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ORIGINAL ARTICLE

Evaluation of the Efficacy of Platelet-Rich Plasma versus Platelet-Rich Fibrin in Alleviating Postoperative Inflammatory Morbidities after Lower Third Molar Surgery: A Double-Blind Randomized Study

Évaluation de l'Efficacité du Plasma Riche en Plaquettes Par Rapport à la Fibrine Riche en Plaquettes Dans le Soulagement des Morbidités Inflammatoires Postopératoires Après une Chirurgie de la Troisième Molaire Inférieure: Une Étude Randomisée en Double Aveugle

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ABSTRACT

BACKGROUND: Postoperative morbidities following impacted lower third molar (M3) surgery is of concern. The influence of platelets concentrates on postoperative inflammatory sequelae of M3 is promising. However, the comparative efficacy of platelet-rich fibrin (PRF) to platelet-rich plasma (PRP) in ameliorating postoperative morbidities remains controversial.

OBJECTIVE: The study aimed to compare the bioactive effects of PRP and PRF on postoperative pain, swelling, and trismus after impacted M3 surgery.

SUBJECTS AND METHODS: A randomized, parallel-group study of 50 subjects was designed. Preoperative and postoperative swelling, degree of mouth opening and pain were assessed on days 1, 3, and 7. Linear mixed model analysis was used to compare the effects of treatment, time-point assessment within the group, and treatment with time interaction.

RESULTS: Interaction estimates show statistically significant pain reduction with PRF (p = 0.00, 95% CI [–0.95, –0.25]. Trismus based on a time-point assessment within the PRP and PRF groups was significantly reduced (p =0.01, 95% CI [0.06, 0.38]) and (p = 0.00, 95% CI [0.12, 0.44]) respectively. Facial swelling within the PRP and PRF groups were significantly decreased (p = 0.00, 95% CI [–0.30, –0.06]) and (p = 0.00, 95% CI [–0.37, –0.13) respectively. There were no statistically significant differences between the groups for trismus and swelling. Age was a significant predictor of trismus in both groups (p = 0.04, 95% CI [–0.07, –0.01]).

CONCLUSION: PRF was more effective in reducing post-operative pain compared to PRP. Furthermore, the study shows that platelet concentrates positively modulate post-inflammatory sequelae of impacted M3 surgery. **WAJM 2022; 39(4): 343–349.**

Keywords: Platelet concentrates, pain, swelling, trismus, third molar.

RÉSUMÉ

CONTEXTE: Les morbidités postopératoires consécutives à une chirurgie de la troisième molaire inférieure (M3) impactée sont préoccupantes. L'influence des concentrés plaquettaires sur les séquelles inflammatoires postopératoires de M3 est prometteuse. Cependant, l'efficacité comparative de la fibrine riche en plaquettes (PRF) et du plasma riche en plaquettes (PRP) dans l'amélioration des morbidités postopératoires reste controversée.

OBJECTIF: L'étude visait à comparer les effets bioactifs du PRP et du PRF sur la douleur, l'enflure et le trismus postopératoires après une chirurgie M3 impactée.

SUJETS ET MÉTHODES: Une étude randomisée en groupes parallèles de 50 sujets a été conçue. Le gonflement préopératoire et postopératoire, le degré d'ouverture de la bouche et la douleur ont été évalués les jours 1, 3 et 7. Une analyse de modèle mixte linéaire a été utilisée pour comparer les effets du traitement, l'évaluation ponctuelle au sein du groupe et le traitement avec l'interaction temporelle.

RÉSULTATS: Les estimations d'interaction montrent une réduction statistiquement significative de la douleur avec le PRF (p = 0.00, IC à 95 % [–0.95, – 0.25]. Le trismus basé sur une évaluation ponctuelle dans les groupes PRP et PRF a été significativement réduit (p = 0.01, 95 % IC [0.06, 0.38]) et (p = 0.00, IC 95 % [0.12, 0.44]) respectivement Le gonflement du visage dans les groupes PRP et PRF a été significativement diminué (p = 0.00, IC 95 % [–0.30, –0.06]) et (p = 0.00, IC 95 % [–0.37, –0.13) respectivement. Il n'y avait pas de différences statistiquement significatives entre les groupes pour le trismus et le gonflement. L'âge était un prédicteur significatif du trismus dans les deux groupes (p = 0.04, 95 % IC [–0.07, –0.01]).

