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Use of demineralized bone matrix in the extremities

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Abstract

Autologous bone graft is considered as the gold standard for all indications for bone grafting procedures but the limited availability and complications in donor site resulted in seeking other options like allografts and bone graft substitutes. Demineralized bone matrix (DBM) is an allograft product with no quantity limitation. It is an osteoconductive material with osteoinductive capabilities, which vary among different products, depending on donor characteristics and differences in processing of the bone. The purpose of the present review is to provide a critical review of the existing literature concerning the use of DBM products in various procedures in the extremities. Clinical studies describing the use of DBM alone or in combination with other grafting material are available for only a few commercial products. The Level of Evidence of these studies and the resulting Grades of Recommendation are very low. In conclusion, further clinical studies of higher quality are required in order to improve the Recommendation Grades for or against the use of DBM products in bone grafting procedures.

Key words: Bone; Grafting; Allograft; Demineralized bone matrix; Non-union

Core tip: Demineralized bone matrix (DBM) is an allograft product that was found to be safe as an option of bone grafting. As far as its effectiveness is concerned, and according to the existing literature: (1) there is a good evidence for its use in bone cysts combined with autologous marrow aspirate; (2) in fracture nonunion and filling the defects after tumor surgery DBM used alone or combined with other grafting material are supported by a lower quality studies; and (3) there is insufficient evidence to make a treatment recommendation for DBM use in fracture treatment of other applications. Furthermore, according to the existing literature there are results of clinical use of only a few DBM products and thus the recommendation concerning the DBM use should probably also be referred to these specific products and not to any DBM product.

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INTRODUCTION

In recent years, the requirements for bone grafting have increased, due to the increasing number of procedures, in orthopaedic, oral and maxillofacial surgery[1]. Autologous bone is considered the ideal graft for any indication providing the best osteogenic, osteoinductive and osteoconductive potential of all grafts, with no immunological rejection[2-5]. Allograft materials and graft substitutes have been developed to avoid limitations of autologous graft, like limited availability and donor site morbidity[6-12].

Demineralized bone matrix (DBM) is an osteoconductive and osteoinductive allograft product, but no osteogenic capacity because of its processing[13-18]. The osteoinductive capacity of DBM can be affected by storage, demineralization process, washing procedure, sterilization method and vary from donor to donor resulting in differences between and within products[19-25]. DBM has no immunological rejection as the antigenic surface structure of the bone is destroyed during demineralization by acid[26], but, on the other hand, it is known that a host immune response can be induced by allogeneic bone[27-30], despite its processing Nevertheless, to the best of our knowledge, there are no studies concerning the possible immunogenicity and its influence on the bone formation for the different DBM products.

Since DBM was found to be effective and safe as an option of bone grafting, it has been used to induce bone formation in various procedures.

The aim of this study is to present a critical review of the existing literature concerning the use of DBM products, alone or as a composite graft, in various procedures requiring bone grafting in the extremities.

The key words "demineralized bone matrix", and "DBM", were used for a MEDLINE search and results were restricted to clinical trials in the English language. Clinical studies of use of DBM in spinal fusion were excluded.

Clinical studies were evaluated using the levels of evidence rating for clinical studies[31] and grades of recommendation are based on this evaluation[32] as follows: (1) Grade-A recommendations: Consistent level-Ⅰ studies; (2) Grade-B recommendations: Consistent level-Ⅱ or Ⅲ studies; (3) Grade-C recommendations: Level-Ⅳ or Ⅴ evidence, or conflicting evidence; and (4) Grade-Ⅰ recommendations: Insufficient evidence to make a treatment recommendation. Twenty one clinical studies were selected for this review. These studies were analysed and described by category of use (Table 1).

USE OF DBM IN FRACTURES

One level Ⅱ[33] and two level Ⅲ[34,35] comparative studies concerning the use of DBM in long bone fractures have been published. In the level Ⅱ study the DBM combined with bone marrow aspirate was used in diaphyseal long bone fractures. In the first level Ⅲ study the DBM combined with allograft cancellous chips was used in patients with periarticular fractures when in the second the DBM with calcium sulfate and vancomycin was used in displaced intra-articular calcaneal fractures.

