

Platelet Rich Fibrin (PRF) Gel as Efficient Vehicle for Local Drug Delivery in Minor Oral Surgical Defects

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Abstract:

Aim and Objectives: To evaluate the effect of platelet rich fibrin (PRF) gel as a vehicle for delivery of diclofenac sodium following transalveolar extraction of impacted mandibular third molar.

Methods: A total of 50 patients for disimpaction were randomly allocated in two equal groups; experimental (25patient) and control (25patient). In experimental group, PRF gel with diclofenac sodium was placed in the extraction socket, whereas in control group only PRF gel was placed. The objective of the study was to compare clinical parameters especially the postoperative pain, swelling, interincisal distance, wound dehiscence, dry socket, soft tissue healing, and infection which were assessed on 1st, 3rd and 7th day following surgical disimpaction.

Results: Results showed significant lower pain scores, reduced facial swelling and improved interincisal opening in experimental group postoperatively when compared to control group.

Conclusion: The present study concludes that the use of simple, cost- effective method of autologous PRP gel as vehicle to localised deliver diclofenac sodium may be beneficial to enhance the wound healing process, promotes bone regeneration and reduced pain.

Keywords: Platelet rich fibrin, Mandibular molar socket healing, diclofenac sodium

Introduction

It is a well-known fact that platelets play a crucial role not only in haemostasis but also in wound healing¹. The development of technologies to obtain platelet concentrates lead to the formation of a new kind of fibrin adhesives concentrated Platelet-rich plasma (cPRP). But due to legal restriction on blood handling procedures, another family of platelet concentrates appeared in France namely Platelet-rich fibrin (cPRF). This new biomaterial has proved to be very useful to Oral and Maxillofacial Surgeons¹.

Fibrin which is the activated form of a plasma molecule fibrinogen is a fibrillary molecule and is massively present not only in the plasma, but also in the platelet alpha-granules. It plays a potential role in platelet aggregation during haemostasis and the fibrin matrix also has the property of angiogenesis.²

PRF is an immune and platelet concentrate containing all the constituents of a blood sample which are favourable to healing and immunity. This new biomaterial looks like an autologous cicatricial matrix, which is neither like fibrin glue nor like classical platelet concentrate. Clinical studies reveal that this biomaterial would be favorable matrix for the development of a coherent healing, without any inflammatory excess³. The premise of successful exodontic surgical treatment is based not only on the correct operative technique but also on the prevention and management of post-operative complications. Post extraction pain has often been a nemesis for dental surgeons.

Non-steroidal anti-inflammatory drugs (NSAIDs) are amongst the most widely used therapeutic class of analgesic compounds used to relieve post extraction pain. Diclofenac sodium is a commonly prescribed NSAID, which exhibits anti-inflammatory, analgesic and anti-pyretic activity⁴. With these fundamental consideration, PRF with diclofenac sodium can be considered as a natural fibrin based biomaterial favorable to the development of a microvascularization and able to guide epithelial cell migration on its surface. Furthermore this matrix contains leukocytes and promotes their migration.³

We conducted this study to seek the effectiveness of PRF as a drug carrier for diclofenac sodium locally so that the systemic use of diclofenac sodium can be minimized and we also can evaluate the efficacy of diclofenac sodium locally to reduce pain.

Aim

To evaluate the effect of platelet rich fibrin as a vehicle for delivery of diclofenac sodium following transalveolar extraction of impacted mandibular third molar.

Methodology

Preparation of standard PRF:

After obtaining consent 10 ml of whole venous blood was collected using a sterile disposable syringe and the blood was immediately transferred to sterile test tube without anticoagulant. This test tube was then placed immediately in a table top centrifuge machine and subjected to centrifugation for 10 min at 3000 rpm [Figure 1].

