UZUN KEMİKLERİN DİAFİZİEL KIRIKLARININ GECİKMİŞ KAYNAMASINDA PLATELET-RİCH PLASMA UYGULANMASININ ETKİLERİ

Effect of Platelet-Rich Plasma Administration on Delayed Union of Diaphyseal Fractures of Long Bones

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Geliş tarihi/Received: 05.11.2015
Kabul tarihi/Accepted: 15.02.2016

Bozok Tıp Derg 2015;6(1):1-6
Bozok Med J 2015;6(1):1-6

ÖZET

Amaç: Dengeli olarak tespit edilmiş, kaynama gecikmesi olan uzun kemiklerin diafiziel kırıklarında plateletten zengin plazmanın etkisini araştırmayı amaçladık.

Metod: Dengeli olarak tespit edilmiş, kaynama gecikmesi olan 30 uzun kemik diafiziel kırığı hastası retrospektif olarak değerlendirildi (Grup 1). Karşılaştırma amacıyla stabil olarak tespit edilmiş kaynama gecikmesi olan 22 uzun kemik diafiz kırığı olan hasta prospektif olarak değerlendirildi (Grup 2). Bu iki grup iyileşme oranı ve zamanına göre karşılaştırıldı

Bulgular: Kırık kaynama oranı Grup 1'de 24 hasta (%80) grup 2'de 20 hasta (%90,9) olarak tespit edildi (p = 0.281). Ortalama kırıkların kaynama süresi grup 1'deki 24 hastada ve Grup 2'deki 20 hastada sırayla 167 (104 - 246) gün ve 161 (116 - 233) gün olarak tespit edildi (p=0.645). Kırıkların kaynama zamanı gözönüne alındığında 2 grup arasında istatistiksel olarak fark yoktu.

Sonuç: Kaynama gecikmesi olan hastalada plateletten zengin plazmanın faydalı etkileri olduğunu söyleyebiliriz. Daha geniş serilerle yapılacak yeni çalışmaların plateletten zengin plazmanın klinik etkilerini daha net şekilde açıklayabilir.

Anahtar kelimeler: *Gecikmiş kaynama; Kırık iyileşmesi; Plateletten zengin plazma*

ABSTRACT

Background: The aim was to investigate the effect of platelet-rich plasm use on delayed union of diaphysis fractures of long bones, having stable fixation.

Material and Methods: A total of 30 patients having stable fixation and delayed union of diaphysis fractures of long bones were retrospectively evaluated (Group 1). For comparative purposes, 22 patients with stable fixation, delayed union of diaphysis fractures of long bones and treated with Platelet rich plasma (PRP) injection were prospectively evaluated (Group 2). The 2 groups were compared in terms of recovery rate and time.

Results: Fracture union was detected in 24 (80%) patients in group 1 compared to 20 (90.9%) patients in group 2 (p = 0.281). The median union time of 24 patients in group 1 and 20 patients in group 2 were 167 (104 - 246) days and 161 (116 - 233) days, respectively (p=0.645). There was no statistically significant difference between the 2 groups regarding fracture union time.

Conclusion: We conclude that platelet-rich plasma has beneficial effects on delayed union. By increasing the number of cases with new studies more clear expressions regarding the clinical efficacy of platelet-rich plasma may be made.

Key words: *Delayed union; Fracture healing; Platelet-rich plasma*

Bozok Tıp Derg 2016;6(1):1-6
Bozok Med J 2016;6(1):1-6

INTRODUCTION

Fracture union is no pain and movement at fracture line clinically and the presence of callus formation in at least 3 cortices of fracture line on 2-axis radiograpically. Union delay is the absence of union findings during the expected time, nonunion is no significant process of union findings clinically and radiographically although 2-3 months after the expected time of union are completed (1).

Union delay and nonunion can be treated using careful regulation of mechanical and biologic factors (2, 3). Recently, Platelet-Rich Plasma (PRP) including more than 30 active proteins known to stimulate fracture healing such as platelet derived growth factor (PDGF), transforming growth factor (TGF) and insulin-like growth factor (IGF) is extensively used in areas of union problem (4-8).

In the present study, we aimed to investigate the effect of PRP administration on union delay of long bone diaphyseal fractures having stable fixation.

