

Can Autologous Platelet-Rich Plasma Gel Enhance Healing After Surgical Extraction of Mandibular Third Molars?

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Purpose: This investigation assesses the effect of platelet-rich plasma (PRP) gel on postoperative pain, swelling, and trismus as well as healing and bone regeneration potential on mandibular third molar extraction sockets.

Patients and Methods: A prospective randomized comparative clinical study was undertaken over a 2-year period. Patients requiring surgical extraction of a single impacted third molar and who fell within the inclusion criteria and indicated willingness to return for recall visits were recruited. The predictor variable was application of PRP gel to the socket of the third molar in the test group, whereas the control group had no PRP. The outcome variables were pain, swelling, and maximum mouth opening, which were measured using a 10-point visual analog scale, tape, and millimeter caliper, respectively. Socket healing was assessed radiographically by allocating scores for lamina dura, overall density, and trabecular pattern. Quantitative data were presented as mean. Mann-Whitney test was used to compare means between groups for continuous variables, whereas Fischer exact test was used for categorical variables. Statistical significance was inferred at $P < .05$.

Results: Sixty patients aged 19 to 35 years (mean: 24.7 ± 3.6 years) were divided into both test and control groups of 30 patients each. The mean postoperative pain score (visual analog scale) was lower for the PRP group at all time points and this was statistically significant ($P < .05$). Although the figures for swelling and interincisal mouth opening were lower in the test group, this difference was not statistically significant. Similarly, the scores for lamina dura, trabecular pattern, and bone density were better among patients in the PRP group. This difference was also not statistically significant.

Conclusion: The PRP group recorded reduced pain, swelling, and trismus as well as enhanced and faster bone healing compared with those in the control. Hence the study showed that topical application of PRP gel has a beneficial effect in enhancing socket healing after third molar surgery.

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Socket healing is a highly coordinated sequence of biochemical, physiologic, cellular, and molecular responses involving numerous cell types, growth factors, hormones, cytokines, and other proteins, which is directed toward restoring tissue integrity and functional capacity after injury.¹⁻³ It is a spe-

cialized example of healing by second intention.

Although the incidence of healing complications is relatively low, the problems created by the disturbances in postextraction wound healing and physiologic sequelae of third molar surgery can significantly

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affect the patient's quality of life.⁴ Various methods have been suggested to enhance socket healing and to minimize the postoperative sequelae after third molar surgery.⁵⁻⁸

PRP is a biologic approach to promote the wound healing cascade by releasing therapeutic growth factors directly to the wound.⁹ These growth factors act on healing capable cells during cell division, matrix synthesis, and tissue differentiation to increase their numbers and stimulate vascular bone ingrowths.¹⁻³

Studies on PRP efficacy in enhancing wound healing in oral and maxillofacial surgery have yielded varied results. The majority of these studies have focused on enhancing graft healing and dental implants.¹⁰⁻¹⁵ Thus, there is the need for more studies to explore its use in extraction sockets. This study was therefore conceived to ascertain the effect, if any, that PRP has on postoperative sequelae and enhancement of bone healing after mandibular third molar surgery.

Patients and Methods

To address the research purpose, we designed and implemented a prospective randomized comparative clinical study. The sample population was composed of all patients presenting to the Dental Hospital, Obafemi Awolowo University Teaching Hospitals Complex Ile-Ife, Nigeria for evaluation and management of third molars between June 2006 and July 2008. To be included in the study sample, patients had to have clinical and radiographic diagnosis of a single impacted mandibular third molar and indicate willingness to return for recall visits. Patients were excluded as study subjects if pregnant, lactating, or smokers or if they had systemic disease. Ethical clearance was obtained from the Hospital's Ethics Committee prior to the commencement of the study. All patients were informed of the risks and benefits of the procedure after which they signed the consent form.

The following demographic information was collected: age, gender, occupation, marital status, and educational level. Furthermore, the position and type of impaction were recorded. The patients were randomly allocated by the Unit House Officer through a single-blind technique where the operator was blinded to the patient allocation. The patients were allocated alternatively into test and control groups. The test group received topical application of PRP, whereas the control group was left to heal without PRP.

A 10-point visual analog scale (VAS) with a score of 0 equals "no pain" and 10 equals "very severe pain" was used to assess pain.

Facial swelling was evaluated using a modification of the method described by Schultze-Mosgau et al,¹⁶ and this entailed measuring the distances from the

tragus to the oral commissure and tragus to the pogonion. The arithmetic sum of the 2 measurements was used to determine the facial swelling at the time point. The percentage facial swelling was calculated from the difference of the measurements made in the preoperative and postoperative periods divided by the value obtained in the preoperative period and multiplied by 100 ($(S_{\text{postop}} - S_{\text{preop}}/S_{\text{preop}} \times 100)$).

