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Mini Review Open Access

State of the art for Bone substitutes

Manuel Bondi*, Laura Piotto, Andrea Pizzoli

Department of Orthopaedics and Traumatology, ASST - Mantova, Carlo Poma Hospital, Mantova, Italy

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***Correspondence:**
*Dr. Manuel Bondi, Department of Orthopaedics and Traumatology, ASST - Mantova, Carlo Poma Hospital, Mantova, Italy; Email: bondimanuel@gmail.com

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Abstract

Background: Bone substitutes are increasing in orthopaedic surgery. The ideal bone substitute should be biocompatible and not evoke any adverse inflammatory response.

Material and Methods: In this mini review we have considered the bone substitutes that are most used in orthopedic surgery, observing their advantages and disadvantages, trying to define the characteristics of the ideal bone substitute.

Results - State of the art: Literature related to orthopaedic surgery reports about the use of autologous bone, allograft, Xenograft based HA ceramics, Synthetic bone substitutes, Growth factor-based substitutes and Polymethyl methacrylate.

Conclusion: The integration of a defect filler into a new bone and its influence on bone healing depend on the osteoconductive, osteoinductive or osteogenic properties of the material. Ideally, bone void filler materials should combine all of these properties.

Introduction

Bone defects are a major and costly problem for health systems. Autologous bone grafts are associated with multiple complications, although they are still considered the gold standard[1].

In addition to autografts, success has been reported with the use of allografts. Like the autografts, these allografts are also limited in supply and there exists a risk of disease transmission and immune rejection. Despite the benefits of both autografts and allografts, the relative concerns over their use have led to the development of numerous synthetic bone substitutes.

Bone grafting is one of the most common transplants in the world and bone substitutes are widely used in orthopedics (prosthetic revisions), traumatology, neurosurgery and oncological surgery. Over two million bone grafting procedures are performed every year[2]. This is thanks to their lower cost, their ease of handling which reduces surgical times, with consequent improved safety[2-3]. Bone substitutes can be divided into bone grafts (autograft, allograft, xenograft), growth factors (platelet-rich plasma - PRP, bone morphogenetic protein - BMP), synthetic or ceramics (hydroxyapatite- HA, tricalcium phosphate- TCP, calcium sulphate) and demineralized bone matrix (DBM)[1,4]. Each of these has its advantages and disadvantages, but the fundamental characteristics of a good bone substitute are biocompatibility and the absence of adverse reactions[5].

One of the most promising groups of synthetic bone substitutes are calcium phosphate ceramics (CaP). The most commonly used CaP are HA and TCP or an intrinsic combination of the two[6-11].

The rationale for the development of CaP has been their similarity in composition to bone mineral and their similarities in some properties of bone, such as biodegradability, bioactivity and osteoconductivity. Another important property of bone, interconnecting porosity can be introduced during the manufacturing process of CaP. Besides these desirable properties, CaP are known to have relatively low mechanical properties and are therefore mostly not suitable for application in load-bearing areas, as they do not provide sufficient structural support[12,13].

Polymethylmethacrylate (PMMA) is well known as bone cement due to its wide utilization in orthopaedic surgery in procedures such as fixation of components in arthroplasties, treatment of osteoporotic vertebral fractures (vertebroplasty, kyphoplasty), filling of cranial defects (cranioplasty). PMMA is an acrylic polymer and is formed by the mixture of a liquid MMA monomer and a powder MMA polymer. However, the interface between the PMMA-based cement and adjacent bone tissue is typically weak as PMMA bone cement is inherently bioinert and not ideal for bone ingrowth[14].

Recently, a novel synthetic hybrid device Cal-Cemex (Tecres S.p.A., Sommacampagna, VR, Italy) which combines the osteoconductive properties of β-TCP and the mechanical strength and the chemical-physical features of PMMA has become available. We have used it in the treatment of tibial plateu fractures with good results[15].

