Review article

SUBSTITUTES FOR AUTOLOGOUS BONE GRAFT IN ORTHOPAEDIC TRAUMA

J. F. Keating, M. M. McQueen

Although bone grafting has a well-recognised role in orthopaedic surgery for the treatment of nonunion, bridging diaphyseal defects and filling metaphyseal defects, it is associated with postoperative pain and morbidity.^{1,2} When extensive grafting is required, as in spinal arthrodesis and the management of large bony defects, inadequate amounts of autologous bone may not be available. Allograft bone has been used as an alternative but it has low osteogenicity, increased immunogenicity and resorbs more rapidly than autogenous bone;³⁻⁶ transmission of disease remains a concern.

Autogenous bone graft is osteogenic, osteoinductive, osteoconductive and completely biocompatible. These characteristics should be present in the ideal substitute. Osteogenic materials have the inherent capacity to form bone, which implies that they have living cells such as osteocytes or osteoblasts, capable of producing it. Osteoinductive materials stimulate cells in the wound or the local environment to undergo phenotypic conversion to osteoprogenitor cell types capable of formation of bone. Osteoconductive materials have no capability to form bone or induce its formation. They merely provide an inert biocompatible scaffold, which local osseous tissue can utilise to regenerate living bone.

There is no substitute for bone-graft yet available which embodies all these qualities. To date most of the available materials have tended to be either predominantly osteogenic or osteoinductive, or purely osteoconductive. This article reviews the substitutes which are commonly available and considers the clinical evidence to support their use in the management of orthopaedic trauma.

Osteogenic and osteoinductive materials

Allograft. The most obvious alternative to autogenous bone graft has been allograft bone, which has been widely used in both structural and morsellised forms depending on the indication. Allograft bone has been employed in fresh, frozen or freeze-dried forms. Fresh allografts are rarely used because of the immune response and the risk of transmission of disease. The frozen and freeze-dried types are osteoconductive but are considered, at best, to be only weakly osteoinductive. The method of preparation is designed to minimise the immune response of the host and therefore in most allografts there are no viable cells to confer osteogenic properties.

Although the risk of transmission of disease is much lower than with blood and blood products, it has occurred. In particular, transmission of HIV and hepatitis C has been described.⁷⁻⁹ The structural quality may be adversely affected depending on the method of preparation. In particular, freeze-drying diminishes the structural strength of the allograft and renders it unsuitable for use in situations in which structural support is required. Sterilisation by gamma irradiation or ethylene oxide can be used to enhance safety. These processes also adversely affect the structural integrity of the material and its osteoinductive and osteogenic activity.

Allograft bone is not commonly used in the management of orthopaedic trauma. It is a useful alternative in patients who require bone grafting of a nonunion but have inadequate autograft bone. This may apply in elderly patients with osteoporosis in whom the supply of autografts of good quality is limited. Bulk allografts can be utilised for the treatment of segmental bone defects.¹⁰ Although their use is well documented for reconstruction after resection of bone tumours, they are not commonly used in this way in reconstruction after trauma in which techniques of bone lengthening and transport are more usually employed.

Collagen mineral composite graft. The main constituent of the organic matrix of bone is type-I collagen. This material is conducive to crystal formation in the associated inorganic matrix. Collagen alone is not effective as an osteoinductive material, but in combination with materials such as hydroxyapatite and tricalcium phosphate, it is osteoconductive. Addition of constituents of bone marrow

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©2001 British Editorial Society of Bone and Joint Surgery
0301-620X/01/111952 \$2.00
J Bone Joint Surg [Br] 2001;82-B:3-8.

gives the material osteogenic and osteoinductive properties.

Bovine collagen may be mixed with hydroxyapatite and is marketed commercially as a bone-graft substitute which can be combined with bone marrow aspirated from the iliac crest of the site of the fracture. The use of this material was compared with autogenous bone graft for the management of acute fractures of long bones with defects which had been stabilised by internal or external fixation.¹¹ In a randomised study of 249 fractures there were no differences in the rates of union or in measures of functional outcome. This composite material is osteogenic, osteoinductive and osteoconductive. It lacks structural strength and requires harvest of the patient's bone marrow. The osteogenic and osteoinductive properties are therefore not standardised. Although no transmission of disease has been recorded the use of bovine collagen is likely to be a source of concern.

Demineralised bone matrix and bone morphogenetic protein (BMP). In 1965 Urist¹² reported that demineralised bone matrix (DBM) induced the formation of heterotopic bone. He subsequently isolated a protein from the bone matrix which was termed bone morphogenetic protein. DBM was digested by bacterial collagenase and the digest dissolved in a mixture of salt and ethylene glycol.¹³ The BMP thus isolated was found to induce formation of bone in a rat model. He was able to show that implantation of DBM in rat muscle resulted in the formation of bone locally in the soft tissues.

