

Original Research Article

Local injection of leukocyte rich platelet rich plasma produced higher radius union scoring system than local injection of pure platelet rich plasma in conservative therapy of intra-articular closed distal radius fractures

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ABSTRACT

Background: Distal radius fracture often occurs both extra-articular and intra-articular, covering all ages. The use of autologous platelet rich plasma (PRP) consisting of leucocytes rich-PRP (L-PRP) and pure-PRP (P-PRP) thought can help in bone healing process. This study aimed to determine that the administration of L-PRP provides a better healing rate than P-PRP in intra-articular closed distal radius fractures after conservative treatment.

Methods: This was a single-blinded experimental study with stratified randomized post-test only group design involving 51 patients with closed distal fractures undergoing closed reduction, consisting of 17 patients per study group. Group 1 received placebo, group 2 received P-PRP, and group 3 with L-PRP. Each group was then re-evaluated using x-ray at week 2, 3, and 6. RUSS score was then measured. Data was analysed using descriptive statistics and normality test, homogeneity test and inferential test were performed to determine the effect of L-PRP, P-PRP on the union rate of fracture distal radius. All obtained data was analysed using SPSS statistics 22 software.

Results: Between control and P-PRP group, there was significant difference in mean RUSS with p value of 0.012. Between control and L-PRP injection group, there was a significant difference in mean RUSS with p value of 0.000. Between P-PRP and L-PRP group, there was also significant mean RUSS difference with p value of 0.003.

Conclusions: There was a significant difference between the control group given placebo and the group P-PRP and L-PRP in closed fractures of the intraarticular radius after conservative therapy.

Keywords: Closed distal radius fracture, L-PRP, P-PRP, RUSS

INTRODUCTION

Injuries to the bone structure can cause malfunction, leading to complications. Distal radius fracture is the most common fracture of the hand and covers a wide range of ages from young to old. Fractures of the distal radius, both extra-articular and intra-articular that are not displaced (non-displaced), can be performed conservatively. Meanwhile, those who are displaced can undergo surgery with direct fixation of the bone using an implant to achieve optimal anatomical reduction and

function after the procedure. In conservative treatment, casting joint motion exercises can be done usually at 5-6 weeks after the configuration of the fracture is stable due to new bone growth that can be identified clinically or radiologically.¹

Various attempts have been made in the field of orthobiology which aims to accelerate the healing of bone tissue after injury to reduce complications. One of these efforts is the development of auto cell-based therapy, namely the use of autologous platelet rich plasma (PRP).

There are two types of PRP dosage forms, namely PRP rich in leukocytes called leukocytes rich-PRP (L-PRP) and PRP without leukocyte content called pure-PRP (P-PRP).²

PRP is plasma with a platelet concentration that is increased beyond normal physiological levels by centrifugation of the patient's own peripheral blood, resulting in higher concentrations of growth factors and cytokines. These growth factors which mainly play a role in bone tissue regeneration include platelet derived growth factor (PDGF), transforming growth factor (TGF β , β 1 and β 2 isomer), vascular endothelial growth factor (VEGF), insulin like growth factor (IGF), and epidermal growth factor (EGF). Other growth factors produced by platelets are platelet factor 4 (PF4), interleukin 8 (IL 8), platelet derived angiogenesis factor (PDAF), platelet derived endothelial growth factor (PDEGF), epithelial cell growth factor (ECGF), and hepatocyte growth factor (HGF). With this high concentration has the potential to accelerate bone healing through the process of recruitment, proliferation and differentiation of 3 cells that play a role in the phases of bone tissue regeneration.^{3,4}

Recent studies have given different results where the interaction of platelets and leukocytes consisting of monocytes, macrophages and neutrophils has high potential in accelerating the healing process during the acute inflammatory phase.⁵

In addition to clinical parameters, post-treatment outcome function assessment in distal radius fractures also needs to be assessed radiologically to determine the bone congestion that occurs. This parameter uses the radius union scoring system scoring (RUSS score). This scoring is said to be easy and simple and has good intra and interobserver reliability to assess postoperative and conservative outcomes. The higher the RUSS value, the better the bone healing rate.⁶

METHODS

This was a pure single-blinded experimental study with a stratified randomized post-test only group design performed in the emergency department (ED) and Orthopaedic and Traumatology Outpatient Clinic in Sanglah General Hospital, Denpasar, Indonesia during the period of July until December 2020.