44 patients were followed-up for an average of 43 months in three centers. Full weight-bearing was allowed on average after 35 days (30 - 60). Neither major nor minor complications were reported. At the 1-year FU, no patients exhibited screw mobilization or fracture reduction loss. CT scans taken at this time point revealed good surface osteointegration without radiolucent lines or osteolysis, providing evidence of interdigitation and bone ingrowth.

Bone Void Fillers

Owing to its osteoinductive and osteoconductive properties and the presence of osteogenic cells, freshly harvested autologous bone graft is the gold standard for skeletal reconstruction where there is inadequate native bone[16]. Today's bone substitutes attempt to achieve a similar profile between original bone and regenerated bone. Currently over 100 products are clinically available[17].

A fundamental requirement for tissue-engineered bone grafts is the ability to integrate with the host bone, while providing the capacity for load bearing and remodelling[18].

In Table 1, the main features of synthetic ceramics (calcium sulphate, calcium phosphate and TCP) in

Table 1: Bone substitutes comparison (main properties)

Material	OC	OI	OG	Structural	Disadvantages
Autograft					
Cancellous	+++	+++	+++	+	Donor site morbidity, increased OR time, increased blood loss
Cortical	+	+	+	+++	As above
Vascularized bone	++	+	++	+++	As above
BMA	+/-	++	+++	-	As above
PRP	-	+++	-	-	Controversial unproven efficacy
Allograft					
Cancellous	+	+/-	-	+	Potential infection transmission, no osteogenic potential, potential host rejection
Cortical	+	+/-	-	+++	As above
DBM	+	++	-	-	No structural properties, potential host rejection
Synthetic ceramics					
CaS	+	-	-	++	Rapid resorption (faster than bone growth); OC properties only
HA	+	-	-	+++	OC properties only
CaP	+	-	-	++	OC properties only
TCP	+	-	-	++	OC properties only
Others					
BMP	+/-	+	+	-	Expensive, limited indications, increasing evidence of neurovascular complications when used in the spine
PMMA	-	-	-	+++	Structural properties only
	OC = osteoconductive OI = osteoinductive OG = osteogenic	BMA = bone marrow aspirate PRP = platelet-rich plasma DBM = demineralized bone matrix BMP = bone morphogenetic protein			
	Adapted from Roberts et al. 2012[19]				

comparison with autografts (cancellous, cortical, vascularized bone, bone marrow aspirate, PRP), allografts (cancellous, cortical, DBM), BMP and PMMA are given. According to the type of applications and needs, the best solution differs.

The specific features of Cal-Cemex which are relevant in a comparison with β-TCP or CaP based products are: mechanical strength and injectability. The presence of PMMA makes Cal-Cemex a benchmark in terms of mechanical strength, which is immediate after application, while injectability is shared by other products.

State of the art

Treatment of bone defects

Bone has a unique ability to regenerate after injury, provided that the defect is stable.

Instable defects, e.g. comminuted fractures, require an appropriate surgical fixation which normally leads to bone healing[20]. The decision to use additionally bone grafts or bone substitute materials depends on the size of the defect and additional factors. If the fracture stumps have excessive diastasis compromising self-repair, or when the conditions for bone repair are not ideal, for example in the presence of poor vascularity, malnutrition or substantial soft tissue loss, bone regeneration can be significantly impaired. In such cases, bone grafts, bone substitutes and/or bioactive factors are used to facilitate and/or enhance the chance of healing.

Bone substitute materials are in general used for bone defect filling. These defects may be due to traumatic, resectional or congenital causes. Examples are defects due to fractures, osteotomies, or cysts due to benign bone tumours. Bone defect filling is required if the gap exceeds a critical size so that very likely it would not heal by regenerating new bone without filling it with either autologous bone or a substitute material[22].

Materials

A wide range of different materials are clinically used for bone defect filling or bone augmentation in orthopaedic and dental surgery, which comprises autologous bone, allograft and many different kinds of calcium-based inorganic bone substitute materials. Among bone void fillers, we have also to include PMMA, the most used commonly used synthetic material used in clinics[22], used in vertebral compression fractures caused by osteoporosis or tumours or to fill bone defects after curettage of benign and malignant bone tumours or in cranioplasty to fill cranial defects.

