


## The Impact of Delayed Osteosynthesis of Bone Healing in Patients with Extra-articular Distal Femoral Fracture

Hamed Tayyebi<sup>1</sup>, Sajad Noorigaravand<sup>1</sup>, Mohammad Reza Baheaddini<sup>2</sup>, Elham Mohammadyahya<sup>2</sup>, Ava Parvandi<sup>3</sup>, Saeid Shirvani<sup>1</sup>, Ali Yeganeh<sup>2\*</sup> 

Received: 24 Aug 2023

Published: 6 Mar 2024

### Abstract

**Background:** In extra-articular distal femoral fractures (EDFFs), nonunion is a serious complication that occurs rarely. In this study, we examined how longer preservation of initial fracture hematoma by delaying the osteosynthesis (OS) affects the fracture union.

**Methods:** In a retrospective cohort study, 98 EDFF patients were included. The OS was done within 2 days of injury in 50 patients (early OS group) and after 2 days of injury in 48 patients (late OS group). Time to callus formation and fracture union, bleeding amount, surgical duration, pain, knee range of motion, knee function, and postoperative complications, including the nonunion, knee deformity, infection, and revision, were compared between the 2 groups. Statistical analyses were done with SPSS. A comparison of the mean between the 2 groups was made with an independent t test or its nonparametric counterpart. A comparison of categorical variables between the 2 groups was made using a chi-square or the Fisher's exact test.  $P < 0.05$  was considered statistically significant.

**Results:** The mean time to callus formation was  $47.1 \pm 17.3$  days in the early OS group and  $46.9 \pm 19.7$  in the late OS group ( $P = 0.950$ ). The mean time to fracture union was  $114.9 \pm 21$  in the early OS group and  $117.4 \pm 28.8$  days in the late OS group ( $P = 0.630$ ). The mean operation time and bleeding amount between the 2 groups did not differ significantly ( $P = 0.230$  and  $P = 0.340$ , respectively). The knee range of motion, pain, and function were not notably different ( $P = 0.620$ ,  $P = 0.790$ , and  $P = 0.770$ , respectively). Nonunion occurred in 3 patients of early OS and 2 patients of the late OS group. Other complications were also comparable in the 2 study groups.

**Conclusion:** Delayed OA in EDFF patients has no significant effect on bone healing and fracture union. Future standard studies are required to confirm these results.

**Keywords:** Distal Femur Fractures, Osteosynthesis, Hematoma, Fracture Nonunion, Fracture Healing

**Conflicts of Interest:** None declared

**Funding:** None

**\*This work has been published under CC BY-NC-SA 1.0 license.**

Copyright© Iran University of Medical Sciences

**Cite this article as:** Tayyebi H, Noorigaravand S, Baheaddini MR, Mohammadyahya E, Parvandi A, Shirvani S, Yeganeh A. The Impact of Delayed Osteosynthesis of Bone Healing in Patients with Extra-articular Distal Femoral Fracture. *Med J Islam Repub Iran*. 2024 (6 Mar);38:25. <https://doi.org/10.47176/mjiri.38.25>

### Introduction

Distal femur fractures are serious injuries with a significant rate of morbidity and mortality. In humans, they constitute almost 0.4% of all fractures, whether intra-articular or extra-articular (1). Extra-articular distal femoral fractures (EDFF) are less common than intra-articular fractures. They are generally managed with lateral locking plates or intramedullary nail fixation. These injuries, however, have not all led to positive outcomes (2).

Young patients with unfavorable fracture patterns and elderly patients with poor bone quality could have fracture nonunion after treatment. Although nonunion in EDFF is rare, it is an extremely significant complication that is generally difficult to treat and results in a high level of disability (3, 4). Consequently, reducing the rate of nonunion in EDFF fractures is of significant importance. Several strategies have been proposed to reduce nonunion in

**Corresponding author:** Dr Ali Yeganeh, [Yeganeh.a@iums.ac.ir](mailto:Yeganeh.a@iums.ac.ir)

<sup>1</sup> Shohadaye Haftom-e-Tir Hospital, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

<sup>2</sup> Bone and Joint Reconstruction Research Center, Department of Orthopedics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

<sup>3</sup> Joint and Related Tissue Research Center, Akhtar Orthopedic Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

#### ↑What is “already known” in this topic:

The nondisplacement of the main fracture hematoma helps fracture healing by exploiting the potential of the initial hematoma in the healing process of bone fractures.