PATIENTS AND METHODS

Long bone diaphyseal fractures of 30 patients having surgical intervention, stable fixation and delayed union diagnosis were retrospectively evaluated between November 2005 and December 2010 (Group 1). Twenty two patients with stable fixation and PRP administration due to delayed union diagnosis were prospectively evaluated between September 2010 and July 2013 (Group 2). The mean age of patients in group 1 was 36 (19-64) years and female/male ratio was 9/21. The mean age of patients in group 2 was 38 (18-69) years and female/male ratio was 6/16. The most common cause of fracture was accident (fall from height and traffic) in both group. There was no more than 1 delayed union of long bone for each patient. Although 2 patients in group 1 and 1 patient in group 2 were operated with the diagnosis of double fracture of the forearm, the diagnosis of delayed union was limited to only one bone.

Eighteen patients (60%) in group 1 and 12 patients (54.5%) in group 2 were operated with the diagnosis of open fracture. According to Gustillo Anderson classification of open fractures, 5 fractures were type I (27.7%), 7 fractures were type II (38.8%) and 6 fractures were type III (33.3%) in group 1, 4 fractures were type I (33.3%), 5 fractures were type II (41.6%) and 3 fractures were type III (25%) in group 2. For fixative purposes, intramedullary nailing (IMN) was preferred in 12 cases and plate-screw was used in 10 cases in group 1. Open fractures of 8 patients were initially fixated using monolateral external fixator (E.fix), then IMN or plate-screw procedure was performed in 7 patients. In group 2, IMN was preferred in 9 patients and plate-screw was used in 7 patients. E.fix was performed in 6 patients and 3 of them underwent IMN or plate-screw procedure after E.fix (Table 1).

Table 1: Fracture distribution and performed surgical fixation methods in both groups

	open fracture / fracture	Femur	Tibia	Humerus	Radius	Ulna	Fixation: IMN / plate-screw / E.fix / E.fix + IMN / E.fix + plate-screw
Group 1	18/12	6	10	7	3	4	12/10/1/4/3
Group 2	12/10	4	9	6	2	1	9/7/3/2/1

Systemic and local factors that may cause union delay were rewieved; diabetes mellitus in 2 patients, smoking in 9 patients, neurologic impairment in 1 patient, additional soft tissue injury in 3 patients, and drug addiction in 1 patient were detected in group 1. Diabetes mellitus in 3 patients, smoking in 7 patients and additional soft tissue injury in 4 patients were observed in group 2 (Table 2).

At the 3rd postoperative mont, patients were treated with PRP injection to fracture lines in group 2. Single PRP injection was used in 8 patients. Double injection was used in 8 patients. Triple injection with 1-month interval was preferred in 6 patients. No patient had no more than 3 injections.

Table 2. Risk factors in both groups.

Risk Factors		Group 1	Group 2
Systemic	Tip 2 diabetes mellitus	(1.4),(1.12)	(2.5),(2.7),(2.19)
	Smoking (>3months)	(1.2),(1.5),(1.9),(1.13), (1.14),(1.18),(1.20),(1.21),	(2.1),(2.9),(2.13),(2.15), (1.25),(2.18), (2.19), (2.22)
	Drug addiction	(1.30)	-
Local	Neurologic impairment	(1.3)	-
	Soft tissue injury	(1.3),(1.8),(1.25)	(2.2),(2.6),(2.11),(2.21)

Patients were classified according to the group, not systematically. e.g. (1.3) means 3rd ranked patient in group 1.

PRP ADMINISTRATION

Sixty cc Gravitational Platelet Separation System (GPS, Biomet, Warsaw, IN, USA) was used as PRP seperating system. In a single-use 60 cc injector 5 cc ACD-A Anticoagulant Citrate Dextrose Solution and 55 cc venous blood sample of patients were mixed and the injector was placed to platelet seperator. After 15-minute 7000 rpm centrifuge procedure, platelet poor plasma was aspirated and removed. Afterwards 5 cc PRP containing 9.3 times more platelets and 5.3 times more white blood cells in mm3 from normal blood values was aspirated using a 10 cc injector. Obtained 5 cc PRP was injected to fracture line with the aid of scopy guidance (Figure 1). After injection patients were hospitalized for an hour and then discharged on the same day. After PRP injection procedure, patients in group 2 were prospectively followed-up and all patients were reevaluated clinically and radiologically. Patients in group 1 were retrospectively evaluated using hospital records including examination findings and same-date plain radiographs. Patients in 2 groups were compared regarding healing rate and time. Chi-square test, student's t-test and Kolmogorov-Smirnov test were used for statistical analyses.