After centrifugation the blood settled into following layers: red lower fraction containing the fibrin clot, middle layer containing the PRF and upper layer containing the plasma [Figure 2]. The upper straw colored layer was then removed and middle fraction which was the PRF was collected using a sterile tweezers or an artery forceps as discussed by *Choukran et al in 2006*³



Figure 1: Table top centrifuge machine and subjected to centrifugation for 10 min at 3000 rpm.



Figure 2: After centrifugation the blood settled into following layers: red lower fraction containing the fibrin clot, middle layer containing the PRF and upper layer containing the plasma

Preparation of drug leaching PRF:

The standard PRF was prepared first as mentioned above then 1 ampoule of Diclofenac Sodium was injected in PRF using 30 gauge needle [Figure 3].



Figure 3: Infusing diclofenac sodium 1 ampoule in PRF using 30 gauge needle

Study Design

Fifty eligible patient meeting the above criteria were randomly divided into two groups: Group A was taken as a test group in which the PRF gel with Diclofenac sodium was placed in the extraction socket of randomly selected 25 patients and Group B was taken as the control group in which PRF gel without Diclofenac Sodium was applied in the extraction socket of randomly selected 25 patients.

Surgical Procedure

Surgical disimpaction of the impacted mandibular third molar was carried out in accordance with established protocols in both the groups. This included pre-operative rinsing for 5 min with 0.12 % chlorhexidine followed by administration of local anesthesia using 2 % lignocaine and 1:200000 epinephrine. The inferior alveolar, lingual, and long buccal nerve blocks were administered. Surgical disimpaction was accomplished with round and fissured carbide burs under constant saline irrigation and tooth sectioning was performed where necessary and then the tooth was removed. Hereafter the procedure differentiated between two groups.

Group A – Test group

After debridement and securing haemostasis, 1 ampoule of Diclofenac Sodium was injected in PRF using 30 gauze needle and placed into the socket. The flaps were then re-approximated with 3-0 silk sutures taking care not to displace the gel.

Group B – Control Group

After debridement and haemostasis of socket, the PRF alone was placed into the socket. The flaps were then re-approximated with 3-0 silk sutures taking care not to displace the gel.

Clinical Parameters:

Various postoperative parameters were used to evaluate the study as showed in table 1.

Post-operative care and follow up

Patients in the test group received antibiotics but NSAIDS were given after 24hrs for a period of 3 days and in control group both antibiotics but NSAIDS were given for a period of 5 days. The standard regimen included Amoxicillin 500 mg perorally 8 hourly, Metronidazole 400 mg perorally 8 hourly and Ibruprofen 400 mg 8 hourly. Patients allergic to penicillin were prescribed Clindamycin 300 mg perorally 6 hourly and in these patients metronidazole were not co prescribed. Other routine instruction concerning dietary modification and oral hygiene maintenance were given.

All patients were followed up on 24hrs,72hrs, and at the end of weeks. Outcome variables such as pain, swelling and interincisal distance were measured using 5 point visual scale, tape and millimeter caliper respectively [Table 1].

Pain	24 hours	72 hours	7 days
Swelling	24 hours	72 hours	7 days
Trismus	24 hours	72 hours	7 days
Wound dehiscence	24 hours	72 hours	7 days
Dry socket	214 hours	72 hours	7 days