It has since been shown that the active components of DBM are a series of glycoproteins, which belong to a group commonly referred to as the transforming growth factor (TGF- β) superfamily. The members of this family are responsible for morphogenetic events involved in the development of tissues and organs. These proteins are found widely in many different species in a closely similar molecular form and are not species-specific.¹⁴ Of particular interest in this group of compounds are the BMPs of which BMP-2 to BMP-6 and BMP-7 to BMP-9 have osteoinductive properties. The latter are sometimes referred to as osteogenic proteins (OP) 1 to 3. Classification as a BMP implies that the material is able to induce the formation of bone by endochondral ossification. The BMPs originally studied were extracted from cortical bone, but the extraction procedures were complex and only small quantities could be obtained. The use of recombinant DNA technology has allowed the production of much larger quantities of some BMPs for use in clinical trials and in basic research. Bone induction produced by BMPs occurs in a specific sequence. The proteins induce chemotaxis of progenitor cells, differentiation of chondrocytes, calcification of the cartilaginous matrix, angiogenesis and vascular invasion, differentiation of bone, mineralisation and remodelling. It seems probable that different BMPs influence different parts of this cycle and, experimentally, a combination of BMP-2 with BMP-7 or BMP-6 has been shown to increase the formation of bone five- to tenfold.¹⁵ A joint BMP-2/

BMP-4 receptor has also been discovered, suggesting that some BMPs may work in combination in vivo,¹⁶ but it is not known which molecules are required absolutely for the osteoinductive process.

DBM is commercially available in a variety of products and has been used mainly in North America. The main clinical indication is for the management of nonunion of fractures. The preparations available are of limited structural strength since they are prepared as putty or paste-like materials. They are not suitable for situations in which bony support may be required, such as in certain metaphyseal fractures. A disadvantage of these materials is the possibility of variable osteoinductive activity between batches. Since the material is of allograft origin there is the theoretical possibility of transmission of disease.

More recently, the active components of DBM have been the subject of intense research. To date, the main delay in developing clinical products has been the need to find a suitable vehicle to deliver the appropriate BMP to the site at which its action is required. Experimentally, BMP-2 and OP-1 (BMP-7) have been shown to stimulate the formation of new bone in diaphyseal defects in the rat, rabbit, dog, sheep and non-human primates.¹⁷⁻²³ Cook et al¹⁹ examined the effect of OP-1 on the healing of segmental defects in non-human primates. The recombinant human OP was expressed in cells from the ovaries of Chinese hamsters. This was then implanted into a carrier consisting mainly of type-I bovine collagen which was freeze-dried. Monkeys were used and defects were created in the ulna and the tibia. These were filled with either OP-1, the carrier alone or autogenous bone graft. Formation of new bone and solid bony union were observed in five of six ulnar defects and four of five in the tibia which had been treated with OP-1. This was superior to that induced by autogenous bone graft and the carrier alone. In other studies the amount of formation of new bone has been shown to be related to the concentration of OP-1,^{17,18} but as yet the optimal dose has not been established.

Other experimental studies have suggested the possibility of the acceleration of fracture repair by BMPs. A single injection of BMP-2 accelerated repair in a rat model when assessed biomechanically.²⁴ Similar findings have been reported in other species²⁵⁻²⁷ and in a rabbit model of distraction osteogenesis in which BMP-2 accelerated the rate of consolidation of bone.²⁸ In clinical studies, OP-1 combined with type-I collagen matrix has been used in the treatment of nonunion of the tibia.²⁹ This was compared with a control group treated with autogenous bone graft. Union occurred in 75% of the OP-1 group compared with 83% of those with bone graft. However, an untreated control group was not available for comparison.

Johnson and Urist³⁰ recently described the treatment of nonunion of the femur with cortical bone allograft used as a delivery system for human BMP. Each allograft had 100 mg of hBMP lyophilised into the implant. In 26 patients with shortening, the cortical bone carrier was used

as a structural interposition in a one-stage lengthening at the time of implantation. In another four it was used as an onlay graft. Interpretation of the results was difficult because autogenous bone graft was used in patients with a defect greater than 2 cm. In 24, healing occurred uneventfully at a mean time of six months.

It is likely that over the next few years many more BMPs will be marketed commercially. Their main role will probably be in the management of bone defects and nonunion. A further potential application may arise from the recent discovery of links between the BMPs and bone remodeling, raising the possibility of new therapeutic approaches to osteoporosis. However, more work needs to be done to define the BMPs or combinations of BMPs and the amount of dosage which is the most appropriate for the management of these problems.