#### →What this article adds:

This study suggests that delayed osteoarthritis in patients with extra-articular distal femoral fractures (EDFF) has no significant effect on bone healing and fracture union.

these fractures (5).

The process of healing a fracture involves multiple immunologic components, including cells, cytokines, and growth factors that work together well (6). In the present fracture healing strategies, initial fracture hematoma is regarded as an important osteoimmunological factor, as it is a rich source of inflammatory cells, which plays a critical role in the recruitment of regenerative cells toward the fracture site through releasing various signaling proteins such as cytokines and chemokines (6). Reviewing the potentials of initial hematoma has revealed its striking angiogenic and osteogenic capacities (6). Considering the importance of initial hematoma in fracture healing, recent treatment strategies are based on the nondisplacement of the main fracture hematoma to help the bone healing process by exploiting this potential (6).

We hypothesized that longer nondisplacement of initial hematoma in EDFF patients could improve the bone healing potential, thereby reducing the rate of nonunion in these patients. In this study, we compared the bone healing and nonunion rate in EDFF patients with early (within 2 days of injury) and delayed osteosynthesis (>2 days of injury) to test this hypothesis.

## Methods

We have received approval from the review board of our institute for this cohort study under code IR.IUMS.REC.1401.724. Medical profiles of EDFF patients who were referred to 3 university trauma centers in Iran between 2020 and 2022 were retrospectively reviewed. The inclusion criteria were referral in the acute phase, distal femoral growth plate closure, or age >18 years, comminuted fractures (type A3 according to AO classification), high-energy traumas, and fracture fixation with a locking plate. Patients with a history of fracture or surgery at the involved side, patients with disorders affecting bone healing, such as osteoporosis and renal osteodystrophy, and congenital bone deformities were excluded from the study. Patients who did not follow postoperative rehabilitation programs and those who did not regularly attend follow-up visits were also excluded.

A total of 98 patients met the study criteria and were divided into the 2 study groups. The first group included 50 patients who underwent osteosynthesis (OS) within 2 days of injury (early OS group). The second group included 48 patients who underwent OS more than 2 days after the injury for various reasons such as multiple trauma, rupture of the liver or spleen, brain injury, and reduced level of consciousness (late OS group).

## Outcome Measures

The patients were visited monthly until the complete union of fractures was achieved. In each visit, anteroposterior and lateral radiographs of the fracture site were obtained for the evaluation of bone healing. Primary outcomes were radiographic healing and included the times of callus formation and fracture union. Callus formation was regarded as the observation of bridging callus in postoperative radiographs. Union was defined as monitoring callus formation on a minimum of 3 out of 4 cortices with

bridging callus in anteroposterior and lateral radiographs (7). It was defined as nonunion of the fracture after 6 months postoperatively if there is no callus forming. Secondary outcomes were intraoperative bleeding, surgical duration, knee range of motion, pain, function, and postoperative complications. The intraoperative bleeding amount and surgical duration were extracted from the patient's medical records. The knee range of motion was evaluated with a standard goniometer. Knee pain was assessed with a visual analog scale (VAS) for pain on a 0 to 10 scale, corresponding to "no pain" and "extreme pain," respectively. Knee function was assessed with a Persian version of the International Knee Documentation Committee (IKDC) score, whose validity and reliability was demonstrated previously (8). Accordingly, each patient achieved a score between 0 and 100. A higher score was indicative of better function. Postoperative complications—such as nonunion, infection, and fixation failure—were also extracted from the medical profiles of the patients.