Table 1: Various postoperative parameters were used to evaluate the study

Result

Postoperative pain

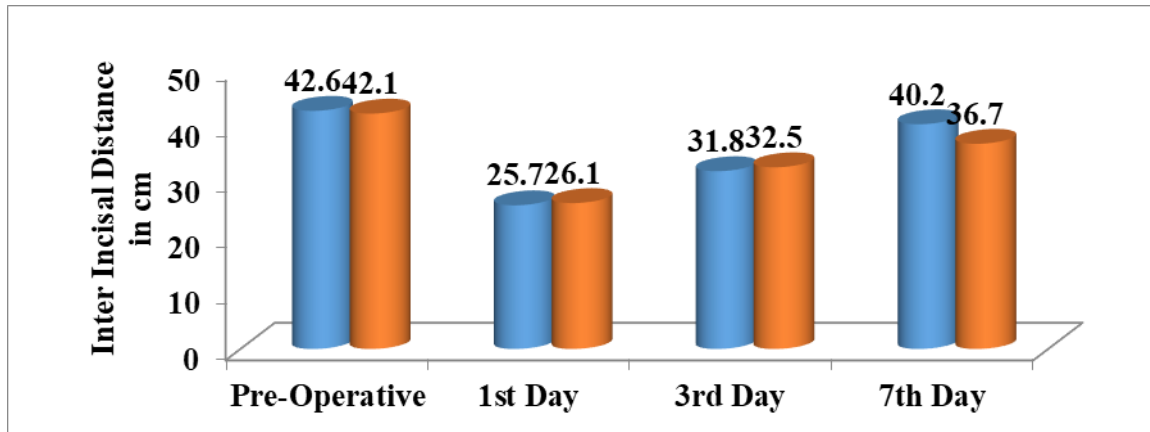
The mean VAS score was consistently higher for the control group on 1st, 3rd and 7th postoperative days as compared to the test group indicating lesser postoperative pain in patients with PRF (test group). These differences were statistically significant on 1st but not on 3th and 7th postoperative days. (Table 2)

	Group	Mean	S.D.	N	T value	Pvalue	Result
1 st Day	Test	3.2	0.63	10	-5.96	0.00	Significant
	Control	4.7	0.48	10			
3 rd Day	Test	1.7	0.67	10	-1.14	0.26	Non-Significant
	Control	2.1	0.87	10			
7 th Day	Test	0.5	0.52	10	-3.53	0.37	Non-Significant
	Control	1.3	0.48	10			

Table 2: Assessment of Pain (Test and Control Groups on VAS Scale)

Interincisal opening:

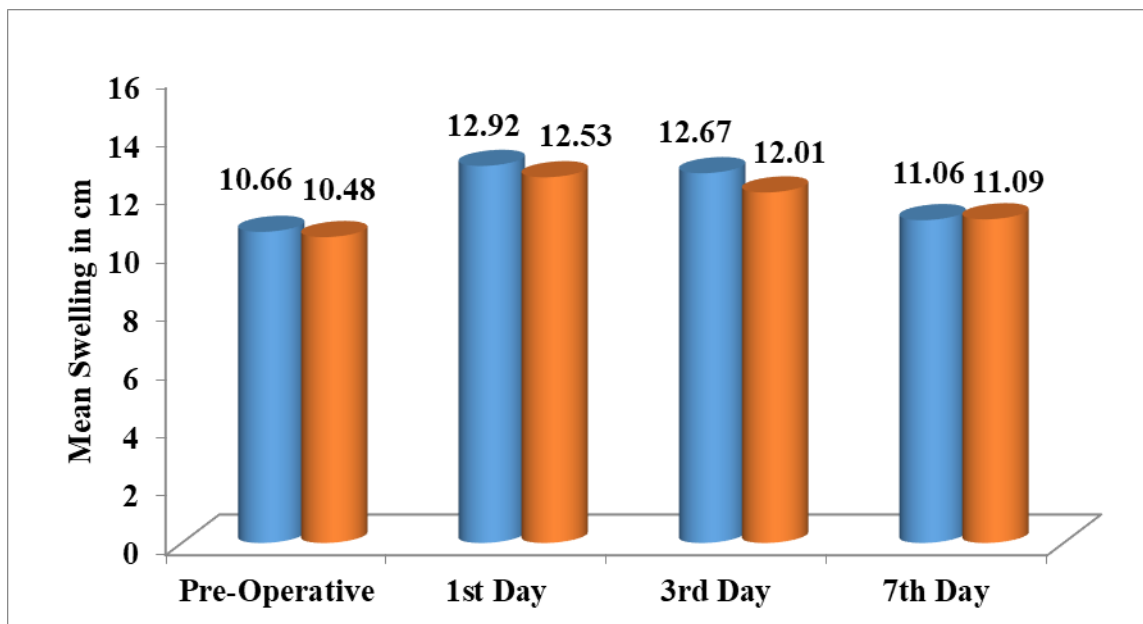
The correlation between both the groups pre and post operatively were statistically non-significant. (Graph 1).