Lindsey *et al*[33], in a prospective randomized pilot study, compared the results in patients with diaphyseal long bone fractures treated with either DBM Grafton® (Osteotech, Eatontown, NJ, United States) combined with aspirated bone marrow or autologous iliac crest bone graft alone. In 12 mo follow up, 90% of the patients who received DBM and aspirated bone marrow achieved full bone formation *vs* 75% of the autologous graft group. Additionally, finally healing rate was 100% in DBM group and 63% in the autograft group. Results suggest that the use of DBM with aspirated bone marrow is comparable with the use of autologous graft, in treatment of long bone fractures.

In a retrospective study, Cheung *et al*[34], compared Grafton® (Osteotech, Eatontown, NJ, United States) with Orthoblast (Gensci, Irvine, CA, United States) in the treatment of periarticular fractures in 28 patients. In both groups allograft cancellous chips were used in combination with the DBM. Bone union was achieved with no complications in 100% with Grafton® and in 69% in Orthoblast. Authors suggest the combination of allograft cancellous chips with Grafton® could be an alternative to autologous grafting for these fractures.

Bibbo *et al*[35] studied retrospectively bone healing and complications in 44 patients with displaced intra-articular calcaneal fractures with bone defect treated with open reduction and internal fixation. DBM with calcium sulfate (AlloMatrix™, Wright Medical, Arlington, TN) and vancomycin used in 33 patients and no grafting in 11 patients. The mean union time in the combined graft group was of 8.2 wk and of 10.2 wk in the control group. There were wound problems in 5 of 33 patients in DBM group (two minor and three serious wound problems), but in mean follow up time of 22 mo, no evidence of osteomyelitis were demonstrated.

USE OF DBM IN NON-UNIONS

One level Ⅲ and three level Ⅳ studies concerning the use of DBM in non-unions were found. The level Ⅲ study is a comparative study between DBM and autologous iliac crest bone graft in humeral delayed and non-unions[36]. The level Ⅳ studies report the results[37,38] and the complications[38] of the DBM use in bone non-unions.

Table 1 Clinical studies of demineralized bone matrix use in extremities

Ref.	Design	Diagnosis/procedures	Type of graft	Main outcomes	Level of evidence
Clinical studies of DBM used in fractures					
Lindsey *et al*[33]	Prospective, randomized pilot study	Patients treated for long bone fractures	DBM (Grafton®) + bone marrow $n = 10$ Iliac crest autograft $n = 8$	Full bone formation in 90% with DBM + marrow and 75% with autograft at 12/12 Totally 100% healed with DBM + marrow and 63% heal with autograft	II
Cheung *et al*[34]	Retrospective comparative study	Periarticular fractures ($n = 28$)	Allograft conductive cancellous chips + DBM Grafton® ($n = 13$) Allograft conductive cancellous chips + DBM Orthoblast ($n = 15$)	Healing on the first graft attempt without complications DBM Grafton®: 69% DBM Orthoblast: 100%	III
Bibbo *et al*[35]	Retrospective comparative study	Patients treated for displaced intra-articular calcaneal fractures	DBM + $CaSO_4$ + vancomycin $n = 33$ Control group $n = 11$	Union in 8.2 wk with graft, while 10.4 wk in control group $P < 0.05$ Wound problems in 15% in graft group	III
Clinical studies of DBM used in nonunions					
Hierholzer *et al*[36]	Retrospective consecutive cohort study	Patients with an aseptic, atrophic delayed union or nonunion of a humeral shaft fracture were treated with ORIF and graft	Autologous iliac crest bone graft $n = 45$ DBM (Grafton®) $n = 33$	Union in 100% with autologous graft *vs* 97% in DBM group Union in 4.5 mo with autologous graft *vs* 4.2 mo in DBM group 44% of the autologous graft group had donor site morbidity	III
Wilkins *et al*[37]	Prospective clinical study	Patients with stiff nonunions of long bones ($n = 66$)	Percutaneous use of a mixture of autologous bone marrow and allograft DBM (AlloMatrix)	61 of 69 patients with stiff nonunion went on to union in an average of 8.1 mo; 7 more healed after a second procedure	IV
Wilkins *et al*[39]	Retrospective clinical study	Patients undergoing surgical intervention for removal of benign tumors ($n = 41$) or treatement of nonunions in multiple bone types ($n = 35$)	AlloMatrix Injectable Putty	38 of 41 patients with benign tumors healed within an average of 4.8 mo, and 30 of 35 patients with nonunion went on to union in an average of 3.5 mo	IV
Ziran *et al*[38]	Consecutive patients	Patients required bone grafting for atrophic/avascular nonunions	AlloMatrix + morselized cancellous allograft chips (1:1 ratio) $n = 41$	51% developed postoperative drainage, 34% developed deep infection, 32% required surgical intervention	IV
Clinical studies of DBM used in bone cysts					
Park *et al*[40]	Retrospective comparative study	Calcaneal unicameral cysts were treated with graft	Lyophilized irradiated CAB + bone marrow $n = 13$ DBM + bone marrow $n = 10$	Complete healing in 9/13 in CAB group *vs* 5/9 in DBM group Healed with defect in 4/13 in CAB group and 3/9 in DBM group No infections or pathologic fractures during 48/12 follow up	III
Di Bella *et al*[41]	Retrospective comparative study	184 patients treated for unicameral bone cysts with cortical erosion	Multiple injection of corticosteroid Single injection of DBM + bone marrow concentrate	38% healed with steroids at 48/12 and 71% healed with DBM + BMC at 20/12 Failure rate after 1 steroid injection was 63% *vs* 24% with DBM + BMC	III
Rougraff *et al*[42]	Consecutive patients	Active unicameral bone cyst ($n = 23$)	Trephination and percutaneous injection of a mixture of demineralized bone matrix (Grafton) and autologous bone marrow	Healing on the first graft attempt: 78%	IV
Kanellopoulos *et al*[43]	Consecutive patients	Active unicameral bone cyst ($n = 19$)	Combination of percutaneous reaming, injection of a mixture of allogenic DBM (AlloMatrix) and autologous bone marrow	Healing on the first graft attempt: 89.5%	IV
Hass *et al*[44]	Retrospective case series	Treatment of juvenile bone cysts at all sites with DBM	Juvenile bone cysts packed with DBM ($n = 9$)	Totally osteodense images after an average of 8 mo, with no other significant changes in 2 yr follow-up	IV