CONCLUSION: Le PRF était plus efficace pour réduire la douleur postopératoire que le PRP. De plus, l'étude montre que les concentrés plaquettaires modulent positivement les séquelles post-inflammatoires de la chirurgie M3 impactée. **WAJM 2022; 39(4): 343–349.**

Mots clés: concentrés plaquettaires, douleur, gonflement, trismus, troisième molaire

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Abbreviations: PRF, Platelet-Rich Fibrin; **PRP,** Platelet-Rich Plasma.

INTRODUCTION

The surgical removal of impacted lower third molar (M3) is a common procedure associated with unpleasant postoperative morbidities such as pain, trismus, and facial swelling. These complications have been reported to cause a decline in the patient's quality of life within the first postoperative week. Measures that have been employed either singly or in combination to alleviate these untoward experiences include flap designs, flap suturing techniques, use of drains, cryotherapy, and use of medications (corticosteroids and analgesics). These have not made the surgical removal M3 more attractive despite their relative beneficial effects on inflammatory postoperative complications.

Platelet concentrates – Platelet-rich Plasma (PRP) and Platelet-rich Fibrin (PRF) have been investigated as possible bioactive autologous adjuncts to ameliorate these complications. Platelet concentrates are reported to have a promising bioactive therapeutic effect on postoperative inflammatory morbidities after lower third molar (M3) surgery.[2]

Marx, *et al*[2] reported the first clinical application of platelet-rich plasma (PRP) in dentistry. PRP requires an external biochemical activation for the release of bioactive proteins (growth factors).[3] A combination of calcium chloride and bovine thrombin were the initial activators used, although the use of bovine thrombin resulted in life-threatening coagulopathies.[4]

Choukroun, *et al*[5] developed platelet-rich fibrin (PRF) that is activated during centrifugation with the release of bioactive proteins from the α granule of platelets entrapped in PRF matrix. Released growth factors like Platelet-derived growth factor (PDGF), Transforming growth factor ((TGFb1 and TGFb2), Vascular endothelial growth factor (VEGF), three isomers of platelet-derived growth factors (PDGF-aa, PDGF-bb, and PDGF-ab), and Endothelial growth factors (EGF) promote vascular angiogenesis, cellular mitogenesis, proliferation, chemotaxis, and clinically result in postsurgical inflammation control, accelerated repair and regeneration of tissues.[6]

Two studies[7,8] comparing the effect of either PRF or PRP against control on postoperative inflammatory morbidity following M3 surgery have reported positive therapeutic outcomes with platelet concentrates. Furthermore, studies have suggested the superiority of PRF to PRP in modulating postsurgical inflammatory morbidities due to the use of bovine thrombin for activating PRP that causes a rapid release of cytokines resulting in suboptimal bioactive effect of PRP on tissues[9,10] and associated life-threatening coagulopathies. On the contrary, PRF does not require external compounds for activation, leading to a more physiologic release of cytokines.[10] Arenaz-Bua et al. however reported no benefits using platelet-rich plasma.[11]

These contrary results could be partly attributed to the effects of variation in centrifuge design on the quality and quantity of platelet concentrates that were not considered.[2,11] The revolution per minute (RPM) of a centrifuge has an equivalent relative centrifugal force (RCF), which is determined by the centrifuge rotor radius.[12] This determines the sedimentation and concentration of cellular components.[12] Consequently, in the preparation of platelet concentrate, the RPM equivalent of the RCF stated in the referenced protocol is determined by the formula, $RCF = (1.118 \times 10^{-5}) \times RPM^2 \times R$, where R is the radius of the study centrifuge rotor in centimetre and RCF is relative centrifugal force stated in the referenced protocol.[13] Inappropriate RPM would result in the preparation of concentrates with growth factor release kinetics and therapeutic effects that differ from the referenced concentrate preparation.[12] These variations have made a comparison of platelet concentrates efficacy challenging.