Inclusion criteria

Patients with closed fracture of the distal radius within 24 hours coming to the ED after onset of injury, patient's age older than 20 year old, patients undergoing local and general anesthesia, intraarticular fractures with type B and C AO/OTA classification, and acceptable result

following closed reduction procedure. Patients were included after providing their consent.

Exclusion criteria

Patients with sepsis prior to surgery, presence of infection around injection area, patients refusing to participate in the study, patients consuming anti-inflammatory medication within 48 hours during PRP or P-PRP administration, patients under corticosteroid therapy within 2 weeks during PRP or P-PRP administration, history of steroid injection on PRP or P-PRP administration site, patients with fever, history of bone malignancy, anemia with hemoglobin less than 10 gm/dl, thrombocytopenia less than 105000/ul, unacceptable result following closed reduction and cast immobilization under radiological evaluation, displaced fracture during observation period and patients undergoing internal fixation were excluded.

Fifty-one patients with closed distal radius fracture undergoing closed reduction were included in this study. Subjects were then divided into three groups: control (placebo) group, P-PRP group and L-PRP group, each consisting 17 patients. Each group was then re-evaluated using x-rays at week 2, 3, and 6 following intervention. RUSS score was then measured. Data was analysed descriptively and normality test, homogeneity test, and inferential test were carried out to determine the effect of L-PRP and P-PRP on the union rate of fracture distal radius. All obtained data will be analysed using SPSS statistics 22 software.

RESULTS

Characteristics of research subjects

The subjects of this study were 47 patients with closed fractures of the intra-articular radius distal who were diagnosed in the emergency department of Sanglah Hospital. Based on the data in Table 1, out of a total of 47 research subjects, 22 (46.8%) were male, and 25 (53.2%) female. The sex distribution of patients based on the procedure performed was 8 (50%) male patients and 8 (50%) female patients in the LR-PRP group, 8 (53.3%) male and 7 female patients. (46.7%) women in the P-PRP group, and 6 (37.5%) men and 10 (62.5%) women in the control group who received placebo.

The mean age of the patients as a whole was 44.53 ± 16.8 years, with a range of 20-78 years. In the group receiving L-PRP, the mean age of the patients was 43.25 ± 15.2 years, while in the group receiving P-PRP the mean age of the patients was 45.60 ± 18.93 years, while in the control group who received placebo it was found that the mean age of the patients was 44.81 ± 17.27 years.

Table 1: Distribution of characteristics of research subjects in each group.

Variables	Group			Total
	L-PRP (n=16)	P-PRP (n=15)	Control (n=16)	
Sex [n (%)]				
Male	8 (17.0)	8 (17.0)	6 (12.8)	22 (46.8)
Female	8 (17.0)	7 (14.9)	10 (21.3)	25 (53.2)
Age (years) (mean±SB)	43.25±15.2	45.60±18.93	44.81±17.27	44.53 ±16.8
AO classification [n (%)]				
B	6 (12.8)	8 (17.0)	7 (14.9)	21 (44.7)
C	10 (21.3)	7 (14.9)	9 (19.1)	26 (55.3)
RUSS score (mean±SB)	5.25±1.0	4.27±1.3	3.19±1.2	4.23±1.4

Table 2: Comparison of the mean value of WBC and PLT count between whole blood and post-centrifugation blood for P-PRP and L-PRP.

Variables	Sample		P value
	Whole blood	Post centrifugation blood	
P-PRP			
WBC (mean±SB)	13.86±4.42	4.16±1.33	0.00
PLT (mean±SB)	259.25±51.09	1024.67±193.77	0.00
L-PRP			
WBC (mean±SB)	16.17±4.15	67.85±17.48	0.00
PLT (mean±SB)	242.58±38.67	1102.74	0.00

Description: WBC = white blood cell, PLT = platelet, L-PRP = leucocyte rich- platelet rich plasma, P-PRP = pure-platelet rich plasma, SB = standard

Based on the type of fracture according to the AO classification, 21 people (44.7%) had distal radius type B fractures, while 26 others (55.3%) experienced type C distal radius fractures. B and 62.5% type C in the group receiving LR-PRP, 53.3% type B and 46.7% type C in the group receiving P-PRP, and 43.8% type B and 56.3% type C in the placebo group. The mean total RUSS score of the 47 study subjects was 4.23±1.4. In the group that received L-PRP, the mean RUSS score was 5.25±1.0, while in the group that received P-PRP the mean RUSS score was 4.27±1.3, and in the control group who received the placebo the mean RUSS score was 3.19±1.2.