RESULTS

In 2 groups, patients with delayed union were compared regarding union time and rate. For 24 patients (80%) in group 1 and 20 patients (90.9%) in group 2 reunion was observed without additional surgical procedure during follow-up. There was no statistically significant difference between the 2 groups (p=0.281). The mean union time of 24 patients in group 1 was 167 (104-246) days and the mean union time of 20 patients in group 2 was 161 (116-233) days. There was no statistically significant difference regarding union time between the 2 groups.

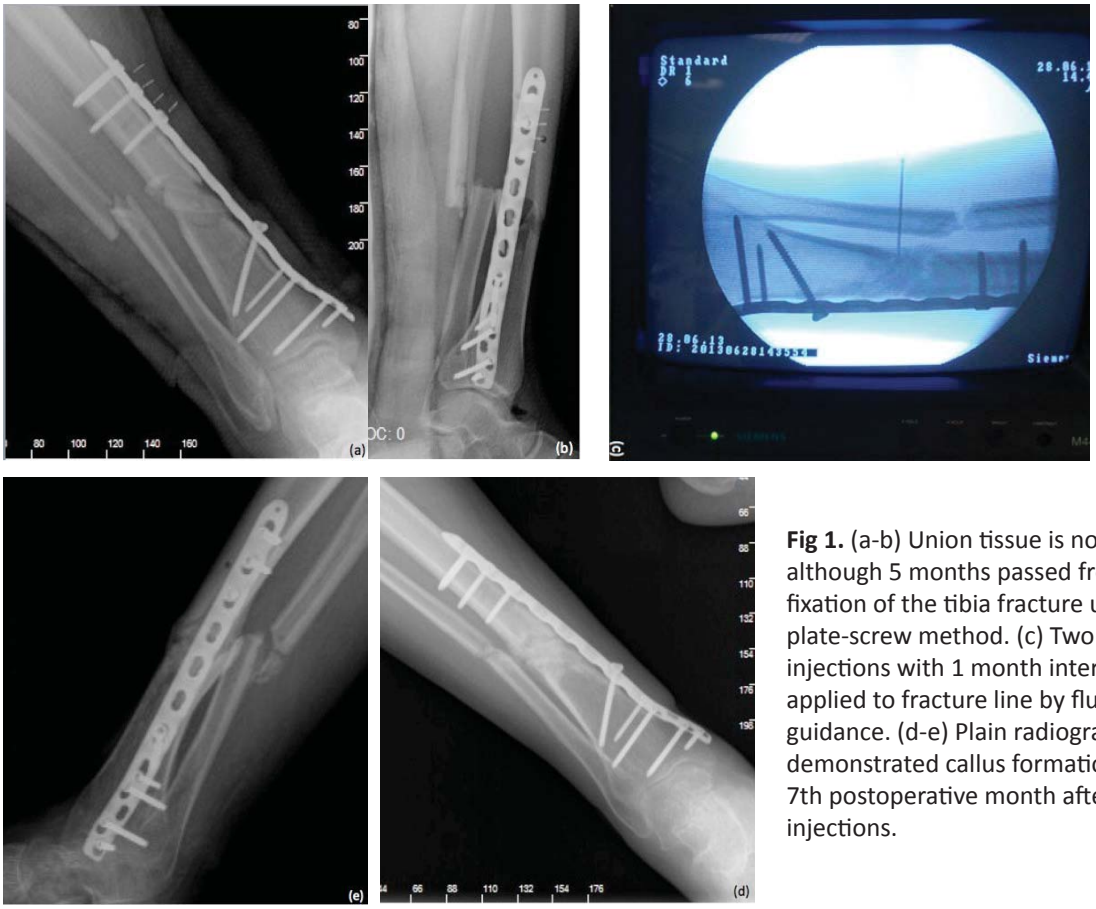

Fig 1. (a-b) Union tissue is not seen although 5 months passed from the fixation of the tibia fracture using plate-screw method. (c) Two PRP injections with 1 month interval were applied to fracture line by fluoroscopy guidance. (d-e) Plain radiographs demonstrated callus formation at the 7th postoperative month after PRP injections.

