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ARAŞTIRMA / RESEARCH

Effect of autogenous bone marrow injection on long bone nonunion fractures

Otojen kemik iliği enjeksiyonunun uzun kemik kaynamamış kırıklarına etkisi

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Abstract

Purpose: The impact on bone union of injecting bone marrow from the anterior iliac crest was examined in patients with non-unions.
Materials and Methods: The present study was prepared following a retrospective study on non-union patients who applied to our clinics who accepted bone marrow injection and were followed up and monitored after the procedure. A total of 14 bones from 13 patients with long bone diaphysis and metaphysis non-union were included in the study from among patients who applied during the dates of November 2016 – December 2019. Bone marrow aspiration from the anterior iliac crest was conducted on the patients under anesthesia which was injected to the fracture line under local anesthesia and fluoroscopy. All patients were monitored on a monthly basis with front-rear and side radiography. The injection operation was conducted three times on seven patients and 2 times on a total of seven non-unions in 6 patients.
Results: A total of 11 unions took place in 14 patients. A union could not be attained in three fractures. The gap was over 2 mm in fractures without union. Fracture union ratio was obtained as 79 %. The mean injection number applied on the patients was 2.5. A statistically significant correlation could not be identified between the fixation method and non-union type and union.
Conclusion: Bone marrow injection is a cheap, effective, easy to use and safe surgical method for the treatment of long bone fractures with non-union.
Keywords:. Bone Marrow, non-union treatment, out-patient surgery, long bone, bone union

Öz

Amaç: Kaynamamış kırığı olan hastalarda anterior iliak kanattan alınan kemik iliğinin kırık hattına enjekte edilmesinin kırık kaynamasına etkisi araştırıldı.
Gereç ve Yöntem: Çalışma kliniklerimize müracaat eden kaynamamış kırığı olan ve kemik iliği enjeksiyonu uygulamasını kabul eden bu uygulama ile takip ve tedavi edilen hastaların retrospektif olarak incelenmesi sonucu hazırlandı. Çalışmaya Kasım 2016 Aralık 2019 tarihleri arasında müracaat eden uzun kemik diafiz ve metafiz kırığı kaynamaması olan 13 hastanın 14 kemiği dahil edildi. Hastalara lokal anestezi altında anterior iliak kanattan kemik iliği aspirasyonu yapılarak lokal anestezi altında kırık hattına skopi kontrolünde enjekte edildi. Tüm hastalar aylık olarak ön-arka ve yan grafiler ile izlendi. Enjeksiyon işlemi yedi hastaya üç defa 6 hastanın yedi kaynamamış kırığına 2 defa tekrar edildi.
Bulgular: Toplamda 14 hastanın 11 kırığı kaynadı. Üç kırıkta kaynama elde edilemedi. Kaynama elde edilemeyen kırıklarda boşluk miktarı 2 mm üzerinde idi. Kırık kaynama oranı % 79 olarak bulundu. Hastalara uygulanan ortalama enjeksiyon sayısı 2.5 idi. Tespit tekniği ve kaynamama tipi ile kaynama arasında anlamlı bir ilişki bulunamadı.
Sonuç: Kemik iliği enjeksiyonu kaynamamış uzun kemik kırıkları tedavisinde ucuz etkili ve günübirlik cerrahi uygulaması olarak güvenli bir yöntemdir.

Anahtar kelimeler: Kemik iliği, kaynamama tedavisi, günübirlik cerrahi, uzun kemik, kemik kaynaması

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INTRODUCTION

Nonunion of long bones; It is defined as the absence of signs of union despite a period of 9 months after the fracture[1]. Insufficient mechanical stability and disrupted biological environment may result in non-union. Whereas callus formation and insufficient mechanical stability are responsible in hypertrophic unions, disrupted biological environment and low or no callus formation is observed in atrophic unions[2]. Natural or synthetic growth factors, demineralized bone matric, electrical stimulation, ultrasound, bone graft and stem cells from mesenchymal cells obtained from the bone marrow are among the methods applied for union.

Autografts are the golden standard in non-union treatment due to their osteogenic, osteoinductive and osteoconductive attributes. However, this application requires the opening up of the fracture region in addition to pain, infection, hematoma, peripheral nerve injury at the donor site. This may result in the devascularization of fracture tips and additional trauma[3].