Sung *et al*[45]	Retrospective comparative study	Patients, younger than 20, treated for humeral and femoral unicameral bone cysts	Corticosteroid injection $n = 94$, curretage + bone graft $n = 39$, Steroids + DBM + bone marrow aspirate $n = 34$	Failure rate was 84% with steroids, 64% with curretage and 50% with SDB $P < 0.001$. Retreatment in 76% with steroids, 63% with curretage and 71% with SDB	III
Clinical studies of DBM used in tumor surgery					
Kim *et al*[46]	Retrospective comparative study	Bony defects after tumor surgery of various bone tumors	ICS $n = 28$ DBM $n = 28$	ICS and DBM success rate = 85.7% (24/28) and 88.9% (24/27) $P < 0.05$ Average healing time for ICS and DBM was 17.3 wk and 14.9 wk $P < 0.05$	III
Wilkins *et al*[39]	Retrospective clinical study	Patients undergoing surgical intervention for removal of benign tumors ($n = 41$) or treatment of nonunions in multiple bone types ($n = 35$)	AlloMatrix injectable putty	38 of 41 patients with benign tumors healed within an average of 4.8 mo, and 30 of 35 patients with nonunion went on to union in an average of 3.5 mo	IV
Clinical studies of DBM used in various long bone applications					
Dallari *et al*[47]	Prospective, randomized control trial	High tibial osteotomy for genu varus	DBSint® (Mg-hydroxyapatite + DBM) $n = 9$ SINTlife® $n = 13$ Lyophilised bone chips $n = 9$	6/52 DBSint® showed higher osseointegration rate than lyophilized bone chips ($P < 0.01$) 52/52 DBSint® was demonstrated as effective and safe as SINTlife® and bone chips	II
Hatzokos *et al*[48]	Retrospective comparative study	Patients were managed with bone transport for the treatment of a tibial bone defect, with 3 types of docking procedures ($n = 43$)	Group A: closed compression Group B: autologous iliac graft Group C: BMC + DBM	Healing time was significantly longer in the compression group as compared with the BMC + DBM $P < 0.05$, no significant difference among the groups in terms of complication rates	III
Wilkins *et al*[49]	Prospective clinical study	Patients requiring bone grafting procedures ($n = 50$)	Combination product of bioassayed DBM (AlloGro®) and calcium sulfate pellets	Healing rate of 98% within an average period of 11.8 wk	IV
Clinical studies of DBM used in osteonecrosis of femoral head					
Feng *et al*[50]	Retrospective comparative study	Treatment of large osteonecrotic lesions of the femoral head with graft	OsteoSet®2 DBM + free vasculated fibular graft $n = 2$, Free vasculated fibular graft + autologous cancellous bone $n = 24$	Improvement in the mean Harris hip score was noted in both groups $P < 0.001$, no significant differences in Harris hip score and clinical outcomes between groups	III
Clinical studies of DBM used in acetabular revision					
Etienne *et al*[51]	Retrospective clinical study	Acetabular revision surgery ($n = 20$)	Acetabular reconstruction using a mixture of DBM (ALLOMATRIX™ C Bone Putty) and cancellous allograft chips	Successful graft incorporation in 18 of 20 patients (90%)	IV
Clinical studies of DBM used in fusion					
Thordarson *et al*[52]	Retrospective Comparative Study	Complex ankle or hindfoot fusion with commercially available DBM formulations that did or did not contain crushed cancellous allograft bone ($n = 63$)	Grafton® + allograft cancellous bone chips $n = 37$ Orthoblast + allograft cancellous bone chips $n = 26$	Clinical and radiological fusion In DBM Grafton: 86% In DBM Orthoblast: 92%	III