Graph 1: Assessment of Inter Incisal Distance (Control Group in centimeters)

Swelling:

Statistically significant swelling was observed in the test group on 1st and 3rd post-op days, while patient in the control group showed statistically significant swelling on 1st, 3rd and 7th postoperative days. (Graph 2)



Graph 2: Comparison of Swelling in Test and Control Group in centimeters

Healing , Dry socket and wound dehiscence:

Significant difference was observed in the test group indicating better healing process less wound dehiscence and less incidence of dry socket in the test group as compare to control group. (Table 3 ,4& 5)

1 st Day	Present	2(20%)
	Absent	8(80%)
3 rd Day	Present	2(20%)
	Absent	8(80%)
7 th Day	Present	2(20%)
	Absent	8(80%)

Table 3: Wound Dehiscence Test Group Significant difference was observed in the test group indicating better healing process in the test group.

1 st Day	Present	2(20%)
	Absent	8(80%)
3 rd Day	Present	3(30%)
	Absent	7(70%)
7 th Day	Present	3(30%)
	Absent	7(70%)

Table 4: wound dehiscence control group and test group

Day	Dry Socket of Control Group		Day	Dry Socket of Test Group	
3 rd Day	Present	2(20%)	3 rd Day	Present	3(30%)
	Absent	8(80%)		Absent	7(70%)
7 th Day	Present	1(50%)	7 th Day	Present	1(10%)
	Absent	9(50%)		Absent	9(90%)

Table 5: Incidence of Dry Socket of control group & Test Group

Overall the test group showed lower incidence of pain, healing, wound dehiscence, and dry socket in compare to control group.

Discussion

Maxillofacial surgeons are in continuous search for ways to improve healing, reduce pain with newer, simpler and direct technique. One of the recent and innovative techniques which is being used is PRF⁵.

Platelets contain important growth factors, which are responsible for increasing cell mitosis, increasing collagen content, replacing other cells to the site of injury to initiate the vascular growth, and induce cell differentiation. These are early steps in wound healing⁶.

The platelets are usually involved in delivering drugs to the peripheral. The concept is to increase the concentration of platelets in a wound site which may help in faster healing. Two forms are used; PRP and PRF⁹. The main difference between the two forms of platelet concentrates (PRP and PRF) is that the PRF does not involve the process of adding bovine thrombin to convert of fibrinogen to fibrin which is necessary in PRP⁷.

PRF is a fibrin matrix, in which platelet and leukocyte cytokines gets embedded during centrifugation. The incorporation of cytokines within the fibrin mesh allows their continuous release, as the network of fibrin disseminates. The easily available PRF membrane thus acts much like a fibrin band which serves as a matrix to increase the wound healing⁸.

Converting fibrinogen to fibrin in PRF takes place slowly in small quantities of physiologically available thrombin present in the blood. A physiologic matrix is formed by slow polymerization which is important for healing process. The fibrin network formed here is very similar to a natural one which leads to more efficient cell migration and proliferation⁹.

According to **Simonpieri et al**¹⁰, the use of PRF during bone grafting gives the following advantages: **First**, the fibrin clot has an important role in maintaining the PRF membrane and protecting the graft material and PRF fragments serving as connectors between bone particles. **Second**, the integration of fibrin network into the regenerative site facilitates cellular migration, mainly for endothelial cells which is necessary for the neo-angiogenesis and vascularisation. **Third**, the platelet cytokines (PDGF, TGF- β , IGF-1) are slowly released as the fibrin matrix disintegrates.