Table 3: Comparison of the average count value of WBC and PLT between P-PRP and L-PRP preparations.

Variables	Sample		P value
	P-PRP (n=15)	L-PRP (n=16)	
WBC (mean±SB)	4.16	67.86	0.00
PLT (mean±SB)	1024.67	1102.74	0.206

Description: WBC = white blood cell, PLT = platelet, L-PRP = leucocyte rich- platelet rich plasma, P-PRP = pure-platelet rich plasma, SB = standard

This study also assessed the count of white blood cells (WBC) and platelets (PLT) in whole blood (WB) before and after centrifugation (Table 2). In the P-PRP group,

there was a decrease in the mean WBC count by 3.3 times (from 13.86 to 4.16) and an increase in the mean PLT count by 3.95 times (from 259.25 to 1024.67) in blood. Post-centrifugation was compared with whole blood, whereas for the L-PRP group, the mean WBC count increased by 4.20 times (from 16.17 to 67.85) and an increase in the mean PLT count was 4.55 times (from 242.58 to 1102.74) in post-centrifugation blood compared with whole blood. In both the P-PRP and LR-PRP groups, WBC and PLT levels before and after centrifugation were significantly different (p value =0.00). After centrifugation, the WBC and PLT count values were calculated for the P-PRP and L-PRP groups (Table 3). It was found that the mean WBC levels from L-PRP preparations were significantly higher than those of P-PRP preparations (p value =0.00). Meanwhile, the PLT levels between the PPRP and L-PRP preparations were not significantly different (p value =0.206)

Furthermore, data analysis was carried out by comparing the mean RUSS scores between the three treatment groups. Before the mean comparison analysis was carried out, it was preceded by the normality and homogeneity test. With a total of 47 research subjects (less than 50 people), the normality test used was the ShapiroWilk test and continued with the homogeneity test using the Levene test. Based on the test results, the samples in this study were stated to be homogeneous and normally distributed.

Table 4: Results of the one way ANOVA test on the RUSS variable of the three treatment groups.

RUSS	Sum of squared deviation	Degrees of freedom	Variance	F	P value
Per group	45.245	2	22.622		
In group	57.308	44	1.302	17.369	0.000
Total	102.553	46			

Table 5: LSD post hoc test results.

RUSS		Different average	P value	Confidence interval 95%	
				Upper limit	Lower limit
Control	P-PRP	-1.079	0.012	-1.91	-0.25
	L-PRP	-2.375	0.000	-3.19	-1.56
P-PRP	Control	1.079	0.012	0,25	1.91
	L-PRP	-1.296	0.003	-2.12	-0.47
L-PRP	Control	2.375	0.000	1.56	3.19
	P-PRP	1.296	0.003	0.47	2.12

Inferential analysis aimed to generalize research results to the population. The inferential statistical test used in this study was one way ANOVA with the LSD post hoc test because the data were normally distributed and the data variants were homogeneous. The one way ANOVA test results showed that the mean RUSS scores of the three groups were significantly different (p value =0.00).

The results of the post hoc LSD test comparing the control group with the P-PRP injection group, the control group with the L-PRP injection group, and between the L-PRP and P-PRP injection groups can be seen in Table 5.

Comparison of mean between groups

Table 4 shows that between the control group and the group that received P-PRP injection, the mean difference was 1.079. This difference was significant with a p value of 0.012 and a 95% confidence interval between 0.25 and 1.91. Table 5 shows that between the control group and the group that received the L-PRP injection, the mean difference was 2.375. This difference was significant with a p value of 0.000 and a 95% confidence interval between 1.56 and 3.19. Table 5 shows that between the group that received the P-PRP injection and the group that received the L-PRP injection, the difference in mean was 1.296. This difference was significant with a p value of 0.003 and a 95% confidence interval between 0.47 and 2.12.