Osteoconductive materials

Osteoconductive materials have been available for longer than osteoinductive or osteogenic substitutes. These inert materials resemble the mineral phase of bone and are biocompatible. They provide a structure or scaffold which can have a close interface with adjacent bone. The cellular elements can grow into the material and gradually regenerate normal bone. They are generally used as a material to fill bone defects which require mechanical support. However, some have a role in extending autogenous bone graft, and more recently have been evaluated as carrier materials for osteoinductive proteins.

Coralline hydroxyapatite. This material is derived from the calcium carbonate of sea coral. The pore structure of coralline calcium phosphate produced by certain species is similar to human cancellous bone, making it a suitable material for an osteoconductive substitute for bone graft. The pore size required for bone ingrowth varies from 100 to 500 μm . Coralline bone substitutes may be natural or manufactured. In the natural form the calcium carbonate skeleton is harvested directly from the natural habitat, cleaned and sterilised. The manufactured form is coralline hydroxyapatite, which is converted from natural coralline calcium carbonate by substitution of the carbonate components with phosphates.

The material is commercially available and is marketed with mean pore sizes of 200 or 500 μm . It has a high compressive strength but is brittle with low tensile strength. It has been used in the management of fractures of the tibial plateau as a filler material and the results have been comparable to those obtained with autogenous bone graft.³¹ The main disadvantages have been the variable strength and rates of resorption.

More recently, coralline hydroxyapatite has been used as a carrier for some growth factors. In a canine model, it has been used as a carrier for BMP with success and in a rabbit model as a carrier for transforming growth factors and fibroblast growth factors.^{32,33}

Calcium sulphate. This material is most familiar to orthopaedic surgeons as plaster-of-Paris and is perhaps the oldest osteoconductive material available. In a review of the history of the material, Tay, Patel and Bradford³⁴ describe reports of it being used to fill bony defects in the last century. Its main drawback is the chemical reaction which occurs during setting which results in a very variable crystalline structure, with consequent inconsistency in the material properties of the final product. It also resorbs very rapidly at a rate which may exceed the capacity of surrounding bone to regenerate. At present, it has been superseded by more reliable osteoinductive materials. It may still have a future role as a carrier for bone morphogenetic proteins.

Ceramics. When naturally occurring mineral salts are subjected to very high temperatures in a process known as sintering, highly crystalline materials termed ceramics are produced. Some of these materials are biocompatible and are osteoconductive. Their structure is quite distinct from the poorly crystalline configuration of normal bone and for this reason they are only resorbed very slowly. The most popular materials have been tricalcium phosphate and the derived ceramic, hydroxyapatite. The latter is a biocompatible ceramic which is produced in a high-temperature reaction and is a highly crystalline form of calcium phosphate. It is very stable and resorbs very slowly. Coralline hydroxyapatite, which has already been discussed, was one of the first ceramics to be used as an osteoconductive material. The main drawbacks of ceramics are the slow resorption and the difficulty in developing a material with favourable handling characteristics which is easy to use clinically.

Ceramics have been used in spinal surgery to extend autogenous bone graft in the long fusion necessary for adolescent scoliosis. Le Huec et al³⁵ compared the use of tricalcium phosphate ceramic mixed with autogenous bone (24 patients) with fusions in which a mixture of allograft and autograft bone was employed (30 patients). No pseudarthrosis occurred in either group. Ransford et al³⁶ carried out a randomised trial in 341 patients, comparing the use of a synthetic porous ceramic with autogenous bone for spinal fusion in idiopathic scoliosis. The results were comparable in both groups, but complications occurred in relation to the donor site of the bone graft. The authors concluded that the ceramic was a safe and effective substitute for autograft. The use of ceramic hydroxyapatite in the management of fractures has been more limited. Itokazu et al³⁷ found that in 17 patients with fractures of the tibial plateau, the material was safe with no evidence of post-traumatic arthritis at a mean follow-up of two years and six months.

The poor bioresorbability and difficulties with the handling of ceramics have stimulated work to develop materials which resemble the mineral phase of bone more closely. This has led to the development of calcium phosphate cements.