DBM: Demineralized bone matrix; CAB: Chip allogenic bone; ICS: Injectable calcium sulfate; SDB: Steroids and demineralized bone matrix and bone marrow aspirate; BMC: Bone marrow concentrate.

Hierholzer *et al*[36], reported the results after open reduction, internal fixation and bone grafting in ninety-eight patient with non-union or delayed union of humeral shaft fractures. No significant difference was found between Grafton® DBM and autologous iliac crest bone graft. The union rate in Grafton® group was 97% with a mean healing time of 4.2 mo while in the autologous graft group the union rate was 100% with a mean healing time of 4.5 mo. However, in the autologous grafting group donor site morbidity was 44%.

Wilkins *et al*[37] treated 66 patients with non-unions of long bone fractures by percutaneous application of DBM (AlloMatrix™) and autologous bone marrow. Union rate was 88% at an average of 8.1 mo after surgery. Authors suggested that this method of treating nonunions is as successful as iliac crest autologous bone grafting,

with additional benefits of reduced cost, decreased morbidity of donor site and shorter hospital stay.

In a retrospective clinical study, Wilkins *et al*[39] used AlloMatrix™ putty in 35 patients with non-union in various bones and in 41 patients after surgical treatment of benign tumors. Union rate for the non-union group was 85.7% in a mean time of 3.5 mo while the heling rate in the tumor group was 92.7% in an average of 4.8 mo.

In the other hand, Ziran *et al*[38], in a series of 41 consecutive patients, who required bone grafting for atrophic/avascular nonunions, presented the complications associated with the use of a specific graft (AlloMatrix™). Patients were monitored for healing and adverse effects, (local or systemic reactions, wound problems, infection). Of the 41 patients, 13 had drainage which required surgical intervention, and 14 patients developed deep infection of the surgical area, of whom 11 patients required surgical treatment. Authors suggest that the use of that type of graft resulted in an unaccepted rate of complications, compared to the complication rate of the use of allograft in literature.

USE OF DBM IN BONE CYSTS

Over the last years DMB becomes more and more popular for the treatment of bone cysts. Several studies present good results of the use of DBM in bone cysts, proving high healing and low complication rate. There are two level Ⅲ[40,41] and two level Ⅳ[42,43] studies, which present the use of DBM and autologous bone marrow in treatment of active unicameral bone cysts, one level Ⅳ[44] study with the use of DBM in juvenile bone cysts and one level Ⅲ[45] study with use of DBM combined with autologous bone marrow and steroids in bone cysts.

