machine (Fig 1) at 3000 rpm for 15 minutes without an anticoagulant. The resultant product consisted of a topmost layer consisting of Acellular Platelet poor plasma (PPP), Platelet-rich fibrin (PRF) clot in middle, and red blood cells at the bottom (Fig 2). The middle layer of PRF plug that was obtained was placed into the extraction socket, and the socket was closed with 3-0 silk. For the control group, no intervention was done.

Fig 1: Centrifuge Machine

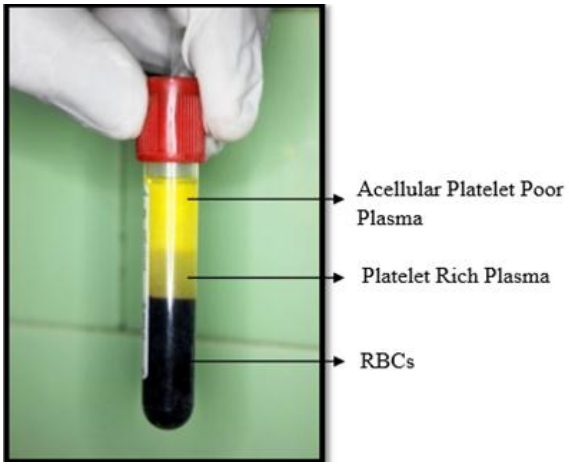

Fig 2: Platelet rich fibrin

After the procedure, patients were instructed to bite firmly over the sterile gauze pack for 30 minutes and to avoid rinsing and to take cold liquid or semisolid diet for first 24 hours. Patients were advised to do warm saline rinses after meals and 0.2% chlorhexidine rinses twice a day after 24 hrs. Antibiotics and analgesics were prescribed for 5 days. Sutures were removed on the seventh post-operative day.

Soft tissue healing was evaluated at the end of the first week and the second week using the healing index of Landry et al[10] by assessing the grading of the colour of tissues, epithelisation of wound margins, the presence of bleeding on palpation, granulation and suppuration. After the third molar removal radiographs were taken at the 1st month, 3rd month and the 6th month for evaluation hard tissue healing.

Bone Density Analysis: All the intra-oral periapical dental radiograph (IOPA) images were digitalized with the help of scanner (HP Scan Jet 7400 C). Bone density analysis was done by digital software program "Adobe Photoshop 7.0" that enlarged the standard intra-oral periapical radiograph with better resolution. Reproducible area of the bony defect post extraction was marked on the contour of the defect, and the histogram was scaled and measured. The graph so formed indicated the grey level of each pixel which was at the right end of the graph for the white and left end of the graph for the black image. This graph was interpreted as bone density as dense bone appears white and empty defect appear black on radiograph[11]. The bone density analysis was done at 1st month, 3rd month and 6th month and compared. Hence, as the values of the histogram at each interval kept on increasing with time, the healing of bony defect was interpreted.

Statistical Tools Employed: The data was analyzed statistically using SPSS (Statistical Package for Social Sciences) Version 19.0, 2010 Statistical Analysis Software (IBM, USA). Since the data was non-normal in distribution with respect to the Grey levels in Histogram, nonparametric test of significance was used to compare it between the two groups using Wilcoxon rank-sum test. For within-group comparison, Friedman test

was used to compare the Grey levels in Histogram values at 1st, 3rd and 6th month postoperatively (Fig.3).

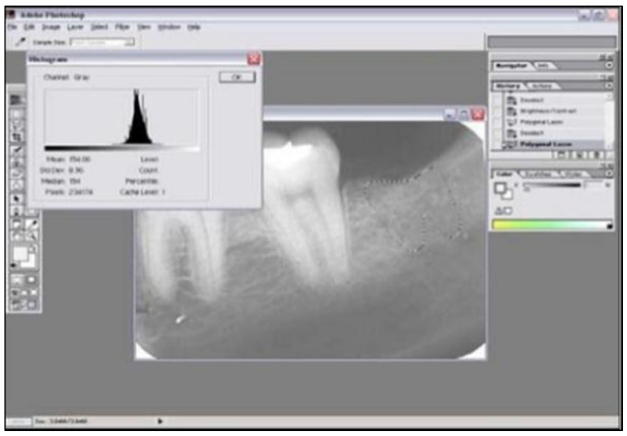

Fig 3: Grey level histogram evaluation from an intraoral periapical radiograph

With respect to soft tissue healing, since the data was in ordinal scale, Wilcoxon signed-rank test was used to compare the healing within the groups at the 7th and the 15th postoperative days. And between the groups comparison at 7th and 15th postoperative day was made using Wilcoxon rank-sum test. For all the comparison, the P value of less than 0.05 (< 0.05) was considered to be statistically significant.

RESULTS

The study was undertaken on 20 patients attending the Out-Patient department of Oral and Maxillofacial Surgery, for surgical extraction of an impacted mandibular third molar. Out of 20 patients enrolled for this study, 12 (60%) were males, and 8 (40%) were females. The overall mean age of the patients in the Group 1 was found out to be the same as that of the Group 2, which was 22.4 years.