## Sample Size and Statistical Analysis

According to the study of Aref et al, the mean union time of EDFF after the open reduction and internal fixation with the locking plate was 15.8 weeks with a standard deviation (SD) of 3.37 weeks. Using this mean and SD, a power of 80%, a type I error of 5%, and an estimated mean difference of 2 weeks between the 2 groups, it was found that 46 patients in each group were sufficient for this study.

Statistical analyses were performed with SPSS for Windows, Version 16 (SPSS Inc). Descriptive statistics were demonstrated by mean  $\pm$  SD for quantitative variables and with frequency and percentage for categorical variables. The normality of distribution was checked with the Kolmogorov-Smirnov test. Independent t tests or nonparametric Mann-Whitney U tests were used to compare mean values between the 2 groups. A comparison of categorical variables between the 2 groups was made using a chi-square or the Fisher's exact test.  $P < 0.05$  was considered statistically significant.

## Results

### Baseline Characteristics

The study population included 80 men and 18 women, with a mean age of  $41.7 \pm 19.2$  years (range, 18-91). The mean body mass index of the patients was  $24.9 \pm 3.8$  kg/m<sup>2</sup> (range, 18-36 kg/m<sup>2</sup>). The mean follow-up of the patients was  $13.4 \pm 4.5$  months (range, 6-21 months). The mean time interval from injury to surgery was  $0.8 \pm 0.7$  days (range, 0-2 days) in the early OS group and  $5.9 \pm 2.1$  days (range, 3-14 days) ( $P < 0.001$ ) in the late OS group. No other significant difference was observed between the baseline characteristics of the 2 study groups (Table 1).

### Outcomes

On average, callus was observed  $47.1 \pm 17.3$  days after operation in the early OS group and  $46.9 \pm 19.7$  days after operation in the late OS group ( $P = 0.950$ ). The mean time to fracture union was  $114.9 \pm 21$  days after the operation

**Table 1.** Comparison of baseline characteristics between patients who underwent early and late osteosynthesis for extra-articular distal femoral fracture

Variable	Early osteosynthesis group (n=50)	Late osteosynthesis group (n=48)	P-value
Age (year)	41.5 ± 17.8	41.9 ± 20.7	0.120
Male	8 (16)	10 (20.8)	0.530
Female	42 (84)	38 (79.2)	
BMI (kg/m <sup>2</sup> )	25.4 ± 3.7	24.5 ± 3.9	0.740
Follow-up	13.6 ± 4.6	13.3 ± 4.4	0.680
Time interval between injury and surgery (day)	0.8 ± 0.7	5.9 ± 2.1	<0.001

Data are demonstrated with mean ± SD or number (%). P<0.05 is considered significant

**Table 2.** Comparison of outcome measures between in patients who underwent early and late osteosynthesis for extra-articular distal femoral fracture

Variable	Early osteosynthesis group (n=50)	Late osteosynthesis group (n=48)	P-value
Callus formation (day)	47.1 ± 17.3	46.9 ± 19.7	0.950
Fracture union (day)	114.9 ± 21	117.4 ± 28.8	0.630
Operation time (min)	75.5 ± 14	79.1 ± 15.7	0.230
Bleeding (ml)	477 ± 219	520 ± 234	0.340
Knee range of motion (°)	115.3 ± 19.9	113.3 ± 19.9	0.620
Visual analog scale for pain	1.42 ± 1.5	1.33 ± 1.8	0.790
IKDC score	87.5 ± 12.9	88.2 ± 13.9	0.770

IKDC: International Knee Documentation Committee

Data are demonstrated with mean ± SD. P < 0.05 is considered significant

in the early OS group and 117.4 ± 28.8 days after the operation in the late OS group ( $P = 0.630$ ).

The mean operation time was 75.5 ± 14 minutes in the early OS group and 79.1 ± 15.7 minutes in the late OS group ( $P = 0.230$ ). The mean bleeding amount was 477 ± 219 mL in the early OS group and 520 ± 234 mL in the late OS group ( $P = 0.340$ ).