Park *et al*[40] compared retrospectively the efficacy of percutaneous local injection of lyophilized chips of allogeneic bone and autogenous bone marrow, *vs* demineralized bone powder (Injecta bone TR, Modumedi Ltd., Daegu, Republic of Korea) and autogenous bone marrow, in 23 calcaneal unicameral cysts. Patients were followed up for an average of four years. Complete healing was achieved in 9 out of 13 cysts treated with chip allogeneic bone and in 5 out of 10 cysts treated with demineralized bone powder. Four of the first group and three of the DBM group healed with a defect, while the other two of the DBM group, classified as persistent cysts. During follow up there was no sign of infection or pathologic fractures.

Di Bella *et al*[41], in a retrospective comparative study of 184 patients with unicameral bone cysts and cortical erosion, compared the outcomes of multiple injections of costricosteroids *vs* single injection of DBM (Musculoskeletal Tissue Bank of the Rizzoli Orthopaedic Institute) and bone marrow concentrate. Minimum follow up of both groups was 12 mo. After first injection, authors observed a healing rate of 21% in the steroids group *vs* 58% in the DBM and bone marrow concentrate group. Multiple injections of steroids followed in the steroid group. Finally 38% healed with corticosteroids when 71% healed with DBM and bone marrow mixture. There was no difference of fracture rates between the two groups. Authors concluded that treating unicameral bone cysts with a single injection of a mixture of DBM and bone marrow concentrate appears to provide high healing rate, and better outcomes when compared with percutaneous corticosteroid injections.

Rougraff *et al*[42] applied percutaneously autologous bone marrow combined with DBM (Grafton®) in 23 patients with bone cysts. The healing rate was 78% in a mean time of 50 mo, while in 5 patients a second procedure was required. No pathologic fracture was reported.

In another series of 19 children, Kanellopoulos *et al*[43], used a combination of percutaneous reaming and an injection of a mixture of DBM (AlloMatrix™) and autologous bone marrow, in the treatment of active unicameral bone cysts. During a mean follow up time of 28 mo, authors reported a healing rate after the first graft attempt, up to 89.5%, while two patients required second surgical intervention. Authors reported no pathologic fracture or other complication.

Hass *et al*[44], treated 9 children with bone cysts (juvenile cysts) with Grafton® packing after curettage of the cyst. Complete healing was achieved in all patients, with totally osteodense radiographic images after an average time of 8 mo. There was only one significant complication in a child, who sustained a pathologic distal tibial fracture five months post-operatively. There were no other significant changes in two years follow up.

In a retrospective comparative study of 167, younger than 20 years old, patients, Sung *et al*[45], presented the failure rates of three surgical managements of humeral and femoral unicameral bone cysts. One therapeutic strategy was the use of corticosteroid injection in 94 patients, the second was curettage of the cyst and use of bone graft in 39 patients and the third was a combination of injection of steroids, DBM (Grafton® gel) and bone marrow aspirate in 34 patients. Mean follow up was 7.3 years and outcomes included treatment failure, defined clinically as pathologic fracture or need for retreatment, and complications. After one treatment, 84% of cysts treated with steroids had failed while, 64% of the curettage group failed and only 50% of the third group with the steroids, DBM and bone marrow mix didn't healed. For unicameral bone cysts requiring retreatment, 76% retreated with steroids had failed *vs* 63% with curettage and 71% with mix composite. Authors concluded that the use of steroids with DBM and bone marrow aspirate is a reasonable first surgical treatment of unicameral bone cysts in young patients.

USE OF DBM IN TUMOR SURGERY

There are at least two studies[39,46], presenting the use of DBM in defects due to surgical intervention of bone tumors. One level Ⅳ study presents the use of an injectable type of graft, which is DBM and calcium sulfate, in bone tumor surgery. The other level Ⅲ study investigates the use of DBM in defects after removal various bone tumors.

Recently, Kim *et al*[46] investigated, retrospectively, the efficacy of injectable calcium sulfate and DBM in bone defects after tumor surgery of various bone tumors. 56 patients, who were surgically treated for bone tumors, randomly allocated in two groups. 28 patients treated with injectable calcium sulfate, while the other 28 with DBM graft (Orthoblast Ⅱ, Integra OrthoBiologics Inc., Irvine, CA, United States). Radiologic and clinical outcomes compared between groups. One case with early pathologic fracture in DBM groups has been excluded from the study, so the reference value of this group was 27 patients. Results showed successful healing in 24 out of 28 patients, in an average of 17.3 wk with injectable calcium sulfate *vs* 24 out of 27 patients, in an average of 14.9 wk with DBM graft. Authors concluded that both grafts appear to be comparable and effective in the treatment of bone defects following tumor surgery.