The method of statistical analysis could also be responsible for the outcome discrepancies. This is because the effects of inconsistencies in time point interval for outcome evaluations and the possible correlation of these outcome variables were not statistically addressed and to the best of the authors' knowledge, this study will be the first to factor in these variables. The mixed model analysis will be employed to eliminate the contingencies in results that occur with the uneven spacing of time-point assessment of study outcome which was observed in previous studies.[14,15] Furthermore, the mixed model analysis also voids the effect of correlation in outcome variables since pain, swelling and trismus observed on the first postoperative day affect the evaluation of outcome measures of subsequent postoperative days.[16]

Presently, there are safe platelet activators like calcium chloride, human thrombin, type 1 collagen, and thrombin receptor activating peptide.[17] Therefore, PRP and PRF bioactive effects on inflammatory morbidities after M3 surgery can be safely investigated in humans. This study was designed to evaluate and compare the therapeutic effects of PRP and PRF on postoperative pain, swelling, and trismus while controlling for centrifuge design and specified fold-increase in platelet count.

PATIENTS AND METHODS

This was a parallel-group, double-blind, randomized study done at our hospital between May 2017 and November 2019. The institution's ethics board approved the study (ADM/E 22/A/VOL. VII/1463) and all participants gave written informed consent. Based on the difference in mean pain scores for the study groups reported in previous studies (2.17 for PRP[1] and 4.716 for PRF[14]), with a 95% CI, and 80% power, the sample size of fifty participants was determined. The inclusion criteria were patients indicated for transalveolar surgery of M3, consenting male and female patients within the age range of 18 to 55 years, mesioangular, Class II and Position B impactions, surgical site clinically free of infection, duration of surgery not exceeding 30 minutes (from time of the first incision), and platelet count within 150,000–450,000 cells/μL. Smokers, alcoholics, and those on oral contraceptives were excluded. A web-based list randomizer (RANDOMIZER.ORG) was used to allot an equal number of participants into the treatment groups.

The study participants and the evaluator of the study outcomes were blind to the type of platelet concentrate placed in the socket. The maximum interincisal opening was measured using a digital vernier caliper. Mean facial

measurement was assessed with tape using three-line measurements.[18] Pain was assessed with the VAS.

Preparation of Platelet-Rich Plasma

- Aseptic venipuncture was performed to obtain 3.5ml of blood which was transferred into a glass-coated test tube containing 0.35ml of 3.2% sodium citrate.[12]
- The double spin protocol by Perez, *et al*[13] was used and the centrifuge radius (from the centre of the centrifuge rotor to the sample) was 5cm.
- The first centrifugation at 1,338 rpm (the equivalent of 100 × g RCF) resulted in three layers and the upper and intermediate layers (1.4ml) made up of platelets and white blood cells (WBC) were transferred into a glass-coated test tube without anticoagulant for the second centrifugation.
- This second spin at 2,675 rpm (the equivalent of 400 × g RCF) produced platelet-poor plasma (PPP) and PRP as supernatant and subnatant respectively.
- The upper one-third (0.47ml) was removed and discarded while the lower two-third was manually resuspended to produce PRP concentrate.

Preparation of Platelet-Rich Fibrin

- The protocol by Choukroun, *et al*[5] was employed.
- Venous blood (10mls) was collected and transferred into a glass-coated test tube without an anticoagulant.
- The test tube with blood was centrifuged at 2,675rpm (the equivalent RPM of 400 × g RCF) which resulted in the formation of the PRF clot.
- The clot was retrieved from the test tube with a sterile tweezer.
  Sterile scissors were used to cut the PRF clot 2mm below the junction it formed with the lower red blood cell layer to incorporate platelets trapped therein.