The materials can be classified according to their origin and biological activity and/or their healing properties. The integration of a defect-filler into new bone and its influence on bone healing depends on the osteoconductive, osteoinductive, or osteogenic properties of the material[23-25]. Ideally, bone void filler materials combine all these properties[19].

Literature related to orthopaedic surgery reports about the use of autologous bone, allograft, demineralized bone matrix, and variety of synthetic materials, biphasic materials and combinations with fibrin. The application forms vary and comprise injectable cement as well as granules and preformed scaffolds[26-28].

The materials used for bone defect filling or bone augmentation can be allocated to the following main groups each showing particular properties:

- Autologous bone graft
- Allograft
- Xenograft based HA ceramics
- Synthetic bone substitutes.
- Growth factor-based substitutes
- PMMA

Characterization of Bone substitute materials

The various bone grafts and bone substitute materials show different properties, depending on their origin, physicochemical composition, and physical appearance. These factors also greatly influenced their bioactivity, which differentiates essentially grafts of biological origin from synthetically derived bone substitute materials, and the resorbability of a bone graft substitute material.

An ideal bone graft or bone substitute should exhibit osteoconductivity, osteoinductivity, osteogenesis, and osseointegration. As a prerequisite all bone substitute materials must be biocompatible within the tissue[19,29].

Osteoinduction is the process by which mesenchymal stem cells from a host are recruited to differentiate into chondroblasts and osteoblasts, which, in turn, form new bone through the process of endosteal and / or periosteal ossification. This process is moderated primarily by growth-factors, platelet derived growth factor (PDGF), interleukins, fibroblast growth factors (FGF), granulocyte-macrophage colony-stimulating factors (GM-CSF) and angiogenic factors such as vascular endothelial growth factor (VEGF). The presence of osteoinductive properties of a material is confirmed by heterotopic bone formation[15,30].

Osteoconduction is a property of a matrix that passively allows ingrowth of host capillaries, perivascular tissue and mesenchymal stem cells from the borders of the defect, supporting the attachment of bone-forming cells to the surface of the bone substitute material for subsequent bone formation. The graft material acts thereby as a permanent or resorbable scaffold material. Among the most commonly used synthetic osteoconductive scaffolds are CaS and $CaPO_4$ cements, HA[15,30].

Osteogenic graft material directly provides cells that are capable of in vivo bone formation[23]. Osteoprogenitor cells can proliferate and differentiate to osteoblasts which become osteocytes during calcification. Mesenchymal stem cells are multipotent and may be induced to differentiate into bone-forming cells by the local environment. Autologous bone graft and bone marrow aspirate are the only examples of osteogenic graft material.

Conclusion

There are many materials available, each with its own positive and negative characteristics, each with its own indications for use. Among the most recent products is Cal-Cemex; this is a high viscosity resin which can be injected with a delivery system (closed surgery) or applied manually (open surgery). Its primary objective is to fill the cavity generated following a trauma. An osteosynthesis means is used to stabilize the fracture. Thanks to the mechanical strength provided by the PMMA component of Cal-Cemex, the construct osteosynthesis means / bone void filler provides immediate fracture stabilization.

Immediate fracture stability potentially favours a quicker fracture healing. In addition, the mechanical strength of the construct of osteosynthesis or bone void filler allows for early full weight-bearing in tibial plateau fractures and early partial weight-bearing in select cases of calcaneal fractures, particularly in complex fractures[15].

Early weightbearing promotes a quicker recovery of the joint function, key for a faster return to normal life (work), better clinical outcomes, while possible mechanical complications are limited.

On the basis of the surgeon's choice and clinical condition of the patient, Cal-Cemex allows the possibility of[15]:

- percutaneous application
- early weight-bearing
- use fewer or less invasive osteosynthesis means
- application before or after osteosynthesis means positioning

Competing Interests

The authors declare that they have no competing interests.

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