At the last follow-up, the knee range of motion was 115.3° ± 19.9° in the early OS group and 113.3° ± 19.9° in the late OS group (0.620). The mean VAS for pain was 1.42 ± 1.5 in the early OS group and 1.33 ± 1.8 in the late OS group ( $P = 0.790$ ). The mean IKDC score was 87.5 ± 12.9 in the early OS group and 88.2 ± 13.9 in the late OS group ( $P = 0.770$ ). Outcome measures are summarized in Table 2.

### Postoperative Complications

Fracture nonunion occurred in 3 patients of the early OS group and 2 patients of the late OS group. One varus deformity (5°) was recorded in the early OS group. Two valgus deformities (5 and 6°) were recorded in the late OS group. Superficial infection occurred in 1 patient of the early OS group and 2 patients of the late OS group. A deep infection occurred in 1 patient of the late OS group. Infected nonunion was seen in 1 patient of each study group. In the early OS group, 2 patients underwent revision surgery, 1 for the plate fracture and 1 for the removal of a screw irritating the joint. In the late OS group, 1 patient underwent revision surgery for nonunion, which was managed with open reduction and internal fixation, and bone grafting.

### Discussion

In this study, we compared the union rate and outcomes between early (within 2 days of injury) and late (after 2 days of injury) OS in EDFF patients. The mean time interval from operation to callus formation and fracture union was not significantly different between the 2 groups. Also, the mean operation time, bleeding amount, knee

range of motion, pain, and IKDC score were not significantly different between the 2 groups. Postoperative complications—including nonunion, knee deformity, infection, and revision surgery—were not considerably different between the 2 groups.

The process of bone healing begins with the formation of hematoma in the acute phase after the rupture of blood vessels during bone damage and fracture (9, 10). This initial phase plays an important role in the outcome of the fracture because it stimulates the migration of regenerative cells such as mesenchymal stem cells and immune cells to the injury site (11). An ossifying bed is created by the fracture hematoma in the first 4 days after trauma (12, 13). Increased expression of bone factors secreted phosphoprotein 1/osteopontin and runt-related transcription factor 2, which are seen in the first 72 hours in human fracture hematoma, indicates the initiation of bone formation (14, 15). In addition to osteogenic potential, fracture hematoma also provides angiogenic potential (14). Angiogenesis in the damaged area is a prerequisite for the continuation of the healing process (16), which coincides with the high concentration of vascular endothelial growth factors in human fracture hematoma (17). The initial stages of the healing process take place during the maturity of the hematoma. The first 3 days of healing show this maturation with the change from M1 macrophages with a proinflammatory phenotype to M2 macrophages with an anti-inflammatory phenotype (18, 19). This switch is adjusted by alteration in gene expression leading to the substitution of inflammatory cytokines (interleukin 1 and 6) with anti-inflammatory cytokines (interleukin 4 and 13). Cytokines play an important role in fracture healing because almost 60 hours after fracture, inflammation and angiogenesis factors are expressed differently, as well as cellular composition in fractures with normal healing process versus fractures terminating in nonunion (14, 20). An analysis of inflammatory, angiogenic, and osteogenic factors in the hematoma 4 and 7 days after the start of bone repair reveals that these factors change over time and mechanically

induced delayed union affects them clearly (21-23). Therefore, it can be concluded that the age of the hematoma plays an important role in bone healing, and impairing the natural course of this process affects the outcomes of fracture. After the removal of the initial fracture hematoma, the regulated interaction between the hematoma and the adjacent tissue is severely disrupted. During healing, the mature hematoma is replaced by an immature hematoma, whose composition does not match the adjacent tissues' healing stages. Such evolutionary mismatch between the new hematoma and the surrounding tissue can cause a delay in fracture healing process, and an increase in the risk of nonunion (7).