Additional surgical intervention due to the detection of nonunion was applied to 1 femoral and 1 humeral fracture in group 1, 2 femoral, 2 tibial, 1 humeral, and 1 ulnar fracture in group 2 at the end of the 9-month follow-up. Reunion was observed in all Gustillo Anderson type III open fractures in group 2, in 3 of 6 patients of group 1 additional surgical intervention was needed for nonunion. When we compared the 2 groups in terms of union rate and time of open and closed fractures, 10 of 12 open fractures (83.3%) healed in 191 (128-233) days in group 2. Healing was observed 12 of 18 open fractures (66.6%) in 178 (134-246) days in group 1 ($p>0.05$) (Table 3). In group 1, only 1 of 8 patients (12.5%) had succesful result only with E.fix procedure, half of 6 patients (50%) healed only with E.fix application in group 2 ($p<0.05$). Reunion occured in all closed fractures of the 2 groups. The mean union time of closed fractures in group 1 was 156 (104-238) days and the mean union time was 131 (116-226) days in group 2 ($p>0.05$).

Table 3. Comparison of 2 groups in terms of union time and rate.

	Group 1 (n=30)	Group 2 (n=22)	P
Healing Time (Day) Total	167 ± 39(n=24)	161 ± 47(n=20)	0.645
Healing Time (Day) Open fracture	178 ± 43(n=12)	191 ± 38(n=10)	0.465
Healing Time (Day) Fracture	156 ± 33(n=12)	131 ± 34(n=10)	0.096
Healing Rate (%) Total	%80(n=24)	%90.9(n=20)	0.281

DISCUSSION

Wide clinical applications have been described for PRP. Although studies with strong evidence also support the clinical use of PRP the majority of these studies is anecdotal and they do not identify the exact role of PRP (9). It has been specified that PRP, which contains active proteins and growth factors and causes biological support, stimulates tissue healing and acceleration of bone union (4, 7, 8). Mariconda et al. have compared a group of patients with nonunion of long bone diaphyseal fracture and having only monolateral E.fix application without opening the fracture line to a group of patients having platelet injection to fracture line in addition to E.fix application. They have found no significant difference in terms of union rate between the 2 groups (10). Galasso et al. have reported that 22 patients with nonunion of long bone diaphyseal fracture underwent IMN and PRP injection to fracture line after the regeneration of fracture ends. Union rate was 91% (11). In contrast to the literature, our study, which contained prospective patients with delayed union of long bone diaphyseal fracture and PRP application (Group 2) and retrospective patients without PRP application (Group 1), investigated the effect of PRP on delayed union not nonunion. The effect of PRP was studied not only for a single fixation method but also for multiple fixation methods. Although PRP applied group had increased union rate compared to control group there was no statistically significant difference between the 2 groups. This insignificance can be explained by small sample size. Kanthan et al. have created 2-cm defects on rabbit tibia, fixed with small plates and placed spacers in fracture line to form delayed union. They divided rabbits into 4 groups. First group had no additional intervention. Second group had PRP administration. Third group had artificial bone graft. Fourth group had both PRP administration and artificial bone graft application. In conclusion, they have found that PRP with bone grafting increased the quality of fracture healing tissue. They have speculated that PRP only application without bone grafting showed minimal benefit and could not provide enough scar tissue formation (12). In our study, repeated injections were performed by considering insufficient effect of PRP when applied alone.

Whereby all Gustilo-Anderson type III open fractures healed in PRP applied group. This success rate was only 50% in the control group. Although the difference was not statistically significant union rate of all open fractures was 83% in PRP group compared to no PRP group. Union time of closed fractures was shorter in PRP group although there was no statistically significant difference. In PRP applied group, union rate of patients with E.fix application was 50% and this rate was only 12.5% in the control group. This important difference between the 2 groups showed that permanent E.fix application with the addition of PRP administration can be related with good clinical results.

There was no significant difference between the 2 groups in terms of internal and external factors affecting fracture healing such as the space between the fracture ends, unstable fixation, infection, extensive osteonecrosis, comorbid conditions, insufficient blood supply, and advanced age. Some literature findings are present regarding PRP use, especially with autologous or allogenic bone materials, and increased rate of bone consolidation has related to good clinical results. Some literature findings related to good clinical outcomes are also present regarding PRP only use without other osteoinductive materials (13-15). In the present study, multiple PRP injections in cases with permanent E.fix significantly decreased the probability of a second surgical attempt.

In conclusion, when we evaluate early clinical results of our study PRP, a safe and easily applicable procedure, has useful effects on delayed union. Further prospective studies with large sample sizes are needed to identify the net clinical benefit of PRP.

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