Percutaneous bone marrow graft and injections are less invasive in addition to being osteogenic and osteoinductive. It has been reported in previous clinical and experimental studies that bone marrow injection is used in the treatment of simple bone cyst, congenital tibial pseudoarthrosis and non-union in fractures[4,5]. The aim of the present retrospective study was to evaluate the percutaneous bone marrow injection results applied on 14 non-unions in 13 patients who applied with non-union complaints. In this study, it was tried to show that successful results can be obtained with bone marrow injection before applying more aggressive surgical treatments in fractures with long bone nonunion. In addition, we believe that this study will contribute to the literature in terms of evaluating the relationship between the amount of space and the treatment of nonunion.

MATERIALS AND METHODS

Sample

The study was prepared based on the retrospective assessment of the patients monitored and followed-up at the Gemlik State Hospital and Bursa State Hospital Orthopedics and Traumatology Departments who applied to the clinics with non-unions and who accepted bone marrow injection application. The study includes patients treated with the same method by two surgeons working in two different hospitals. Institution records are prepared by the clinical secretaries and stored on the automation system used by the Ministry of Health. The present study was conducted in accordance with the Helsinki Declaration Principles following the required permit obtained from the Uludağ University Faculty of Medicine Council of Ethics dated June 10, 2020 and numbered 2020-10/9. The authors declare that there is no conflict of interest in this study.

A total of 13 patients were included in the study with long bone diaphysis and metaphysis fracture identified during the dates of November 2016 – December 2019. A total of 20 patient files were examined. Among these patients, 4 patients were excluded from the study because the application was performed due to delayed union and 3 patients did not come for follow-up. The inclusion criteria wer having a minimum of 9 months passed after the index fracture, having proper alignment and stable bone fixation or no instability. Exclusion criteria were having an active infection or osteomyelitis anamnesis, insufficient fixation or unacceptable alignment and delayed unions.

Age, gender, the duration of time that passed after the first surgery, the number of defects along the fracture line and the number of bone marrow injections were recorded.

Surgical procedure

The patients were hospitalized as day patients and were discharged on the same day. Single dose of Cefazolin Na 1 gr was administered intravenously for prophylaxis. The fracture region and the donor site were covered separately in the supine position at the surgery room. 16 G bone marrow biopsy needle was used under local anesthesia to enter from the anterior iliac crest with 50 cc bone marrow for femur, tibia and humerus was drawn in to the injector washed with heparin to avoid clotting. The bone marrow aspirate obtained under local anesthesia and under fluoroscopy control was injected near the fracture line using 18 G pink tip needle. In cases where the injection to the fracture line was difficult due to fibrotic tissues, the application was performed with the 18 G needle with the pie crusting technique and by changing the entry site. Pressure dressing was applied on the donor and injection sites. Parasetamol was prescribed to the patients as an analgesic who were discharged after a clinical follow-up of one hour.

The controls were carried out on a monthly basis. Injection was repeated monthly until the radiological findings of union were observed in all three cortexes. The fracture region was monitored radiologically during clinical follow-up for local pain via front, rear and side radiographs with bridging of the fracture line with callus in a minimum of 3 cortexes and the lack of local pain considered as union.

Statistical analysis

Statistical analyses were conducted via SPSS 22.0 software. Non-union time was indicated as 12 months since a value had to be appointed for non-union time during statistical analyses. Mann Whitney-U Test from among non-parametric approaches was used to put forth the correlations between the union status and gap amounts as well as fracture type and union time due to the low number of samples and the inability to attain normal distribution in addition to the fact that the union status and the fracture type variables emerge as a rank scale. Spearman Rank Correlation was used for the correlation between union time and the gap amounts since it is suited for identifying the correlation between two continuous variables in the absence of normal distribution. Finally, the Chi-square Test of Independence is used to reveal the relationship between fracture type and union status. The chi-square test of independence is a convenient method when two classifiers or ordinal scaled variables are involved.

RESULTS

The mean age of the patients was 44,5 (± 16,9). A total of two female and 11 male patients were included in the study. Injection was applied on two separate long bone non-unions of one patient. Fracture distribution was as such; 4 femur shaft, 5 humerus shaft, 2 tibia shaft, 2 ulna shaft and 1 distal radius fracture. Hypertrophic non-union was observed in two fractures with atrophic non-union in the other 12. An average of 25,14 months (±15.73) had passed from the index surgery. The average gap in the fractures was measured as 16,21 mm (±5,37). A total of 2 or 3 injections were applied on the patients. The mean injection number was 2,5 (± 0,52).

While union could not be attained in three fractures, clinical and radiological union was attained in 11 fractures. Union ratio was 79 %. Local or systemic complications were not observed in any of the patients. Table 1 presents a detailed overview of the cases.