DISCUSSION

Based on the results of this study, the basic characteristics of research subjects had a difference of less than 20% so that the baseline for each group could be compared and avoid bias. In detail, the proportion of research subjects who were female was more than male, namely 25 people

(53.2%) women and 22 people (46.8%) men. This is in accordance with the literature that the incidence of distal radius fractures in the second decade is generally more common in women than men, which are closely related to osteoporosis and hormonal causes.^{7,8} In this study, it was found that the mean age of the patients was 44.53 years with an age range of 20-78 years. The literature states that the most adult age in the second decade of distal radius fracture cases is between 57-66 years. Based on gender, where the average age of women is 60 years and men are 40 years old. Fracture classification based on AO/OTA in this study was found to have more type C fractures, namely 26 people (55.3%) compared to type B as many as 21 people (44.7%). This is in accordance with the literature which states that the incidence of closed fracture cases distal to the intraarticular radius is more AO/OTA type C, amounting to 25-35% when compared to type B, which is 9-16%.^{7,8}

Based on treatment analysis, P-PRP decreased WBC by 3.3 times and increased PLT concentration by 3.95 times after centrifugation compared to WB. For the L-PRP group, there was an increase in WBC by 4.20 times and an increase in PLT by 4.55 times after centrifugation compared to WB. In both the P-PRP and LR-PRP groups, WBC and PLT levels before and after centrifugation were significantly different (p value =0.00). Based on these data, it can be concluded that the concentrations of PLT and WBC produced in P-PRP and L-PRP were significantly higher than those in WB. When calculating the ratio of WBC and PLT concentrations in the P-PRP group compared to L-PRP, the results showed that the WBC concentration in L-PRP was significantly higher than P-PRP (p value =0.00). Meanwhile, the PLT concentration between the P-PRP and L-PRP preparations was not significantly different (p value =0.206) so that the PLT difference between P-PRP and L-PRP was not a confounding factor. The results above are consistent with research conducted by Devereaux et al,

that in general the PLT levels in PRP are in the range of 3-5 times the WB value. WBC levels in L-PRP are more than 100% levels in WB.⁹ In Kenmochi's study, almost the same results were obtained, namely that the PLT concentration increased by 4.8 and WBC increased by 2.6 times in L-PRP.¹⁰

In this study, the results obtained were that the group of research subjects who received P-PRP injection showed that the mean RUSS score was significantly higher than placebo in the 6 week post-injury period (p value =0.012, CI 95% =0.25-1.91). This indicated that P-PRP significantly increased callus formation more effectively than placebo. This is in line with the results of a previous study conducted by Paramarta et al on 22 distal radius fracture patients who were treated conservatively and administering P-PRP in the fracture area which significantly resulted in a higher RUSS score than the placebo group.¹¹ The same results were also obtained in a study in India of 25 patients who experienced closed fractures of the distal radius treated conservatively who were given P-PRP showed radiological union that was statistically significantly faster than controls.¹² In a randomized controlled study by Namazi et al also showed a better PRWE score at follow-up for 6 months after intraarticular injection of P-PRP compared to placebo in distal radius fractures.¹³

In this study, it was found that the group of study subjects who received L-PRP injection in the fracture area showed a significantly higher mean RUSS score in the 6-week post-injury period 68 compared to the placebo group (p value =0.00, CI 95% =1.56-3.19). This indicated that L-PRP was significantly able to increase callus formation compared to placebo. The same results were also obtained in a study of 33 patients with tibial mid-shaft fractures who were fixed by interlocking tibial nails and given Autologous L-PRP gave a significant result of faster callus formation than those who were not given L-PRP after 3 months of follow-up.¹⁴ Similar results were obtained in the study of Dallari et al, who reported a randomized controlled trial of L-PRP in patients undergoing medial-opening wedge osteotomy of the proximal tibia. The addition of L-PRP to lyophilized bone chip increases the osteogenetic potential of lyophilized bone chip and can be useful in the treatment of patients with massive bone defects.¹⁵