The comparison of soft tissue healing index values between the study and the control groups at different but definite time intervals showed statistically significant difference in healing at the 7th postoperative day signifying relatively faster healing of soft tissue by the 7th postoperative day in the study group in which Platelet-Rich Fibrin was placed. There was statistically no difference in the soft tissue healing values between both the groups at the 15th postoperative day (Table 1).

In comparison of the bone densities at different time intervals within the groups, the increase in the grey level histogram values was highly significant in both study and control groups, exhibiting good bone formation in each group at 1st, 3rd and 6th month postoperatively when compared with their respective baseline values (immediate postoperative day) (Table 2).

In the comparison of the grey level histogram values between the study and the control groups at different but definite time intervals, there was no statistically significant difference in the bone density values at the immediate postoperative day and the 1st-month postoperative day. However, there was statistically significant difference in the grey level histogram values between the control and the study groups at the 3rd month and 6th month postoperatively signifying definite increment in the bone density at 3rd and 6th month postoperatively in the study group treated with Platelet-Rich Fibrin (Table 3). None of the patients in the study as

Time interval	Groups	Number of cases	Mean	Std deviation	Z value	P value
7 days post op	Control group	10	3.10	1.10	-2.466	0.01
	Study group	10	4.20	0.63		
15 days post op	Control group	10	5.00	0.00	0.001	0.99
	Study group	10	5.00	0.00		

Table 1. Comparison of soft tissue healing index between the groups

Groups	Time interval	Number of cases	Mean	Std deviation	Chi square test	P value
Control group	Immediate post op	10	122.10	5.02	30	0.001
	1 month post op	10	129.90	4.38		
	3 months post op	10	140.00	4.37		
	6 months post op	10	151.50	4.67		
Study group	Immediate post op	10	122.60	4.99	30	0.001
	1 month post op	10	133.30	4.16		
	3 months post op	10	149.70	7.69		
	6 months post op	10	161.90	5.32		

Table 2. Comparison of variables within the groups at different time intervals (Gray level Histogram Values)

Time interval	Groups	Number of cases	Mean	Std deviation	Z value	P value
Immediate post op	Control group	10	122.10	5.02	-0.341	0.733
	Study group	10	122.60	4.99		
1 month post op	Control group	10	129.90	4.38	-1.675	0.094
	Study group	10	133.30	4.16		
3 months post op	Control group	10	140.00	4.37	-2.950	0.003
	Study group	10	149.70	7.69		
6 months post op	Control group	10	151.50	4.67	-3.292	0.001
	Study group	10	161.90	5.32		

Table 3. Comparison of variables between groups at different time intervals (Grey level Histogram values)

well as the control group developed any intraoperative or postoperative complications relating to the intraoral procedure and at the blood withdrawal site.

DISCUSSION

Wound healing is a physiological process involving a cascade of events to restore and replace the function of a damaged tissue. The healing of a surgically extracted molar can be explained in the coagulative, proliferative and the osteogenic-remodelling phase. The coagulative phase lasts from immediately after completion of the extraction until up to 3 days involving filling up of the socket with the clot and the inflammatory process initiation. The release of various growth factors from the platelets, fibroblasts and endothelium begins in this phase. The proliferative phase lasting from then onwards till 20 days to 2 months after extraction that brings about the dissolution of the blood clot, formation of connective tissue matrix, development of blood supply to the wound, initiation of the osteoblastic and osteoclastic activity. The osteogenic-remodelling phase is the last and the longest of the phases of healing of an extraction socket lasting from weeks to months. This involves the secretion of osteoid, mineralization of the matrix and remodeling of bone.

In 1965, Christ first identified Bone Morphogenic Proteins (BMPs) when demineralized bone matrix implanted in ectopic sites in rats was found to induce bone formation. Bone Morphogenic Proteins play a role in the differentiation, proliferation, growth inhibition and arrest of maturation of a wide variety of cells, depending on the cellular microenvironment and the interactions with other regulatory factors. As Bone Morphogenic Protein therapy comes with demerits like high cost, large dose requirement, short half-life and poor distribution, alternative methods promoting bone formation and regeneration have been coming up[12]. Transforming Growth Factor(TGF) β1 and β2 have shown to inhibit bone resorption, as well as to trigger rapid maturation of collagen in early wounds. Platelet-Derived Growth Factor (PDGF) increases the population of wound-healing cells and recruits other angiogenic factors to the wound site. It is, therefore, a reasonable hypothesis that increasing the concentration of platelets in bone defects may lead to improved, faster healing and may stimulate new bone formation.[13,14]

The first generation platelet concentrate, Platelet Rich Plasma, is not only autologous in nature but also rich in growth factors. In contrast to natural human blood clot which contains of 95% red blood cells, the Platelet-rich plasma contains 95% of platelets which is a rich source of vaious growth factors like platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and insulin-like growth factor 1 (IGF-1). The plaetelet rich plasma requires activation with .[15,16] Sanchez et al[17] reported that the use of bovine thrombin for polymerizing of Platelet-rich plasma might be linked with the development of antibodies to factor V, XI and thrombin, resulting in the risk of life-threatening coagulopathies. It also involves biochemical handling of blood and addition of chemicals (anticoagulant).