Various studies have been performed on the role of initial fracture hematoma in bone healing both in human and animal models. Most of these studies have demonstrated differential expression of a variety of bone healing factors in hematoma of the compromised bone-healing situation compared to normal bone-healing (7, 11, 21, 22, 23). However, the impact of delayed osteosynthesis on the outcome of bone healing has been scarcely evaluated. Streubel et al evaluated the mortality of distal femur fractures in 92 elderly patients. Patients who underwent OS more than 4 days after admission had greater 6-month and 1-year risk of mortality compared to those who underwent OS within 2 days of admission. However, the impact of delayed osteosynthesis on the healing of fractures was not evaluated (24). In a historical study, Taillard et al suggested delaying the internal fixation of femoral shaft fractures in adults by 2 weeks after the injury to allow the formation of a physiological callus, thereby protecting the osteosynthesis (25).

In the present study, we did not observe any advantage of performing OS more than 2 days after the injury. There are, however, some limitations to consider in interpreting this result. The retrospective design was the main limitation of the study that could have significantly affected the results in various ways. For example, we included both the young and elderly populations, while the bone healing potential is compromised in the elderly population. In addition, the time interval from injury to surgery was very heterogeneous, ranging from 3 to 14 days. Some delayed surgery groups excluded hematomas during surgery for anatomical reduction, which limited our study. Therefore, future prospective and standard studies are required to better explore the role of delayed OS in the healing of EDF. F.

## Conclusion

Compared to EDF patients who underwent OS within 2 days of injury, delayed OS (more than 2 days of injury) did not accelerate callus formation and fracture union time. The rate of union was not considerably different between the 2 groups. According to these results, delaying osteosynthesis does not improve bone healing in EDF.

## Acknowledgment

The authors thank all those who contributed to this study.

## Authors Contribution

S.N., M.B., S.S., E.M., A.P., and S.S. developed the theory and carried out the calculations. All authors participated in the final manuscript, supervised the results, and confirmed the methods of analysis used throughout this work.

## Ethical Approval

This cohort study was approved by the review board of our institute (IR.IUMS.REC.1401.724).

## Conflict of Interests

The authors declare that they have no competing interests.