There are many ways a drug can be administered. It can be given by oral, I.V, I.M, patches etc. The most common route of drug availability for NSAID is oral route which can cause complication like gastrointestinal tract irritation and ulcers like peptic ulcers and bioavailability of drug also decreases in this route. So to get rid of these complications we tried to find out some other way to deliver the drug locally to the site of injury like extraction socket. We used PRF as local drug delivery system for diclofenac sodium which can help in increasing the healing and reduce pain more over it reduces the usage of NSAID too.

In our study we tried to resolve the above contentious issue related to the use of PRF in wound healing and as a vehicle for local drug delivery. The mandibular third molar extraction procedure was chosen for evaluation of these benefits. As this procedure is a minor oral surgical procedure.

When we tried mixing diclofenac sodium in the blood in a table top centrifuge machine; the PRF was not formed the reason being the anti-aggrerant drugs impair platelet granules secretion and formation¹¹. Hence after preparing PRF diclofenac sodium was infused from outside using a 30 gauze needle and this PRF was given multiple puncture after placing it in the socket so that the drug can be leached out.

The mean postoperative pain score (VAS) was lower for the PRF with Diclofenac sodium group at all times when compared with the control group and this was statistically significant and is consistent with observation of **Del Corse et al**¹², **Ogundipe OK et al (2011)**¹³ and **Kedarnath N.S¹⁴ et al**, **Rutkowski et al**¹⁵ however there was difference in post operative pain, with PRF without Diclofenac sodium. Inflammatory phenomenon may be considered to be directly related to surgical trauma.

The above two studies used PRP while the present study deals with the effect of PRF with diclofenac sodium in the test group compared with the effect of PRF without diclofenac Sodium. The use of platelet concentrates is believed to allow a reduction in percentage of prostaglandin such as PG2 and this might be responsible for lower pain perception in the test group.

Lesser swelling was found in the test group which is due to the anti-inflammatory effect of platelet. Since PRF is not only a platelet concentrates but also a way to stimulate faster defence mechanisms. It is a more common fact that the inflammatory regulation present on surgical sites treated with PRF with diclofenac sodium is due to the control effects from cytokines trapped in the fibrin network which are released during the formation of this matrix¹.

Assessment of healing has been carried out by different authors. **Gawande et al**⁶ used digital gray scale histogram for assessment of density and credit the benefits of this method **Damante et al**¹⁶, **Mancuso JD (2003)**²⁵, **Del corse et al**¹², **Ogundipe OK et al**¹³ and **Kedarnath N.S. et al**¹⁴. These authors have reported superior healing with the use of PRF.

Better healing may also be explained by the fact that the fibrin is a support for bone morphogenic protein (BMP). Therefore, the fibrin matrix associated with BMPs may have angiogenic, hemostatic, and osseo conductive properties. BMPs get incorporated in the fibrin matrix which is continuously released to induce bone. This continuous release of cytokines is common feature of in-vivo natural fibrin clot and likely of PRF. (**Kanwamura et al**¹⁷). The study conducted by **A.Aftaba et al**¹⁸ in 2020 and **S Singha**¹⁹ in 2019 showed promising post operative results in pain score, facial swelling and trismus when the socket is packed with PRP gel.

In our study we found that better healing was present in the study group due to the use of PRF with diclofenac sodium.

Post-operative wound dehiscence was also lower in the PRF with diclofenac sodium group as compared to the control group. This is probably due to better epithelisation and lesser oedema at the surgical site in PRF with diclofenac sodium treated cases.

Conclusion

Any insult to the tissue causes inflammatory response and literature has showed that the use of PRP/PRF aids in faster wound healing. From the summary of this study it can be concluded that PRF is a viable material for local drug delivery (in this study diclofenac sodium) further studies are requested to evaluate other drugs like antibiotics and possibly multiple drugs.

Conflict of Interest

The authors declare no conflict of interest.

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