Operative Procedure

All surgical procedures were performed by the first author. Local anaesthesia was achieved with 3.6mls of 2% lidocaine with adrenaline (1:100,000). A mucoperiosteal triangular flap was raised and tooth delivery involved sectioning of the tooth when indicated. PRP was activated with 0.19mL of 10% calcium chloride and injected at 1mm away from the end of the distal limb of the triangular flap incision after suturing of the flap. PRF clot was placed in the extraction socket with a sterile tweezer. Wound closure was done with 3–0 polyglycolic acid sutures.

Participants had oral amoxicillin trihydrate 500mg and metronidazole 400mg, taken 8 hourly for 5 days. Diclofenac potassium 50mg 12 hourly was prescribed for 3 days. Participants were placed on warm saline mouth wash 8 hourly daily for seven days.

Postoperative Data Collection

The outcome variables were evaluated on postoperative days (PODS) 1, 3, and 7, by the third author. The study participants and the evaluator of the study outcomes were blind to the type of platelet concentrate placed in the socket. The maximum interincisal opening was measured using a digital vernier caliper. Mean facial measurement was assessed with tape using three-line measurements.[17] Pain was assessed using the VAS.

Statistical Analysis

The linear mixed models were used to examine pain scores, trismus, and facial swelling measurements over the time points (Day 1, 3, and 7) for the two groups. The Restricted Maximum Likelihood method of estimation was used to analyse the repeated measured data of the outcome variables, and the unstructured covariance matrix was applied for correlation among the random effects (random intercept and random slope of each subject). The variables included in the models for each of the outcome variables were treatment group, time-point, and treatment by time–point interaction. The impact of adding covariates such as sex and age was also evaluated. A p-value of < 0.05 was statistically significant. The SPSS software (Version 22, IBM, Chicago) was used for the statistical analyses.

RESULTS

Fifty participants completed the study as shown in Figure 1. The majority (n=29, 58%) of the study participants were below 25 years of age and the mean age of participants was 26.5 ± 7.8 years. The male to female ratio of the study cohort was 1:1.9 (Table 1). There was no significant difference in age and sex between the study groups ($p = 0.23$ and $p = 0.77$ respectively).

The test for fixed effects with pain as a dependent variable indicated significant effects due to treatment ($p = 0.00$), time ($p = 0.00$), and treatment by time interaction ($p = 0.00$) implying that these parameters are potential predictors for pain relief after administering the platelet concentrates. In the estimates of fixed effect for pain (Table 2), the (fixed) intercept of 0.51 represents the baseline (day 0 or preoperative) mean VAS score of the PRP cohort. The baseline mean VAS score for the PRF cohort is (1.71 – 0.51 = 1.20) higher than that of the PRP cohort and the difference was statistically significant ($p = 0.00$, 95% CI [1.00, 2.41]). Intra-cohort estimates show that there was a statistically significant reduction in the mean pain scores ($p = 0.00$, 95% CI [–0.80, –0.36]) with time only in the PRF cohort. The interaction estimates between the platelet concentrates and time show that the mean pain score for PRF cohorts was 0.60 lower than that of the PRP cohort and the difference was statistically significant ($p = 0.00$, 95% CI [–0.95, –0.25]).

For evaluation of trismus (using inter-incisal distance), the test for fixed effects in the model indicated that time ($p = 0.00$) and age ($p = 0.05$) could be potential predictors for trismus.