Wilkins *et al*[39] analysed retrospectively a series of 41 patients with benign tumors treated with removal of the lesion and use of AlloMatrix™ Injectable Putty for grafting. In the same study, 35 patients with nonunions in multiple bone types, treated with the same graft, as mentioned above. Bone healing was observed at an average of 4.8 mo in 38 out of 41 patients in the tumor group. Complications developed in 12 patients, in both groups, including infection in two patients, continued sterile wound drainage in five patients, refracture in two cases, hardware failure in one case, one postoperative neuroma formation, and one case of decreased range of joint motion. A recurrence of the tumor occurred in three patients. In this study, AlloMatrix™ Injectable Putty used as bone void filler in bone defects after tumor surgery. Authors believed that the use of DBM shows results equal to those reported with autograft.

DBM IN VARIOUS LONG BONE APPLICATIONS

In a prospective randomized control trial, Dallari *et al*[47] investigated the bone healing ability of DBSint®, which is a biomimetic composite, obtained by mixing SINTlife® (Fin-Ceramica SpA, Faenza, Italy) and human DBM, produced in authors Institute Bone Bank (Rizzoli Orthopaedic Institute, Bologna, Italy), *vs* a Mg-hydroxyapatite graft (SINTlife®) and lyophilized bone chips, in high tibial osteotomies for genu varus. Nine patients randomly received DBSint®, 13 patients SINTlife®, and nine patients received allograft lyophilized bone chips, as a control group. Radiological, clinical and histomorphological outcomes were evaluated. At six-weeks follow-up, DBSint® showed a higher osseointegration rate in comparison with lyophilised bone chips. while, at the same time, histomorphometry of computed tomography guided bone biopsies showed that a good osteogenetic potential was demonstrated with DBSint®, as well as with SINTlife® and the control group. At final follow-up of 1 year, all patients had relief from knee pain and improvement of walking ability. The Knee Society Functional Score was significantly different between groups, but all recorded values were in normal range. The study concluded that DBSint® was demonstrated as effective and safe as SINTlife® and lyophilized bone chips, within the limits of the study.

Hatzokos *et al*[48], evaluated the use of different grafts in the docking site in patients who managed with bone transport for treatment of a tibial defect. All 43 patients were divided into three groups according to the "docking site procedure" used. In group A, closed compression was applied, in group B surgical debridement of the docking site followed by the application of autologous iliac bone graft, and in group C, debridement followed by the application of bone marrow concentrate and DBM (Grafton Putty DBM OST Development SA, Clermont-Ferrand, France). Docking site consolidation was assessed both radiographically and clinically. Healing time was significantly longer in the first group treated only with closed compression, compared with DBM group, while there was no difference between the grafting groups. There was no significant difference in complication rates between the different groups. Authors concluded that the application of DBM and autologous bone marrow concentrate is equivalent to autologous bone graft in management of docking site during distraction osteogenesis, proving that it is an effective and safe treatment option.

In a prospective clinical study, Wilkins *et al*[49] reported that a mixture of calcium sulphate pellets and DBM (AlloGro®). In this level Ⅳ study, 50 patients underwent bone grafting for a variety of diagnosis including benign bone lesions (n = 35), non-union of long bones (n = 11), osteomyelitis (n = 3), and one patient for acute fracture. Results showed high efficacy of grafting, since 49 out of 50 patients healed in an average of 11.8 wk. The complication rate was very low, with a re-infection in one patient, and a recurrence of a bone cyst in another patient. According to the authors this mixture of calcium sulphate pellets and AlloGro® DBM was safe with no graft-related complications and effective for bone regeneration.

USE OF DBM IN OSTEONECROSIS OF FEMORAL HEAD

In a level Ⅲ study, Feng *et al*[50] studied the safety and efficacy of a type of DBM (OsteoSet®) in treatment

of patients with large osteonecrotic lesions of the femoral head. In a retrospective study the authors compared 24 patients that underwent free vascularized fibular grafting and OsteoSet® with 24 patients who underwent fibular grafting and autologous cancellous bone grafting. There was no significant difference in clinical outcomes, Harris Hip Score or complication rates between the two groups. The authors concluded that in patients with femoral head osteonecrosis treated with free vasculated fibular grafting, harvesting autologous bone can be avoided using the equally effective OsteoSet® DBM.