Mouth opening was taken as the maximum distance between the maxillary central incisors and the mandibular central incisors using a millimeter caliper. Trismus was expressed as a percentage and was calculated from the difference of the mouth opening measurements in the preoperative and postoperative periods divided by the value obtained in the preoperative period and multiplied by 100 ($(T_{\text{preop}} - T_{\text{postop}}/T_{\text{preop}} \times 100)$).

Bone healing of the third molar socket was assessed radiographically using a standard periapical x-ray. Unlabeled films developed, fixed, and rinsed under standard conditions were independently evaluated using image view box with magnification viewer. The criteria for bone healing and the scoring system are based on a modification of the method used by Kelley et al.¹⁷ Three radiographic parameters, namely, lamina dura, overall density, and trabecular pattern, were used for assessment of bone healing. It was agreed in advance that baseline radiography will be the reference radiograph and will receive a score of 0. A score of +2 to -2 represented gross variance from baseline radiographic score and a score of +1 to -1 represented significant variation from normal. The descriptions of the different scores for each radiographic parameter are listed in Table 1. Immediately after the procedure, details of each procedure were recorded, including the duration of surgery in minutes (from the first incision to insertion of the last suture), volume of anesthetic solution, and any intraoperative complications. Each patient received identical postoperative antimicrobial drugs (Amplicox Beecham caps 500 mg, and metronidazole 400 mg 8 hourly for 5 days), analgesic (tabs ibuprofen 400 mg 8 hourly for 3 days) regimen, and post extraction instructions (verbal and written). They were further instructed not to take any drugs other than the prescribed medications.

Patients were then recalled at 1-, 3-, 5-, 7-, and 14-day postoperative intervals. During such visits, data were recorded for postoperative pain, facial swelling, and maximum mouth opening. Patients were also recalled at the 4th, 10th, and 16th week postoperatively for radiographic assessment.

PRP Preparation Protocol

PRP was prepared using a modification of the method of Sonnleitner et al.¹⁸ Before surgery, 10 mL of venous blood was collected into sterile tubes con-

Table 1. MEAN RADIOGRAPHIC SCORE FOR ASSESSMENT OF BONE HEALING AT DIFFERENT TIME POINTS BETWEEN GROUPS

Variable	PRP Group	Non-PRP Group	P Value
Lamina Dura Score			
4 th week	1.4 ± 0.5	1.2 ± 0.4	>.1*
10 th week	1.8 ± 0.4	1.3 ± 0.5	>.1*
16 th week	1.9 ± 0.3	1.6 ± 0.5	>.1*
Density Score			
4 th week	1.4 ± 0.5	1.3 ± 0.5	>.1*
10 th week	1.6 ± 0.5	1.4 ± 0.5	>.1*
16 th week	1.6 ± 0.5	1.4 ± 0.5	>.1*
Trabecular Pattern Score			
4 th week	1.3 ± 0.4	1.2 ± 0.4	>.1*
10 th week	1.5 ± 0.5	1.4 ± 0.5	>.1*
16 th week	1.5 ± 0.5	1.4 ± 0.5	>.1*

Lamina dura

- +2 Lamina dura essentially absent, may be present in isolated areas
- +1 Lamina dura substantially thinned, missing in some areas
- 0 Within normal limits
- 1 Portions of lamina dura thickened, milder degrees
- 2 Entire lamina dura substantially thickened
- 0 Within normal limits

Overall density

- +2 Severe increase in radiographic density
- +1 Mild to moderate increase in radiographic density
- 0 Within normal limits
- 1 Mild to moderate decrease in radiographic density
- 2 Severe decrease in radiographic density

Trabecular pattern

- +2 All trabeculae substantially coarser
- +1 Some coarser trabeculae; milder degrees
- 0 Within normal limits
- 1 Delicate finely meshed trabeculations
- 2 Granular, nearly homogenous patterns; individual trabeculations essentially absent

*Not significant.

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taining 0.5 mL citrate phosphate dextrose from each patient in the experimental group using standard, sterile phlebotomy techniques. The tube was gently agitated to thoroughly mix the anticoagulant with the venous blood. Blood samples for baseline platelet count were drawn into sterile Venoject bottle (without citrate) and subjected to manual count. The tube was first spun at 1,200 rpm (200 g) for 10 minutes and then at 1,000 rpm (160 g) for 10 minutes using a standard electronically controlled bench-top laboratory centrifuge (PowerSpin Fx Centrifuge; Unico, Dayton, NJ). The first spin was to separate red blood cells from plasma, whereas the second spin separated platelets from the buffy layer containing platelet poor plasma and white blood cells. One milliliter of platelet-poor plasma (supernatant) was pipetted out and

the remainder was shaken together for 15 minutes to resuspend the platelet concentrates in 2 mL plasma. Small aliquots were removed for platelet count (pocH 100i Automated Hematology Analyzer; Sysmex Corporation, Kobe Japan; Dynal Sample Mixer; Invitrogen Corporation, Carlsbad, CA) without violating the sterility protocol. Activation of PRP was performed with a mixture of 0.5 mL 10% calcium chloride and 1,000 U bovine thrombin. Five drops of this mixture was added to 2 mL PRP; the mixture was allowed to solidify at room temperature.