In the estimates of fixed effect for trismus (Table 3), the mean baseline inter-incisal distance for the PRF group was lower that the (fixed) intercept of 4.23 for the PRP group. This difference was not statistically significant ($p = 0.96$). Intra-cohort estimates show that there was a statistically significant increase in the mean difference in inter-incisal distance across time within the PRF ($p = 0.00$, 95% CI [0.12, 0.44]) and the PRP ($p = 0.01$, 95% CI [0.06, 0.38]) groups. The interaction estimates for mean inter-incisal distance show that mouth opening was 0.08 higher

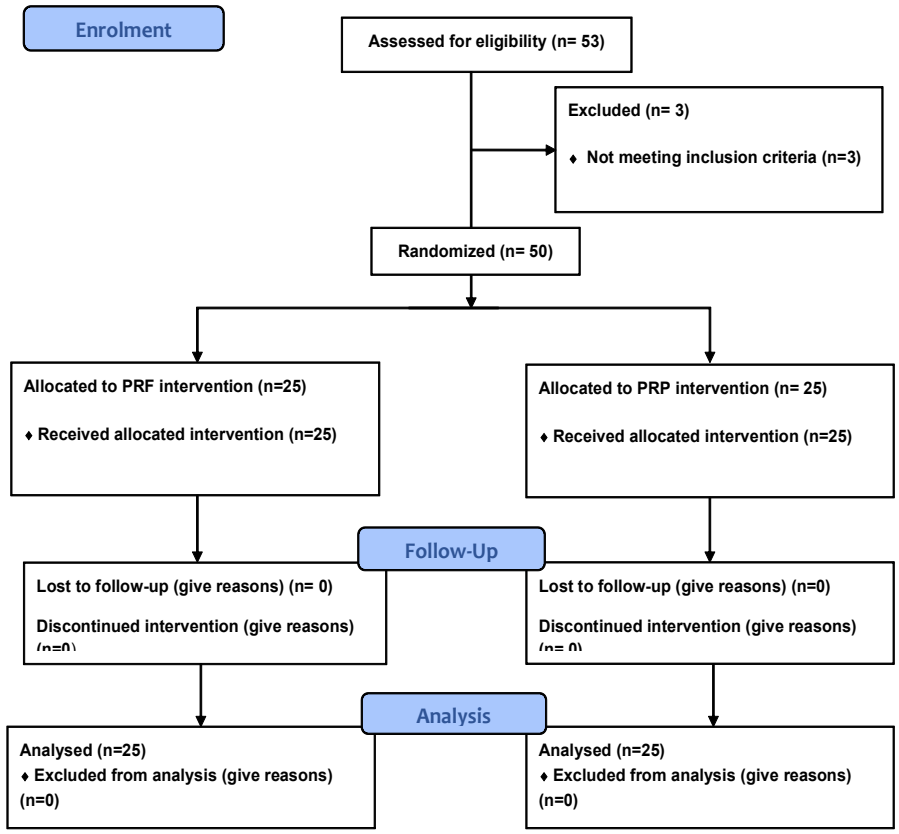

Fig. 1:

Table 1: Demographic and Clinical Characteristics of Study Participants

Variable	N	PRF (n %)	PRP (n %)	χ^2	t	P-value
Age				4.956		0.175†
18 – 25	29	18 (72)	11 (44)			
26 – 35	15	4 (16)	11 (44)			
36 – 45	4	2 (8)	2 (8)			
46 – 55	2	1 (4)	1 (4)			
Mean Age	50	25.1 ± 8.1	27.8 ± 7.5		1.223	0.227*
Gender				0.089		0.765†
Male	17	8 (32)	9 (36)			
Female	33	17 (68)	16 (64)			
Side of Extraction				0.104		0.747†
Right	13	7 (28)	6 (24)			
Left	37	18 (72)	19 (76)			

** t-test, † Pearson's Chi-squared test*

in the PRF cohort compared to the PRP group, although the increase was not statistically significant (p = 0.49). Age was a predictor for trismus and a year increase corresponds to a 0.03cm decrease in mouth opening (p = 0.05, 95% CI [–0.07, –0.01]).