USE OF DBM IN ACETABULAR REVISION

Etienne *et al*[51] in a level Ⅳ retrospective study reported the results after bone grafting for bone loss in acetabulum revision surgery in 20 patients. The authors used allograft cancellous bone mixed with DBM (Allomatrix™). Successful graft incorporation was found in 90% of the patients in a mean follow-up of 27 mo.

USE OF DBM IN FUSION

There is one level Ⅲ study, of Thordarson *et al*[52], comparing two different DBM products used in 63 patients with ankle or foot fusions. In 37 patients Grafton® putty was used, and in the rest 26 patients Orthoblast used to enhance fusion. All patients followed-up, clinically and radiographically to fusion or non-union time, with a minimum follow-up of 1 year. The Grafton group succeeded a fusion rate of 86%, while the Orthoblast group healing rate reached 92%. Authors concluded there was no significant difference between union rates of those two grafts.

CONCLUSION

Although there is an able number of studies in the literature, examining the use of DBM products either alone or in combination with other grafting materials, in several applications in extremity operations, there is little information concerning the true efficacy of most of these products.

There are very few studies that examine the true efficacy of specific DBM products alone as a graft. In the other hand there are a lot of studies, which examined the use of DBM in combination with osteogenic grafts such as bone marrow, with osteoconductive bone-void filler such as calcium sulphate, and other allografts like cancellous chips.

It is also obvious that from a big variety of available DBM in the market, there are clinical studies available for only a few commercial products. Although information from clinical data is limited, pre-clinical studies have shown that there are differences between the different products concerning their osteoconductive and osteoinductive characteristics. Therefore, our recommendations should probably also be referred to the specific products as well as to the levels of the available studies.

INDICATIONS AND RECOMMENDATIONS

Use of DBM in fractures

According to the existing literature there is insufficient evidence to make a treatment recommendation (grade-Ⅰ recommendations).

There is only (1) one Level Ⅱ[33] comparative study where the DBM combined with bone marrow aspirate was used in diaphyseal long bone fractures; (2) one Level Ⅲ study[34] where the DBM combined with allograft cancellous chips was used in patients with periarticular fractures; and (3) one Level Ⅲ[35] study where the DBM with calcium sulfate and vancomycin was used in displaced intra-articular calcaneal fractures.

Use of DBM in nonunions

Four studies (one Level Ⅲ[36] and three Level Ⅳ studies[37-39]) concerning the use of DBM in non-unions were found (grade-C recommendations).

Although there is a comparative study between DBM and autologous iliac crest bone graft in humeral delayed and non-unions[36] (level Ⅲ study) this is the only comparative study.

Use of DBM in bone cysts

There are four studies (two Level Ⅲ[40,41] and two Level Ⅳ[42,43] studies), presenting the use of DBM and autologous bone marrow in treatment of active unicameral bone cysts, one level Ⅲ[45] study with use of DBM combined with autologous bone marrow and steroids and one level Ⅳ[44] study with the use of DBM alone.

Therefore it is suggested that the use of DBM and autologous bone marrow in treatment of active unicameral bone cyst is a good option (grade-B recommendations).

Use of DBM in tumor surgery

There is only one retrospective comparative (Level Ⅲ) study[46] between injectable calcium sulfate and DBM and one level Ⅳ study presenting the results of an injectable DBM (grade-C recommendations).

DBM in various applications

There is insufficient evidence to make a treatment recommendation (grade-Ⅰ recommendations) as there is only one available study for the following procedures: (1) High tibial osteotomy for genu varus[47] (level Ⅱ study); (2) Docking site procedure in bone transport for the treatment of a tibial bone defect (level Ⅲ study)[48]; (3) Various bone grafting procedures (level Ⅳ study)[49]; (4) Treatment of large osteonecrotic lesions of the femoral head with graft (level Ⅲ study)[50]; (5) Acetabular revision surgery (level Ⅳ study)[51]; and (6)

Complex ankle or hindfoot fusion (level Ⅲ study)[52].

In conclusion, further clinical studies of higher level of Evidence are required in order to improve the Recommendation Grades for or against the use of DBM products (alone or combined with other grafting material) in bone grafting procedures.

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