Bielecki et al reported a case of tibial non-union infected with a fistula, with a positive microbiology for MSSA, given percutaneous injection of L-PRP. Five months after the injection of L-PRP there was union and healing of the wound. This report shows that L-PRP has antibacterial activity and repair ability, which can overcome infection and non-union simultaneously.^{16,17} Clinical study of 50 knee patients with OA and mostly OA grade III and IV with extensive cartilage defects given L-PRP injection for 4 times and observed for 7 months showed that the defect was repaired and covered with fibrocartilage tissue which led to clinical improvement of the patient significance.¹⁰

In this study, it was found that the group of study subjects who received L-PRP injection in the fracture area showed a significantly higher mean RUSS score in the 6 week post-injury period compared to the group receiving P-PRP injection (p value =0.003, CI 95% =0.47-2.12). This indicates that L-PRP significantly increases callus formation more effectively than PPRP. This result is in line with the research of Ziegler et al which showed that L-PRP produced growth factors PDGF-AA, PDGF-AB, PDGF-BB, VEGF, EGF, TGF- β_2 which were significantly higher than P-PRP and BMC.¹⁸ The same study also stated that the presence of leukocytes in PRP increased growth factors. It was proven in research that the addition of leukocytes resulted in higher levels of TGF- β_1 , PDGF-AB and PDGFBB compared to PRP without leukocytes in oral and dental surgery cases.¹⁹ Leukocytes also play a role in synthesizing fibronectin + extracellular matrix rapidly at the hematoma fracture site within 48 hours post-trauma before stromal cells secrete it. The role of leukocytes in this phase has been known that leukocytes are able to produce fibrin trobus by depositing fibronectin matrix in gap fractures.^{20,21} Leukocytes also produce proteinases such as serine and MMP which play a role in activating growth factors such as TGF- β , because when they are released they are still in an inactive form. TGF- β and bFGF are stored bound to the extracellular matrix, and degradation of the matrix by these proteinases excludes these growth factors. MMP also has a role in the remodeling of bone and cartilage tissue and in the angiogenesis process.¹⁹ Monocytes circulating in peripheral blood can differentiate into 2 types of macrophages, namely M₁ and M₂ depending on the activator stimulus. If stimulated due to infection with microorganisms it produces M₁ macrophages which have a pro-inflammatory effect which produces an antimicrobial effect by inhibiting bacterial proliferation by producing nitric oxide and the proinflammatory cytokines IL-6 and TNF-alpha. If stimulated by anti-inflammatory agents (marked by increased IL-4, IL-5, IL-9 and IL-3) it will become M₂ which has a tissue regeneration function by producing angiogenic factors and several cytokines. This is the basis that the interaction of leukocytes and platelets in the injured area produces anti-inflammatory molecules, although some still argue that leukocytes can increase inflammatory factors.²² Some journals say that the addition of leukocytes to PRP in the management of bone fractures is still under debate because naturally there will be a balance that controls the overproduction of the cellular types that play a role. The premise is that neutrophils first enter the area of injury and release ROS to kill foreign bodies and clear necrotic tissue due to injury. On the other hand, macrophages can also induce neutrophil apoptosis to prevent the potential for excess negative effects of neutrophils.¹⁹ From the results of this study, it is said that in pathological cases or fractures that expect increased vascularization or better bone healing, the administration of L-PRP can be a major consideration because the concentration of growth factors is higher than P-PRP or BMC.¹⁸

This study has several limitations, in the form of a low sample size, so that it cannot represent the population as a whole, the follow-up time is limited, given that the radiological parameters of distal radius fracture (including RUSS) can continue to change for up to 12 weeks, even after 1 year. Post injury, future studies require a longer follow-up time. This study also did not evaluate the functional outcome of the patient, so it cannot be determined whether a high RUSS score is associated with functional outcome in these patients

CONCLUSION

Injection of P-PRP and L-PRP in the fracture area was shown to produce a higher RUSS score compared to placebo in closed fractures of the intraarticular radius after conservative therapy. Injection of L-PRP in the fracture area was shown to produce a higher RUSS score when compared to P-PRP in closed fractures of the intraarticular radius after conservative therapy.

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