The test for fixed effects in the model for the assessment of facial swelling showed that the time within the groups was the only predictor (p = 0.00). The estimates of fixed effect in Table 4 showed a significant decrease in mean facial swelling within the PRF (p = 0.00, 95% CI [–0.37, –0.13) and the PRP (p = 0.00, 95% CI [–0.30, -0.06]) groups. The interaction estimates showed a 0.07 decrease in facial swelling among the PRF group compared to the PRP, albeit not statistically significant (p = 0.42).

DISCUSSION

Available evidence supports the claim that platelet concentrates alleviate postsurgical inflammation, though there are few contrary studies.[2,5] This study found a statistically significant reduction in mean pain score with PRF compared to PRP. A possible reason for this could be due to the property of PRF that allows for it to be transformed into a membrane state following compression. This can cover the exposed surfaces of the socket and provide a shield effect from physical stimulation.[19]

The reduction in pain intensity within the PRF participants is consistent with the previous literature.[20,21] On the contrary, Ruga, *et al*[22] and Ozgul, *et al*[1] found no positive effect of PRF on pain. This difference in findings could probably be a consequence of carrying out the bilateral extractions on the same day in both studies [1,22] thus allowing for difficult interpretation of pain experience.

The mean pain within time points was slightly increased among the PRP cohorts. This contrasts with the findings of Ogundipe, *et al*[23] and Haraji, *et al*[14] that reported a significant positive effect of PRP on pain following third molar extraction. This discrepancy could be ascribed to the difference in the protocol of PRP preparation (centrifuge design and centrifugation) that is reported to influence the platelet concentration obtained.[12] A higher platelet concentration makes the bioactive proteins (such as TGF, PDGF, and VEGF) readily available for therapeutic effect. A 5-fold increment in platelet count (the minimal benchmark for therapeutic PRP preparation)[24] is obtainable with the PRP preparation technique used in this study compared to the 11-fold increment reported by Ogundipe, *et al.*[23] It is pertinent to note that other studies[6,14] that corroborated the findings of Ogundipe, *et al*[23] did not state the fold-increase in platelet count obtained in their studies. The better therapeutic effect observed with PRF could be attributed to the mechanism of activation that excludes any biochemical additive. Ehrenfest, *et al*[3] suggest that the use of

Table 2: Estimates of Fixed Effects for Pain Scores

Parameter	Estimates of Fixed Effects[a]				
	Estimate	Std. Error	Sig	95% Confidence Interval	
				Lower Bound	Upper Bound
Intercept	0.51	0.25	0.047	0.02	1.00
PRF	1.71	0.36	0.000	1.00	2.41
PRP	0[b]	0			
Time (within treatment)					
PRF	–0.58	0.11*	0.000	–0.80	–0.36
PRP	0.02	0.11*	0.857	–0.20	0.24
PRF × Time	–0.60	0.18	0.001	–0.95	–0.25
PRP × Time	0[b]	0			

a, Dependent variable: Pain.

b, This parameter is set to zero because it is redundant (used as baseline).

**The standard errors are similar as each treatment group was used as baseline relative to the other in alternate models which included the interaction effect of time and treatment.*

Table 3: Estimates of Fixed Effects for Trismus.

Parameter	Estimates of Fixed Effects[a]				
	Estimate	Std. Error	Sig	95% Confidence Interval	
				Lower Bound	Upper Bound
Intercept	4.23	0.52	0.000	3.21	5.25
PRF	–0.02	0.34	0.963	–0.69	0.65
PRP	0[b]	0			
Time (within treatment)					
PRF	0.28	0.08*	0.001	0.12	0.44
PRP	0.22	0.08*	0.006	0.06	0.38
PRF × Time	0.08	0.11	0.487	–0.14	0.29
PRP × Time	0[b]	0			
Age	–0.03	0.02	0.046	–0.07	–0.01

a, Dependent variable: Degree of mouth opening (cm).

b, This parameter is set to zero because it is redundant (used as baseline).

