ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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COMPARISON OF FREEZE-DRIED BONE ALLOGRAFTS AND DEMINERALIZED BONE MATRIX COMBINATION TO ALLOGRAFTS IN PATIENTS WITH BENIGN CYSTIC LESIONS AND NONUNIONS

BENİGN KİSTİK LEZYONLARI VE KAYNAMA YOKLUĞU OLAN HASTALARDA DONDURULARAK KURUTULMUŞ KEMİK ALLOGREFTLERİ İLE DEMİNERALİZE KEMİK MATRİKS KOMBİNASYONUNUN ALLOGREFTLERLE KARŞILAŞTIRILMASI

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Öz

Amaç
Bu çalışmanın amacı, kaynama yokluğu görülen ve benign kistik lezyonu olan olgularda, kortikospongioz kurutulup dondurulmuş allogreft (AG) ile Demineralize Kemik Matriks (DBM) kombinasyonun uygulandığı hastalar ile yalnız AG uygulanan hastaların klinik ve radyolojik sonuçlarını karşılaştırmaktır.

Gereç ve Yöntem
Retrospektif olarak olarak planlanan bu çalışmaya kırık sonrası kaynama yokluğu gelişen (nonunion) ve benign kistik lezyonu olan, operasyon sırasında DBM ve/veya allogreft kullanılan ve radyolojik ve klinik takibi yapılan hastalar alındı. Benign kistik lezyonu olan hastalar Grup I'e, nonunion tanısı alan hastalar Grup II'ye dahil edildi. Grup I ve Grup II hastalar kullanılan greft türlerine göre A ve B olmak üzere iki alt gruba ayrıldı. DBM-AG uygulanan hastalar A grubuna, sadece AG uygulanan hastalar ise B grubuna alındı. Greftin görünümü ve kaynama potansiyelini için, Goldberg'in radyolojik değerlendirme skalası kullanıldı.

Bulgular
Çalışmaya 101 hasta alındı. Grup I'e 48 hasta, grup II'ye 53 hasta alındı. Grup IA ve Grup IB karşılaştırıldığında radyolojik değerlendirmede skor açısından anlamlı fark bulundu (p=0.011). Grup IIA ve Grup IIB karşılaştırıldığında skor açısından aralarında anlamlı fark bulundu (p=0.014). Grup IA ve IIA skorları istatistiksel olarak anlamlı derecede yüksek bulundu.

Sonuç
Otogreftlerin yetersiz olduğu olgularda allogreftler kullanılabilir. Kullanılan allogreftler, DBM ile karıştırılıp kullanıldığında klinik ve radyolojik olarak hem daha iyi, hem de daha hızlı kaynama elde edilebilir.

Anahtar Kelimeler: Demineralize Kemik Matriksi (DBM), Dondurulmuş Kurutulmuş Kemik Allogreftleri (AG), Benign Kistik Lezyon, Kaynamama

Abstract

Objective
This study aimed to compare the clinical and radio-

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logical results of the patients who treated the combination of Corticospongiosis dried and frozen allograft (AG) with a Demineralized Bone Matrix (DBM) and the patients who treated AG in the patients who had benign cystic lesions (BCLs) and nonunion.

Materials and Methods
This retrospective study included patients who had BCLs and nonunion, who underwent DBM and/or AG during the operation, and who followed radiologically and clinically. Patients with BCLs were included in Group I and the patients with nonunion were included in Group II. Group I and Group II patients were divided into two groups as A and B. Patients who treated DBM-AG were included in group A and those who treated AG were included in group B. Goldberg's radiological evaluation scale was used to evaluate the graft appearance and its union potential.

Results
In this study, 101 patients were included.48 patients in group I and 53 patients in group II were included. When comparing Group IA with Group IB, there was a significant difference in terms of their radiological scores (p=0.011). When comparing Group IIA with Group IIB, there was a significant difference in terms of their radiological scores (p=0.014). The Group IA and IIA scores were statistically significantly higher.

Conclusion
In the treatment of BCLs and nonunion,the AG-DBM combination is more effective than AG alone as clinically and radiologically.

Keywords; Demineralized Bone Matrix, Freeze-Dried Bone Allografts, Bening Cystic Lesion, Nonunion.

Introduction

In orthopedic surgery, especially in post-traumatic treatment, delayed union, nonunion, malunion, and bone loss can be important problems. The anatomical integrity and stable fixation of the bone are required for a successful reconstruction; therefore, grafting or bone transfer may be necessary to fill the defects in the bone(1). Bone grafts are the second most common tissue transplanted and they are an essential treatment tool in the field of acute and reconstructive traumatic orthopedic surgery. Autogenous, allogenic, and xenogenous bone grafts and alloplastic materials are commonly used when repairing bone defects. Autogenous bone grafts are widely used to accelerate healing; however, there are limits to their availability, and donor site morbidity is an important problem. Bone studies of alternative graft options are still ongoing(2,3,4).