Platelet-Rich Fibrin is a second-generation platelet concentrate, prepared from centrifuged blood without the addition of any anticoagulant, introduced by Joseph Choukroun et al.[6] Platelet-Rich Fibrin represents a new revolutionary step in the platelet gel therapeutic concept. Unlike other platelet concentrates, this technique does not require any jellifying agent, but not more than centrifugation of the natural blood without additives. Choukroun et al. developed the Platelet-Rich Fibrin in 2001 at France and introduced the production protocol of Platelet-Rich Fibrin. It contains platelets, leucocyte cytokines suspended in fibrin network which plays a vital role in therapeutic benefit of platelet rich fibrin. Advantages of Platelet-Rich Fibrin over Platelet-Rich Plasma[19,20] are no biochemical handling of blood, simplified and cost-effective process, use of bovine thrombin and anticoagulants not required, favorable healing due to slow polymerization, more efficient cell migration and proliferation, platelet-rich fibrin has the supportive effect on immune system and helps in hemostasis.[21,22,23,24] Various reports suggest its role in inducing bone formation either with or without bone grafts, sinus lift procedures, dental implant procedures, gingival recession cases as well as in reconstruction procedures.[6,7,25]

The major disadvantage with Platelet-Rich Fibrin is the quantity in which it is obtained. For the larger defects, large volume of blood needs to be withdrawn and even highly mechanized apparatus to get a Platelet-Rich Fibrin clot of a relatively larger size. The present study was designed to evaluate the role of Platelet Rich Fibrin in terms of soft tissue healing and bone regeneration potential in impacted mandibular third molar extraction sockets. In this study, Platelet-Rich Fibrin was prepared by the method described by Choukroun et al[6] wherein 4 ml of blood sample was collected from patients in pre-sterilized test tubes without an anticoagulant and centrifuged immediately at 3000 rotations per minute for 15 minutes. Su et al[26] along with Choukroun et al. have published about the importance of quick handling of the blood sample. In this particular study instead of a digital centrifuge, a conventional Medico/Doctor centrifuge, Remi Laboratory Centrifuges was used. The centrifuge was calibrated to give 3000 rotations per minute as the maximum speed. The sample was made to run for 15 minutes as the Platelet-Rich Fibrin was not obtained in 13 minutes as prescribed by Choukron.

The Platelet-Rich Fibrin clot, of about 0.8 - 1 ml volume, so formed was retrieved from the test tube and placed in the extraction socket. The Platelet-poor plasma and RBCs at the bottom were discarded. According to Su et al[26] the remaining fluid after removal of the Platelet-Rich Fibrin clot, can be recovered as an additional source of growth factors to the surgical site. In our study, we discarded the remaining fluid and used only the Platelet-Rich Fibrin

clot. After placing Platelet-Rich Fibrin in the extraction socket, assessment was done for soft tissue healing and bone density at different time intervals.

In order to scrutinize whether or not Platelet-Rich Fibrin had influenced healing of soft tissue overlying the extraction sockets, Soft tissue Healing Index by Landry et al.[10] was used in the present study. The median score recorded for Platelet-Rich Fibrin applied side on the 7th postoperative day was 4.20 (very good) whilst that of control side was 3.10 (Good), differences between the two groups was statistically significant. Findings of the current clinical trial are in conformity with the studies of Vinaya Kumar et al[27], Jankovic S.[28], Sammartino et al[29], and Simonpieri et al[24]. These authors in their respective studies have quantified soft tissue healing and concluded their results with noticeably better soft tissue healing. Care was exercised when drawing conclusions from these results concerning the effect of Platelet-Rich Fibrin on soft tissue healing because data on reproducibility, accuracy and validity of this index for the assessment of soft tissue of extraction sockets were not sought in this study.

Bone density analysis was done by software program "Adobe Photoshop 7.0". It enlarges the standard IOPA dental radiograph with better zooming and resolution. Reproducible area of the bony defect post extraction was marked on the contour of the defect, and the histogram was scaled and measured. The graph so formed indicated the grey level of each pixel which was highest for white and lowest for the black image. This graph was interpreted as bone density as dense bone appears white and empty defect appear black on radiograph (Jansen et al.).[11] This method appraises the bone density that was based on the proposals of Diamante et al,[30] which measured the radiographic density to assess the resolution of the bone cyst and recommended the technique as a useful adjunct to assess hard tissue healing. The bone density results of our study were correlating with the studies of Chang et al[9], Zhao et al[31]

The drawbacks of our study include low sample size and the oral environment was different for each case in both study and control group. The oral hygiene maintenance, diet, lifestyle of each patient is expected to be different which is going to affect the outcomes of the study. Bone height and width have not been quantified and platelet quantity, quality and growth factor quantification was not assessed

CONCLUSION

This prospective, longitudinal, clinical study shows statistically significant improvement in the soft tissue healing and faster regeneration of bone after third molar surgery when platelet-rich fibrin clot is placed in the socket. The preparation of Platelet-Rich Fibrin is a simple, cost effective and less time taking procedure.

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