Surgical Procedure

The procedure was the same in all cases and performed by the same surgeon. Local anesthesia was obtained using 2% lignocaine hydrochloride with 1:100,000 epinephrine. A full-thickness 3-sided mucoperiosteal flap was raised to expose the buccal aspect of impacted third molar and the cortical plate. Bone removal was performed with a round bur in a straight hand piece under continuous irrigation with 0.9% saline. The tooth was removed with a Coupland elevator. Subsequently, PRP gel was placed and adapted to the extraction sockets of patients in the PRP group with a tissue forceps. Wound closure was carried out with simple interrupted 3.0 black silk sutures, whereas it was accomplished in the control group without topical application of PRP.

The data were evaluated using Intercooled Stata Version 9 (StataCorp, College Station, TX). Quantitative data were presented as mean values ± standard deviation. Mann-Whitney test was used to compare means between groups for continuous variables, whereas Fischer exact test was used for categorical variables. Statistical significance was inferred at $P < .05$.

Results

The mean age of the sample population was 24.7 (±3.6) years (range 19 to 35 years). There was no statistically significant difference in the age, gender, and type of impaction between both groups (Table 2). The platelet concentration procedure increased the platelet numbers on average from 268,667 (±64,678) platelets/mL³ to 3,157,667 (±984,380) platelets/mL³. The whole blood baseline measurements ranged from 150,000 to 410,000 platelets/mL³. The concentration procedure resulted in an average 11.8-fold increase in platelet concentration.

In both groups, the mean postoperative pain score (VAS) was highest at postoperative day 1 and gradually reduced over the following 14 days (Fig 1). The mean postoperative pain score (VAS) was lower for the PRP group at all time points when compared

Table 2. DESCRIPTIVE STATISTICS FOR DEMOGRAPHIC AND INTRAOPERATIVE VARIABLES GROUPED BY TREATMENT

Variable	PRP Group	Non-PRP Group	P Value
Mean age (yr)	24.4 ± 3.3	24.9 ± 3.8	.677
Gender (frequency)			
Male	14 (46.7)	11 (36.7)	.432
Female	16 (53.3)	19 (63.3)	
Impaction type (frequency)			
Mesioangular	15 (50.0)	16 (53.3)	1.00
Distoangular	7 (23.3)	7 (23.3)	
Vertical	5 (16.7)	4 (13.3)	
Horizontal	3 (10.0)	3 (10.0)	
Mean duration of surgery (min)	34.3 ± 15.5	24.6 ± 11.1	.005
Mean amount of local anesthetic (mL)	3.6 ± 0	3.6 ± 0	>.05*

NOTE. Data presented in parentheses are percentages.

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with the control and this was statistically significant ($P < .001$).

The percentage facial swelling for the PRP group relative to baseline value was 4%, 1.1%, and 0.1% on postoperative days 1, 7, and 14, respectively, whereas it was 4.8%, 2.0%, and 0.2%, respectively, in the non-PRP group for the same period. The percentage facial swelling was highest at postoperative day 1 and gradually reduced over the following days (Fig 2) for both groups. The mean percentage swelling was lower for the PRP group at all time points when compared with the control. However this difference was not statistically significant.

Patients in the control group consistently had lower maximal interincisal mouth opening from the 1st to the 14th postoperative day when compared with the PRP group. Thus, interincisal mouth open-

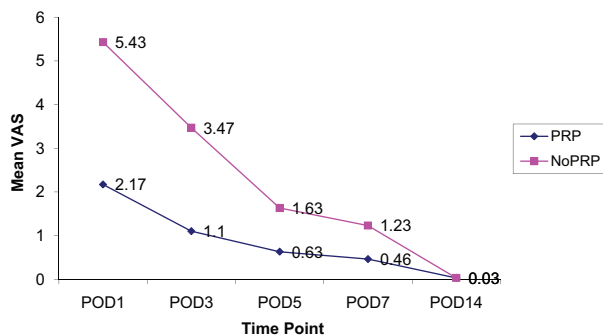


FIGURE 1. Mean postoperative visual analog scale (VAS) in PRP versus no PRP group.