**The standard errors are similar as each treatment group was used as baseline relative to the other in alternate models which included the interaction effect of time and treatment.*

Table 4: Estimates of Fixed Effects for Facial Swelling

Parameter	Estimates of Fixed Effects[a]				
	Estimate	Std. Error	Sig	95% Confidence Interval	
				Lower Bound	Upper Bound
Intercept	14.18	0.14	0.000	13.90	14.45
PRF	0.22	0.19	0.252	–0.15	0.59
PRP	0[b]	0			
Time (within treatment)					
PRF	–0.25	0.06*	0.000	–0.37	–0.13
PRP	–0.18	0.06*	0.003	–0.30	–0.06
PRF × Time	–0.07	0.08	0.416	–0.23	0.09
PRP × Time	0[b]	0			

a, Dependent variable: swelling at day 1 (cm).

b, This parameter is set to zero because it is redundant (used as baseline).

**The standard errors are similar as each treatment group was used as baseline relative to the other in alternate models which included the interaction effect of time and treatment.*

biochemical additives in PRP acts as foreign bodies that could elicit inflammatory responses. The certainty of this occurring and the degree of the inflammatory response generated needs to be investigated. Furthermore, it is hypothesized that PRF has a natural fibrin framework and can protect growth factors from proteolysis and causes a steady and gradual cytokine release over 1 to 4 weeks.[25]

Unakalkar, *et al*[26] and Bhujbal, *et al*[15] compared the efficacy of PRF against PRP on pain following impacted M3 surgery with no significant difference in pain control. However, caution was taken in making a comparison with our findings because neither the method of platelet concentrate preparation nor the number of fold increase in platelet count attained was stated.

It is documented that trismus results from the inhibitory effect of muscle pain on the further movement of the traumatized site to protect the musculature.[27] The positive effect on postoperative interincisal distance observed within the groups with time in this study corroborates the findings of Hanif and Sheikh[28] and Singha, *et al*[29] who reported better mouth opening with PRP and PRF when compared to controls. The positive effect of platelet concentrates on mouth opening observed could be due to the sustained cytokine (TGF-β1, PDGF-BB, VEGF) release associated with platelet clot.[2] The cytokines bind to receptors and inhibit signalling pathways that code for IL-6, IL-7, IL-8, and IL-13 associated with jaw muscle spasm. Inter-group comparison of the effect of PRF with PRP on trismus did not reveal any statistical difference and this is consistent with the finding from an earlier study.[26]

A significant reduction in facial swelling with time within each study group was observed, although there was no significant difference in the facial swelling in the inter-group comparison. This is consistent with the study by Unakalkar, *et al*[26] but contrasts with that of Singha, *et al*[29] that reported reduced facial swelling in the PRF cohorts only. The reduction in swelling observed within the groups could be ascribed to the release of growth factors that are reported to have anti-inflammatory effects.

Females and older subjects are more predisposed to complications of third molar surgeries.[30] However, we observed that gender was not significant for the pain, swelling, and trismus although the reason for this could not be adduced. The observed negative effect of increased age on mouth opening could be attributed to the high density of the bone associated with increased age with the attendant potential for more trauma and severe postoperative complications.

A major limitation to this study was the use of postoperative non-steroidal anti-inflammatory drugs that have a therapeutic effect on the outcome measure of pain and swelling. However, the authors also recognise that it will be unethical not to place the patients on analgesics. The same prescription of analgesics was given to all study participants to obviate this confounding effect.

CONCLUSION

There was no significant difference in trismus and swelling between PRF and PRP. However, a significant reduction in pain was observed in the PRF cohort. Furthermore, within-group assessment, there was a significant benefit in pain, trismus, and swelling reduction in the PRF group while the PRP group had a positive effect on trismus and swelling only. This study, therefore, shows that platelet concentrates do not prevent post-inflammatory sequelae but can positively modulate them.

Ethics Statement/Confirmation of Patient Permission.

This study was approved by the Heath research ethics committee of the University of Benin Teaching Hospital (ADM/E 22/A/VOL. VII/1463). Patients' written informed consent were obtained.

Conflict of Interest

We have no conflict of interest.

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None.

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