Calcium phosphate cements. These materials are growing in popularity and are a promising osteoconductive sub-

Fig. 1a

Fig. 1b

Fig. 1c

Radiographs showing a) a split-depression fracture of the lateral tibial plateau, b) satisfactory reduction achieved with minimal internal fixation and calcium phosphate cement and c) reduction maintained but persistence of cement two years after implantation.

stitute for bone graft. Their structure is closer to dahllite, the carbonated hydroxyapatite which forms the bulk of the mineral phase of bone. They are prepared in a fashion analogous to acrylic cement. A combination of mono-calcium phosphate, tricalcium phosphate and calcium carbonate in powder form is mixed in a solution of sodium phosphate. This forms a paste which sets to a hard material in 10 to 15 minutes and after 24 to 48 hours has a compressive strength similar to normal cancellous bone. These cements are produced without polymerisation and the reaction is therefore almost non-exothermic. The materials are weak in tension with strengths of 1 to 10 MPa, but are strong in compression at 10 to 100 MPa, depending on the formulation. They will not resist shear forces and are therefore not suitable for use in diaphyseal fractures. They are a poorly crystalline structure similar to the mineral phase of normal bone.

Animal studies have shown the material to be biocompatible. The surrounding bone gradually utilises the material to restore the normal bony architecture.^{38,39} In man, however, complete resorption has been shown to occur very slowly, if at all. In a study of the use of a calcium phosphate cement in fractures of the distal radius and tibial plateau, the material was still present two years after implantation.⁴⁰ Resorption therefore cannot be predicted with confidence and the material may be regarded as a permanent implant.

Published clinical studies have been promising and have mainly dealt with the use of Norian SRS (Norian Corporation, Cupertino, California). This material has a compressive strength of 50 MPa when fully set, which is greater than that of cancellous bone. Most published articles describe its use in the management of fractures of the distal radius. Kopylov et al⁴¹ compared it with external fixation in such injuries. The early functional outcome in terms of grip

strength was superior in the group with calcium phosphate cement but there was no difference at a later follow-up. Loss of reduction was noted in both groups. In a prospective, randomised trial,⁴² 110 patients were treated with either calcium phosphate cement (Norian SRS) and a cast for two weeks or by standard closed reduction followed by a cast for six weeks. The functional outcome was better in the group with calcium phosphate cement at one year, with satisfactory results in 82% compared with 56% in the group with a cast, and there was a reduced rate of malunion of 18% as opposed to 42% in those with a cast. These results suggest that there may be a useful role for calcium phosphate cements in the management of these fractures. Their main function, however, may be as an adjunct to existing methods to limit the amount or duration of other fixation.

Calcium phosphate cement has also been utilised in the treatment of fractures of the calcaneum. Schildhauer et al⁴³ described the use of the cement in 36 such fractures treated by internal fixation. They concluded that early weight-bearing was possible with the cement. Biopsies were performed in 12 patients at the time of removal of metal or debridement of the wounds. In cases without infection there was complete bone apposition and evidence of resorption by surrounding bone. The presence of infection compromised the bone apposition.

It has been suggested that this material could improve the compressive strength of the vertebral bodies in osteoporosis. Injection of calcium phosphate cement has been shown to be feasible and it does improve their compressive strength,⁴⁴ but this application is unlikely to translate into an easily applicable clinical technique. The material has been shown to enhance the strength of fixation by pedicle screws in a burst-fracture model,⁴⁵ and it was suggested that its use might obviate the need for anterior fixation in these fractures.

The use of calcium phosphate cement in fractures of the tibial plateau may be a more practical application. Keating and Hajducka⁴⁶ have used it in the treatment of depression and split-depression fractures of the lateral tibial plateau (Fig. 1) in conjunction with minimal internal fixation in 41 patients. Anatomical reduction was achieved in 78% and maintained in 66% at one year. Slight loss of reduction occurred in five. Significant loss of reduction occurred in one patient associated with deep infection. The functional outcome was reported to be satisfactory in most cases. The authors concluded that the material was safe and probably more effective than autogenous bone grafting in these fractures.

Conclusions

Bone graft substitutes of two main types are now available. Osteoinductive materials incorporate a BMP in a carrier material which, after implantation, induces local tissue to form bone. Osteoconductive materials are an inert scaffold which allows bony ingrowth from local osseous tissue. Some of these products have compressive strengths similar to that of cancellous bone. Many are still being evaluated experimentally. There is increasing interest in combining an osteoinductive protein in an osteoconductive carrier medium with more desirable structural properties. It is probable that a second generation of products with these characteristics will appear in the foreseeable future. At present, osteoconductive materials have been shown to be effective in the treatment of defects in metaphyseal bone in association with some fractures, notably in the distal radius, the tibial plateau and the calcaneum. Osteogenic proteins have met some success in the treatment of bone defects and nonunion, but more work is needed to define the most effective protein and the optimum local dosage required.

Autologous bone grafting will, for the moment, continue to play an important role in the treatment of nonunion. In the future, however, it seems likely that the requirement for this treatment will diminish and with the development of more effective alternatives it may eventually become obsolete.

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