Table 1: Cases

Cases	Broken bone	Sex	Age	Fixation method	Level of union	Number of injections	Union time (month)	Gap (mm)	Type of Nonunion	IS(month)
1	Femoral shaft	M	37	IMN	1	3	3	14	HT	20
2	Femoral shaft	M	21	IMN	1	2	2	16	AT	22
2	Humeral shaft	M	21	IMN	1	2	2	14	AT	22
3	Humeral shaft	F	58	IMN	1	2	2	17	AT	11
4	Distal radius	M	42	PLATE	1	3	3	8	AT	9
5	Humeral shaft	M	54	PLATE	0	3		25	AT	18
6	Femoral shaft	F	41	IMN	1	3	3	18	AT	17
7	Humeral shaft	M	35	PLATE	1	2	2	12	AT	14
8	Humeral shaft	M	60	PLATE	1	2	2	15	AT	24
9	Ulna shaft	M	36	N/A	1	3	3	12	AT	60
10	Ulna shaft	M	36	PLATE	0	2		24	AT	58
11	Tibial shaft	M	65	IMN	0	3		26	HT	36
12	Tibial shaft	M	37	PLATE	1	3	3	14	AT	23
13	Femoral shaft	M	81	IMN	1	2	2	12	AT	18

IMN:Intramedullar fixation, İS: Index surgery HT: hypertrophic, AT: Atrophic N/A: No Fixation M: Male F: Female

The statistical analyses conducted revealed a statistically significant correlation (*p-value*=0.01<0.05) between the gap amount and fracture union with nonunion in patients with gaps of greater than 2 mm. The union status and union time did not differ at a statistically significant level subject to the type of non-union and the method of fixation used in the index surgery (p>0.05). A positive and statistically significant (*p-value*=0.000<0.05) rank correlation was observed between the union time and gap amount. Figure 1 shows the positive correlation between the union time and the gap amount.

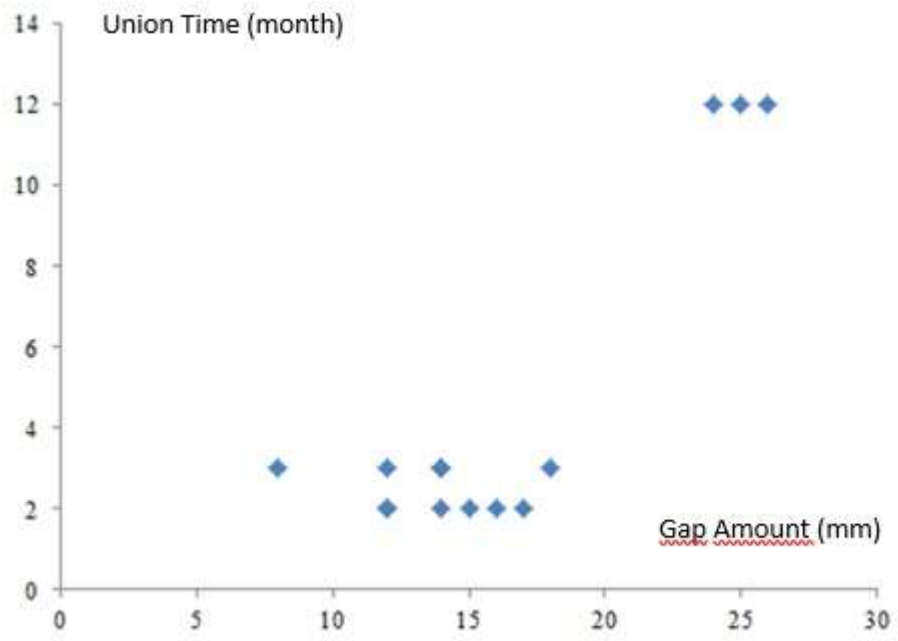

Figure 1. Scatter diagram for union time and gap amount

Table 2. The relationship between union status, gap amount and fracture types

	n	n	p-Value
Union Status-Gap Amount Mann Whitney-U Test	< 2mm n:11	>2mm n:3	0.01
Union Time-Gap Amount Spearman Rank Correlation	< 2mm n:11	>2mm n:3	0.000
Fracture Types-Union Time Mann Whitney-U Test	Atrophic nonunion n:12	Hypertrophic nonunion n:2	0.845
Fracture Types-Union Status Chi square test	Atrophic nonunion n:12	Hypertrophic nonunion n:2	0.287

Photo 1 shows the radiographs for cases subject to three doses of bone marrow injection due to non-union of tibia and femur before the application and during the final follow-up.