Several substances can be used to replace bone, such as allografts, xenografts and ceramics (real and synthetic), demineralized bone matrix (DBM), bone morphogenetic protein (BMP), autologous bone marrow, growth factors, and composite grafts(2-5). One of the commonly used substitutes is an allogeneic bone graft. The use of demineralized freeze-dried bone allograft (AG) whether alone or in combination with other bone substitutes, showed significant improvements in bone augmentation procedures. AGs, in addition to their osteoconductive effects, are also beneficial osteoinductive agents(6). The osteoinductive potential of AG is mainly attributed to morphogenetic proteins (BMPs) stored in the matrix. Growth and differentiation factors are present in AG preparations(7).In maxillary sinus augmentation procedures, AG showed 29% new bone formation while autogenous grafts showed 40% in comparison(8).

DBM, which is obtained by removing the inorganic material (minerals) from the bones through various chemical processes, exhibits osteoinductive activity equal to that of autogenous bone grafts. With DBM, revascularization occurs rapidly, and it can be used to improve fracture healing and repair bone defects. The biggest advantage of DBM is that it can be used in the desired amount, shortening the operation time, and consequently, decreasing blood loss(3,4).

The main advantage of allografts is that they eliminate the need for a donor site besides it can be used in large quantities if necessary. But there is a controversy about the effectiveness of bone allografts in bone regeneration between studies.

The purpose of this study was to compare the combination of freeze-dried bone AGs plus DBM and AGs alone in patients exhibiting BCLs and nonunions based on the results of clinical and radiological evaluations.

Materials and Methods

This study was carried out following the principles of the Helsinki Declaration of 2008. This retrospective study was performed in the Department of Orthopedics and Traumatology at the University of Ondokuz

Mayis Faculty of Medicine in Turkey, between January 01, 2000, and December 31, 2004, after the approval of the ethics committee of the university. This study was conducted between 01.01.2000-31.12.2004.

The patients' information was obtained from the automated hospital records system and the files in the hospital archives. Written consent was obtained from all the patients included in the study and their relatives. The study included patients aged ≥18 years, who had BCLs and nonunion, who underwent DBM and/or allograft during the operation, and who followed radiologically and clinically. Patients were aged<18, who did not have a file, whose radiological and clinical follow-up was not completed were excluded from the study.

Two infected patients were excluded from the study.

Diagnostic criteria for the presence of BCLs in bone were the presence of well-defined radiolucent lesion seen on radiographs, presence of fluid on aspiration, and histopathological confirmation regarding the type of cyst and its origin. Cyst treated with curettage with bone grafting, a surgical procedure performed at the study site, and having a minimum follow-up at least a period of 6 months after surgery were included in the study. Cysts treated with other methods (intramedullary stabilization, bone marrow injection), or cysts located in the spine or the skull, infected cysts, and metastatic cysts were excluded from the study.

In our clinic, the patients are rechecked 4 times with follow-ups 1 day, 1 month, 3 months, and 6 months after surgery. At these appointments, anteroposterior, lateral, and oblique radiographs are taken. The patients participating in this study were invited to a final follow-up in January of 2005 to evaluate their clinical and radiological findings. The evaluations and follow-ups of the patients were performed by two orthopedic physicians. Anteroposterior and lateral radiographs were obtained from all of the patients for the radiological evaluation, which was performed via direct digital radiography.

A standard worksheet was created, and the patients' information was recorded on this form. Those patients with BCLs were placed in Group I, and those that exhibited nonunions were placed in Group II. Then, the Group I and Group II patients were subdivided into two groups each, A and B, according to the type of graft used. The patients treated with DBM combined with frozen corticospongiosis bone AGs were assigned to subgroup A, while those patients treated with only the AGs were assigned to subgroup B.