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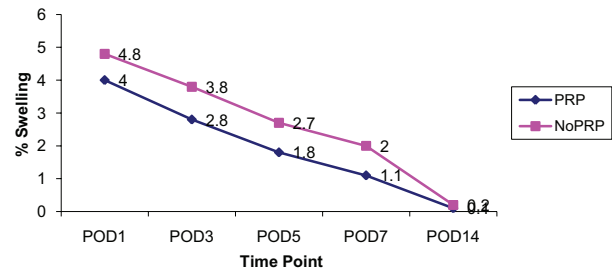


FIGURE 2. Percentage swelling in PRP versus no PRP.

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ing values were better among patients in the PRP group over the following 14 days compared with the controls, although this is not statistically significant (Fig 3).

The mean lamina dura scores at the 4th, 10th, and 16th week were 1.35 (±0.4), 1.8 (±0.4), and 1.9 (±0.3), respectively, for the PRP group, whereas it was 1.2 (±0.4), 1.3 (±0.5), and 1.6 (±0.5), respectively, for the non-PRP group. The lamina dura score was higher in the PRP group than the non-PRP group over a 16-week period; however, the difference was not statistically significant. Table 1 summarizes the mean bone scores for overall density and trabecular pattern at different periods in both groups, showing slightly higher scores in the PRP group.

Discussion

Uneventful and enhanced wound healing is desirable and critical in ascertaining quality of life after third molar surgery. This will continue to attract the attention and priority of many clinicians and researchers. This study examined the effect of PRP gel on postoperative pain, swelling, and trismus as well as healing and bone regeneration potential on third molar extraction sockets.

The mean postoperative pain score (VAS) was lower for the PRP group at all time points and this was statistically significant ($P < .05$). Furthermore, the

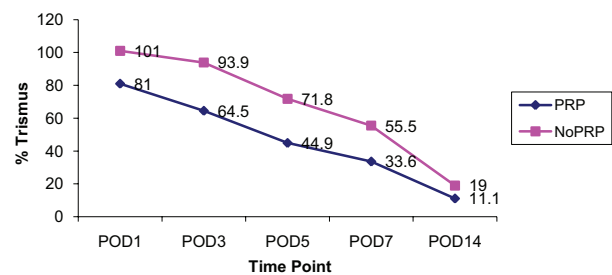


FIGURE 3. Percentage trismus in PRP versus no PRP.

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figures obtained for swelling and interincisal mouth opening were lower in the test group; this difference was not statistically significant. In this series, the mean values for pain assessment with VAS, facial swelling, and trismus were lower at all time points for the PRP group when compared with the controls. This suggests that topical application of PRP may improve the postoperative course after third molar surgery. Simon et al,¹⁹ in a prospective study, similarly reported reduced pain and better mouth opening when topical PRP gel was used in third molar extraction sockets. Furthermore, a recent retrospective study reported that PRP reduced the incidence of alveolar osteitis by 62%.⁸ This beneficial effect is thought to be related to high growth factor content of PRP and its ability to initiate and stabilize blood clot in the extraction socket.⁸

Similarly, the scores for lamina dura, trabecular pattern, and bone density were better among patients in the PRP group; this difference was also not statistically significant. Sammartino et al²⁰ established that PRP induced increased bone formation in extraction sockets as evidenced by improved clinical attachment level. Similarly, Choi et al²¹ showed in an earlier study a concentration-dependent increase in viability and proliferation of alveolar bone cells in a canine model. It is noteworthy that higher lamina dura scores were observed at the fourth week in the PRP group compared with the non-PRP group and this continued throughout the evaluation period, suggesting faster and enhanced bone healing in the PRP group. However, this finding should be interpreted with caution because the difference was not statistically significant. It is instructive that no difference was shown in mean overall bone density and trabecular pattern at the 10th and 16th weeks for both groups. We therefore opine that the lamina dura may be a more sensitive radiographic indicator of bone healing than overall density and trabecular pattern. Digital subtraction radiography and histomorphometry have provided more sensitive methods of assessing bone healing but are quite invasive and expensive especially in a resource-limited environment like ours.

The typical baseline measurement for whole blood ranges from 150,000 to 410,000 platelets/mL³ and was within the normal human range for the environment. The mean platelet enrichment factor (11.8) achieved in the present study is higher than that reported by Marx et al,¹² but compares with figures reported by Dugrillon et al.²² This difference may be attributed to the lower speed of centrifugation and the flexible open system used in the preparation rather than the automated devices applied in other studies.

The fact that the beneficial effects of PRP are more noticeable during the early phase of healing may be

traceable to the lifespan of platelet and bioavailability of the released growth factors. Marx⁹ noted that there is massive initial secretion of growth factors by platelet on activation and the effect continues but to a lesser extent until the platelets die off after 9 days when the secretory role of platelet is taken over by other chemical mediators.

The results of the present report suggest that topical application of autologous PRP gel may have a beneficial effect on the healing of extraction sockets after third molar surgery. However, a larger sample size in a multicenter study may be necessary before its routine use in extraction socket can be justified.

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