Photo 1. Direct radiographs for sample cases before the application and after 3 doses of bone marrow injection

DISCUSSION

Non-union may result in severe complications for the patients in addition to posing a difficult treatment process for orthopedic surgeons. Various treatment methods are utilized in non-union treatment such as implant changes, autogenous bone grafts and the utilization of synthetic grafts. All these applications may lead to infections, donor site morbidities, painful scar tissue formation, hemorrhage and various other complications in the patients[6-9]. We are of the opinion that the method applied in our study to attain union can be used safely since it has not led to an additional complication in the donor site or the fracture region in any of the patients. Other surgical non-union treatments result in extended hospitalization durations and increased implants costs. The procedure applied in the present study is comfortable for the patient due to its low cost and single day surgical operation compared with other methods.

Agarwal V. et al. conducted a prospective study during which 50-60 ml bone marrow aspirate was taken from the iliac crest which was then applied to 35 patients in 5 repetitions on average in three week intervals until the radiological proofs were obtained for the union as a result of which union was attained in 30 patients with the union rate reported as 85.7 %[10]. Whereas Sing A.K. et al. carried out a study in which they evaluated a total of 12 patients with union delay and non-union and indicated that they aspirated 30-40 ml bone marrow for long bones and 20 ml bone marrow for metacarpus[11]. It was reported as a result of the applications that union has been attained in 12 patients with union rates of 83 %. It has been put forth in another study conducted by Sim R. et al. that injection has been applied to the fracture line with bone marrow aspiration from the iliac crest under fluoroscopy on 11 fractures of 10 patients. It was indicated that 10 ml bone marrow injection has been applied for ulna, 30 ml for Radius and 50 ml to 200 ml for other bones with union attained in nine of the 11 patients[12]. Gark et al. carried out a study as a result of which they attained union in 17 out of 20 patients in an average of 5 months following two doses of 15-20 ml bone marrow injection. Whereas Kassem M.S. reported that 30 mlt bone marrow aspirate was taken for the union delay and non-union treatment of ulna fractures and 80 mlt bone marrow aspirate was taken for femur and tibia fractures with union attained in 19 out of 20 patients over an average time period of the 2.95 months[13]. Gross JB et al. conducted a study reporting the results of bone marrow injection on 45 non-union patients over a period of eight years indicating success rates of 69 % for tibia and 63 % for femur fractures[14]. All patients included in our study had non-union and patients with union delay were not included in the study. In this study, union rates were found to be 79%, which is consistent with the literature. Gap amount was greater than 2 mm in three cases for which union

could not be attained. The present study is important for indicating that the applied method can be more effective in non-unions with gap amounts not greater than 2 mm.

Konde et al. drew 20-40 ml bone marrow aspirate and made an injection in their prospective study. They attained union in 16 out of a total of 20 hypertrophic non-unions and 6 unions out of 8 atrophic non-unions[2]. Union was attained in one out of two hypertrophic non-unions in the present study and a correlation could not be observed between the non-union type and attaining union as a result of the statistical analyses carried out. Despite the small number of cases, we are of the opinion that there is a necessity to conduct further studies on the applicability of this method on hypertrophic non-unions without implant failure.

It can be observed when a literature survey is conducted that mesenchymal stem cell applications obtained from various tissues are also used along with concentrated bone marrow injections for fracture union. The union rates for these applications vary between 79-88 %. It is not possible to apply these methods in all hospitals due to the costs involved and the requirement for additional devices[3,15-17]. It is also necessary to carry out prospective comparative studies with similar non-union groups to put forth its superiority over standard bone marrow.

Weakness of this study; The number of cases is low and the bones with fractures are not homogeneous and contain different long bones.

In conclusion, bone marrow injection is a cheap and effective method that can be used for same-day surgeries for the treatment of long bone fractures with non-union. Even though there are no data for the number and amount of applications, a minimum of three repetitions can be conducted until attaining union with minimum 50 ml for femur, tibia, humerus and 30 ml for other large bones and 20 ml for small bones. As can be seen from the aforementioned studies, the use of the suggested method as a minimal invasive and same-day surgical method on patients with union delay may prevent the possible non-unions. We are of the opinion that the presented method is a treatment option that should be tried prior to resorting to more invasive methods for atrophic non-union cases without fixation inadequacy and alignment problems with gap amounts of less than 2 mm.

Yazar Katkıları: Çalışma konsepti/Tasarımı: AK, BÖ, ET; Veri toplama: AK, BÖ, ET; Veri analizi ve yorumlama: AK, BÖ, ET; Yazı taslağı: AK, BÖ, ET; İçeriğin eleştirel incelenmesi: AK, BÖ, ET; Son onay ve sorumluluk: AK, BÖ, ET; Teknik ve malzeme desteği: AK, BÖ, ET; Süpervizyon: AK, BÖ, ET; Fon sağlama (mevcut ise): yok.
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