Group 1A: The patients who had BCLs and treated with DBM combined with frozen corticospongiosis bone AGs
Group 1B: The patients who had BCLs and treated with only the AGs
Group 2A: The patients who had nonunion and treated with DBM combined with frozen corticospongiosis bone AGs
Group 2B: The patients who had nonunion and treated with only the AGs

Group IA and Group IB were compared both clinically and radiologically, and Group IIA and Group IIB were compared both clinically and radiologically. The Goldberg radiological evaluation scale was used to evaluate the graft appearance and its union potential. The scores for the graft appearance were: resorbed = 0, mostly resorbed = 1, largely intact = 2, and reorganized = 3. The union potential (proximal-distal) scores were: nonunion = 0, possible union = 1, and radiological union = 2. The total points based on the category were: graft = 3, proximal union = 2, distal union = 2, and maximum score = 7

Graft appearance
Rezorbe 0
Very resorbed 1
Large intact 2
Reorganized 3
Union (proximal-distal)
Non-union 0
Possible union 1
Radiological union 2
Total Points by Category
Graft 3
Proximal union 2
Distal union 2
Max score 7
(Source: Bone transplantation, Berlin, Heidelberg, 1989)

Statistical Analysis
The statistical analysis was performed using IBM SPSS Statistics for Windows (version 21.0; IBM Corp., Armonk, NY, USA). The mean, standard deviation, and numerical values were used when providing descriptive analyses. The 2x2 design was compared using Pearson's chi-squared test and Fisher's exact test. For the normally distributed (parametric) variables evaluated between the groups, the Student's t-test was used. In the paired comparisons of the independent groups, for those showing normal distributions, the Mann-Whitney U test was used. A p-value of less than 0.05 was considered to be statistically significant.

Results

In this study, 101 patients have included: 39 (39%) females and 62 (61%) males. The mean age of the patients was 33.3±17.6 years old, and the mean follow-up period was 3.3±1.6 years. Group I contained 48 patients (47.5%) with BCLs, and Group II contained 53 patients (52.5%) with nonunions. The mean age of Group I patients was 32 ± 9 years and the mean age of Group II was 35 ± 12 years (p = 0.187). The mean follow-up period was 33 ± 12 months for group 1 patients and 29 ± 9 months for group 2 patients (p = 0.101).

Of the 48 patients in Group I, the BCLs were located in the following bones: 12 (25%) in the femur, 10 (20.8%) in the tibia, 6 (12.5%) in the calcaneus, 5 (10.4%) in the humerus, 5 (10.4%) in a hand phalanx, 4 (8.3%) in the fibula, 3 (6.3%) in a metatarsal, 2 (4.2%) in a foot phalanx, and 1 (2.1%) in the radius. Moreover, 23 (47.9%) of the Group I patients had solitary bone cysts, 11 (22.9%) had enchondromas, 8 (16.6%) had aneurysmal bone cysts, 3 (6.3%) had nonossifying fibromas, 2 (4.2%) had osteoid osteomas, and 1 (2.1%) had fibrous dysplasia. In Group I, 18 (37.5%) patients were included in the DBM and AG combination subgroup IA, and 30 (62.5%) patients were included in the AG-only subgroup IB. The mean age was 34 ± 11 years for group IA patients and 32 ± 8 years for group IB patients (p = 0.376). The mean follow-up period was 32 ± 14 months for group IA patients and 34 ± 7 months for group IB patients (p = 0.491).

When comparing Group IA with Group IB, there was a significant difference in terms of their radiological scores (p=0.011). The Group IA score was statistically significantly higher (Table 1).

Of the 53 patients in Group II, the nonunions were located in the following bones: 21 (39.6%) in the tibia, 16 (30.1%) in the femur, 9 (17%) in the humerus, 3 (5.7%) in the forearm, 2 (3.8%) in the ulna, and 2 (3.8%) in the scaphoid. In Group II, 20 patients were included in the DBM and AG combination subgroup IIA, and 33 patients (64.2%) were included in the AG-only subgroup IIB. The mean age of the group IIA patients was 35 ± 15 years and the mean age of the group IIB patients was 35 ± 7 years (p = 0.901). The mean follow-up period was 34 ± 11 months in group IIA patients and 31 ± 8 months in group IIB patients (p = 0.271).

There was a significant difference between the two groups in terms of their radiological scores (p=0.014). In Group IIA, the score was statistically significantly higher. (Table 2)

Discussion

In bone grafting procedures, autogenous bone grafts are widely used. When compared with AGs and other graft products, autografts are standard. Autografts may be an osteoprogenitor cell source (osteogenesis), induce the formation of osteoprogenitor cells from the surrounding tissues (osteoinduction), and provide mechanical support for vascular and bone growth (osteoconduction). Although autogenous bone grafts are clinically effective, additional surgical time is needed to collect the autogenous grafts. Moreover, the morbidity associated with the collection, and the autogenous bone limitations of some patients have encouraged the development of appropriate bone graft substitution materials. Therefore, various bone graft products, including autografts, AGs, xenografts, polymers, ceramics, and some metals, have been used to support bone reconstruction(1,9,10).