## References

- Khan AM, Tang QO, Spicer D. The epidemiology of adult distal femoral shaft fractures in a central London major trauma centre over five years. *Open Orthop J*. 2017;11:1277.
- Yarboro SR, Ostrum RF. Management of Distal Femoral Fractures (Extra-articular). In: Castoldi F, Bonasia DE, editors. *Fractures Around the Knee*. Cham: Springer International Publishing; 2016. p. 25-37.
- Ebraheim NA, Martin A, Sochacki KR, Liu J. Nonunion of distal femoral fractures: a systematic review. *Orthop Surg*. 2013;5(1):46-50.
- Vaishya R, Singh AP, Hasija R, Singh AP. Treatment of resistant nonunion of supracondylar fractures femur by megaprosthesis. *Knee Surgery Sports Traumatology Arthroscopy*. 2011;19(7):1137-40.
- Sharifpour S, Moharrami A, Mortazavi SMJ. How to Prevent Distal Femoral Fracture Non-Union? Educational Corner. *J Orthop Trauma*. 2019;103-6.
- Schell H, Duda G, Peters A, Tsitsilonis S, Johnson K, Schmidt-Bleek K. The haematoma and its role in bone healing. *J Exp Orthop*. 2017;4(1):5.
- Shisha T. Parameters for defining efficacy in fracture healing. *Clin Cases Miner Bone Metab*. 2010;7(1):15.
- Rahimi A, Nowrouzi A, Sohani SM. The Validity and Reliability of the Persian Version of the International Knee Documentation Committee (IKDC) Questionnaire in Iranian Patients after ACL and Meniscal Surgeries. *Arch Physiother*. 2013;14(2):116-24.
- Opal SM. Phylogenetic and functional relationships between coagulation and the innate immune response. *Crit Care Med*. 2000;28(9):S77-S80.
- Yeganeh A, Amiri S, Otoukesh B, Moghtadaei M, Sarreshtedari S, Daneshmand S, et al. Characteristic Features and Outcomes of Open Gunshot Fractures of Long-bones with Gustilo Grade 3: A Retrospective Study. *Arch Bone Jt Surg*. 2022;10(5):453-8.
- Kolar P, Schmidt-Bleek K, Schell H, Gaber T, Toben D, Schmidmaier G, et al. The early fracture hematoma and its potential role in fracture healing. *Tissue Eng Part B Rev*. 2010;16(4):427-34.
- Mizuno K, Mineo K, Tachibana T, Sumi M, Matsubara T, Hirohata K. The osteogenic potential of fracture haematoma. Subperiosteal and intramuscular transplantation of the haematoma. *J Bone Jt Surg*. volume. 1990;72(5):822-9.
- Ghaznavi A, Baghdadi T, Bagherifard A, Fakoor S, Shirvani S, Sadat Kiaei SM, et al. Comparison of Eight-plate with Reconstruction-plate in Temporary Hemiepiphysiodesis to Correct the Idiopathic Genu Valgum in Pediatrics. *Arch Bone Jt Surg*. 2022;10(7):585-91.
- Schmidt-Bleek K, Schell H, Lienau J, Schulz N, Hoff P, Pfaff M, et al. Initial immune reaction and angiogenesis in bone healing. *J Tissue Eng Regen Med*. 2014;8(2):120-30.
- Kolar P, Gaber T, Perka C, Duda GN, Buttgerit F. Human early fracture hematoma is characterized by inflammation and hypoxia. *Clin Orthop Relat Res*. 2011;469:3118-26.
- Schmidt-Bleek K, Kwee BJ, Mooney DJ, Duda GN. Boon and bane of inflammation in bone tissue regeneration and its link with angiogenesis. *Tissue Eng Part B Rev*. 2015;21(4):354-64.
- Street J, Winter D, Wang JH, Wakai A, McGuinness A, Redmond HP. Is human fracture hematoma inherently angiogenic? *Clin Orthop Relat Res*. (1976-2007). 2000;378:224-37.
- Sinder BP, Pettit AR, McCauley LK. Macrophages: their emerging



- roles in bone. *J Bone Miner Res.* 2015;30(12):2140-9.
19. Ghaznavi A, Hemmatyar A, Mahdavi SM, Amiri S, Daneshmand S, Malakooti SM. Treatment of Symptomatic Flexible Flat Foot in Pediatrics with A Modified Mosca's Lateral Column Lengthening. *Med J Islam Repub Iran.* 2022;36:93.
  20. Schmidt-Bleek K, Schell H, Schulz N, Hoff P, Perka C, Buttgerit F, et al. Inflammatory phase of bone healing initiates the regenerative healing cascade. *Cell Res.* 2012;347:567-73.
  21. Lienau J, Schmidt-Bleek K, Peters A, Weber H, Bail HJ, Duda GN, et al. Insight into the molecular pathophysiology of delayed bone healing in a sheep model. *Tissue Eng Part A.* 2010;16(1):191-9.
  22. Lienau J, Schmidt-Bleek K, Peters A, Haschke F, Duda GN, Perka C, et al. Differential regulation of blood vessel formation between standard and delayed bone healing. *J Orthop Res.* 2009;27(9):1133-40.
  23. Otoukesh B, Moshiri SF, Jahangiri B, Jafarlou KM, Amiri S, Baniasadi N, et al. Digital monitoring of weight-bearing improves success rates and reduces complications in lower extremity surgeries. *Eur J Transl Myol.* 2023;33(4).
  24. Streubel PN, Ricci WM, Wong A, Gardner MJ. Mortality after distal femur fractures in elderly patients. *Clin Orthop Relat Res.* 2011;469:1188-96.
  25. Taillard W, Papadimitriou G, Bagnoud F, Tschanz P. Delayed osteosynthesis of diaphyseal femoral fractures in adults. *Rev Chir Orthop.* 1976;62(3):309-20.