AGs are obtained from cadavers, after which they are sterilized and subjected to deimmunization. They are mainly osteoconductive. AGs do not contain cells that

Table 1 Comparison of radiological scores of group IA and group IB patients

Diagnosis	GRAFT	SCORE	FREQUENCY	%
Group IA	DBM +AG	6	10	55.6
		7	8	44.4
	Total		18	100 .0
Group IB	AG	4	14	46.7
		5	14	46.7
		6	2	6.6
	Total		30	100 .0

DBM: Demineralized Bone Matrix, AG: Corticospongiosis dried-frozen allograft

Table 2 Group IIA and Group IIB Patients Comparison of Radiological Scores

Diagnosis	GRAFT	SCORE	FREQUENCY	%
Group IIA	DBM + AG	5	2	10.0
		6	5	25.0
		7	13	65.0
	Total		20	100 .0
Group IIB	AG	3	1	3.0
		4	13	39.4
		5	12	36.4
		6	7	21.2
	Total		33	100 .0

DBM: Demineralized Bone Matrix, AG: Corticospongiosis dried-frozen allograft

can provide bone formation because all of the live cells are destroyed during the AG preparation process. Despite the many asepsis measures, AGs still carry with them the risk of transmitting viruses, such as hepatitis or the human immunodeficiency virus(11).

In one prospective study, it was found that AGs provided less fusion than autografts in posterior lumbar fusion surgery; therefore, it was suggested that AGs should not be used alone in posterior lumbar fusion procedures(12). In a retrospective study of nonunion cases, patients with autografts, AGs, AG/autograft combinations, and recombinant human BMP-2 and/or adjuvant bone grafts were compared. In this study, the mean age of the patients was 44 ± 13.6 years and there was no age difference between the groups. In the autograft group, the union duration was shorter, and the surgical revision and postoperative infection rates were lower than in the AG cases(13). In another study, patients who had no graft and patients who were treated with AG and treated with platelet-rich plasma (PRP) enriched AG were compared in the treatment of maxillofacial bone defects. In this study, it was shown that PRP enriched AG is superior to others in new bone formation(2). Based on these results, it is believed that the procedures applied during the preparation of AGs directly affect the fusion potential, and their osteoconductive effects are extremely limited.

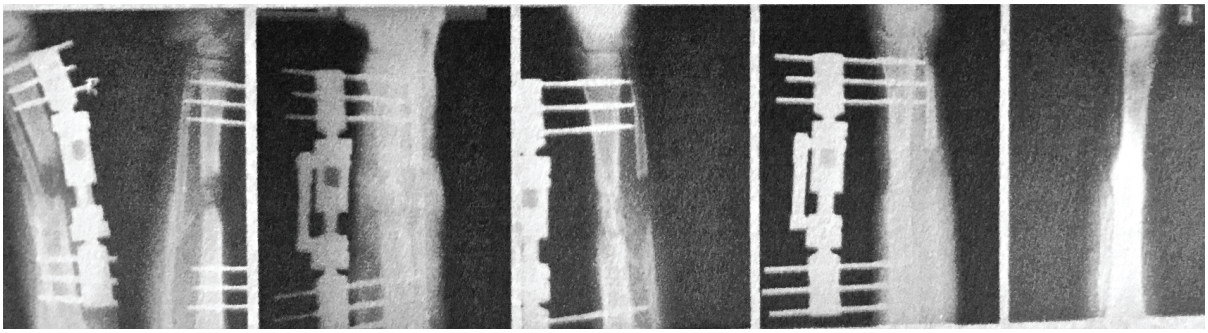
DBM is obtained by removing the minerals from the bone with acid treatment. The remaining substance includes type I collagen, growth factors, and noncollagenous proteins. Therefore, DBM does not provide structural support; however, it does exhibit osteoinductive properties. This DBM feature was later understood to be related to the BMP content. In addition to its superior osteoinductive capacity, DBM has a lower resorption rate than AGs. Over the long term, its biomechanical features are similar to those if autografts(14-16). In one prospective study of DBM, it was reported that bone marrow mixed with DBM provided a rate of fusion similar to that seen when using an autograft(13). Additionally, in another multicenter prospective study, it was suggested that an iliac crest autograft was not very different in terms of the fusion rate. In a Systematic Review investigating the fusion efficacy of allograft and demineralized bone matrix (DBM) in the degenerative lumbar disorders, For the allograft, fusion rates were calculated from 58% to 68% for non-instrumented and from 68% to 98% for instrumented procedures. For DBM, fusion rates were measured 83% for non-instrumented and between 60% and 100% for instrumented lumbar fusion procedures. ın this study, the patients were follow-up 2 years(19).

Based on these articles, the use of DBM has been recommended to increase the overall amount of a graft instead of using it by itself. In an arthrodesis study of the posterior ankle and ankle, AG plus DBM treatments and AG plus DBM plus bone marrow aspiration treatments were compared. However, there was no significant difference between the two groups in terms of the fusion speed, fusion time, heterotopic ossification number, revision rate, and the amount of DBM used. The AG plus DBM plus bone marrow aspiration treatment is a good alternative to an AG plus DBM treatment because it provides similar efficacy without causing any increase in the number of complications and nonunions(20).Other study has compared the outcome after subtrochanteric atypical femur frac-

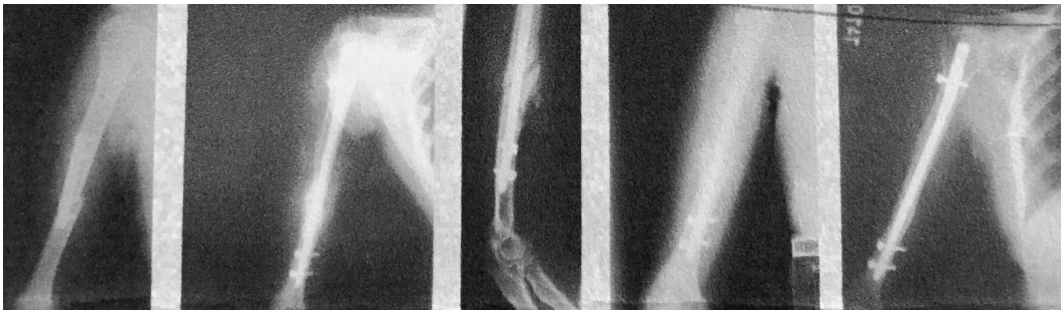
ture fixation with and without DBM. In this study, the mean age of the patients was 67 years (range 56–81 years) and there was no age difference between the groups. In this study, the DBM group had shown a significantly shorter healing time than the Non-DBM group (DBM:28.1 ± 14.4 versus non-DBM: 57.9 ± 36.8 weeks, p = 0.04)(21).

In our study, the types of grafts used to increase osteogenesis were compared without considering the surgical treatment methods and union types. In our study, the mean age of the patients was 33.3 ± 17.6 years. There was no age difference between the groups. In our study, unlike the other studies, our patients were at an earlier age. However, our results showed that the combined use of DBM and an AG was more effective concerning the clinical and radiological improvements than an AG alone.

In the treatment of bone cysts, fine needle biopsy aspiration, local steroids plus autogenous bone marrow plus DBM, curettage, grafting, or a subtotal resection can be performed. The aims here are to prevent the formation of pathological fractures, increase the healing rate of the cyst, and prevent a recurrence. In one study of bone cyst patients with cortical erosions, repeated corticosteroid injections, and a single bone marrow transplantation were compared. In this study, the mean age of the patients was 10 years (range, 2–21 years), and there was no difference between the groups in terms of age, sex, clinical appearance, and lesion location. Based on the steroid treatment, the combination of DBM and bone marrow provided a higher rate of improvement (22). In a similar study in patients with active unicameral bone cysts, the patients were treated with DBM and bone marrow. Cortical remodeling took 6–9 months in these patients, and they reached the necessary union at the end of 1 year(23). In another study, the patients with a unicameral bone cyst had treated with intramedullary decompression followed by grafting of demineralized bone matrix. The mean age of the study patients was 11.1 years (range, 3-19 years). In this study, 19 of 25 cysts had completely consolidated after a single procedure. The mean time to healing was 6.6 months (range, 3–12 months)(24).In our study, the mean age of the patients who had BCLs was 35 ± 12 years. Although the age of our patients was more advanced, the combination of an AG and DBM in the patients with BCLs exhibited better results than in the patients treated with AGs alone. Based on these results, it was concluded that the DBM increased the AG healing effects.



Picture 1
22y, male, B groub (AG) patient



Picture 2
34 y, female , A groub (DBM+ AG) patient

Another issue that cannot be ignored is the treatment cost. The use of an AG and DBM adds a very high cost to the treatment. However, the limitations of the human autograft reserves concerning long-segment vertebral fusion, filling a large bone defect, and revision arthroplasty make the use of an AG inevitable (25).

Limitation

The limitation of our study was that different age groups were not included in the study. Results may vary in different age groups, especially in children and in older ages.

Conclusion

In the treatment of both CDLs and nonunion, the AG-DBM combination is more effective than AG alone as clinically and radiologically. However, additional, wider studies are needed to verify these results.

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