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Review Article

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Bone Substitute Options for Spine Fusion in Patients With Spine Trauma-Part I: Fusion Biology, Autografts, Allografts, Demineralized Bone Matrix, and Ceramics

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Spinal trauma accounts for a large portion of injuries to the spine area, particularly as societies are entering an era of aging populations. Consequently, spine fractures accompanied by osteoporosis are becoming more prevalent. Achieving successful fusion surgery in patients with spine fractures associated with osteoporosis is even more challenging. Pseudarthrosis in the spine does not yield clinically favorable results; however, considerable effort has been made to achieve successful fusion, and the advancement of bone graft substitutes has been particularly crucial in this regard. Autograft bone is considered the best fusion material but is limited in use due to the quantity that can be harvested during surgery and associated complications. Accordingly, various bone graft substitutes are currently being used, although no specific guidelines are available and this mainly depends on the surgeon's choice. Therefore, the purpose of this review, across part I/II, is to summarize bone graft substitutes commonly used in spine surgery for spine fusion in patients with spine trauma and to update the latest knowledge on the role of recombinant human bone morphogenetic protein-2.

Keywords: Spine fusion; Allograft; Demineralized bone matrix; Bone graft substitutes; rh-BMP

INTRODUCTION

Fusion is one of the most common techniques used to treat various pathological conditions of the spine, from degenerative diseases to tumors.[4,24,45] Successful fusion is absolutely necessary, especially in patients with spine trauma who have instability in the spine. Successful fusion forms a solid bone union between the vertebras, eliminating motion and stabilizing the spine.[9,40,46] Many attempts have been made to preserve and overcome the loss of spine motion, which is a major limitation of the fusion technique, but have not yet shown better results than the fusion technique.[31,35] Bone graft substitutes have been widely used in the spine field to achieve successful fusion.[21,23,27] Autologous bone has been used as the gold

standard for spinal fusion because this provides all the required biological characteristics, including osteogenic, osteoconductive, and osteoinductive properties. However, the exclusive use of autologous bone as bone graft material is limited because of complications related to harvesting of autograft and lack of supply.[13,17,41] Therefore, as an alternative, many bone graft substitutes have been researched, developed, and used in the spine market and exhibit improved osteogenic properties and produce successful fusion results.[6,22,23,27,28] However, firm guidelines are still lacking for bone graft substitutes that must be used for successful bone fusion, and the selection is made based on the experience and preferences of surgeons. In this review, our aim is to provide an overview of commonly used bone graft substitutes in spine fusion, with a particular focus on an updated review of recombinant human bone morphogenetic protein (rh-BMP), which has grown in prominence as a bone material in recent years. Furthermore, this review is intended to serve as a basis for selecting the appropriate fusion material during fusion surgery to achieve successful fusion.

BIOLOGY OF SPINE FUSION

The process of spine fusion, which includes interbody fusion and intertransverse process fusion, is similar to that of fracture healing and involves a combination of intramembranous and endochondral ossification. Human studies are unavailable because of clinical and ethical issues, and information related to fusion biology is indirectly obtained through animal studies.[5,38] Boden et al.[3,4] explained the process of spine fusion using a rabbit model. The authors divided the process of autograft bone fusion into five stages. The first stage is the inflammatory process (weeks 1–2). During endplate preparation for interbody fusion, the cartilage endplate is removed, and the bony endplate is decorticated, causing the formation of a hematoma around the endplate and bone graft. Inflammatory cells invade, inducing the generation of cytokines. Fibroblast-like cells in the formed inflammatory tissue transform into a fibrovascular stroma. In the second stage, the vascularization process (week 3) occurs. Vascular buds appear in the fibrovascular stroma. Subsequently, primary membranous bone formation occurs at the decortication site, and collagen and cartilage scaffolds start forming between the decorticated sites for endochondral ossification. The region of membranous ossification is referred to as the outer zone of fusion, and the endochondral ossification region is called the central zone. Following this, osteoinduction and osteoconduction processes occur. This is the reparative phase and occurs in weeks 4–5. The osteoinduction process is characterized by increased vascularization, the reabsorption of necrotic tissue, and the differentiation of pluripotential mesenchymal cells into chondroblasts and osteoblasts. New bone extends into the central zone of the fusion mass, and the cortical portion of the graft continues to be reabsorbed. The osteoconduction process involves new bone ingrowth into the host bone, and a fusion bridge is observed in the central zone, uniting the upper and lower halves of the fusion. The cartilaginous tissue undergoes calcification but remains immature and in a woven bone form, signifying the early stages of fusion. After 6 weeks, the remodeling process begins, where immature woven bone transforms into mature lamellar bone, incorporating both cortical and cancellous components. While this process predominantly occurs around 12 weeks after surgery, the overall remodeling process is typically completed within 1 year.[22,23] Bone maturation is more pronounced and faster in the outer zone but also takes place in the central zone, albeit at a slower pace. This temporal delay in maturation in the central zone is known as the central "lag effect," which can help explain why nonunion is more likely to develop in the central zone of the fusion mass. The above stages are summarized in **FIGURE 1**.

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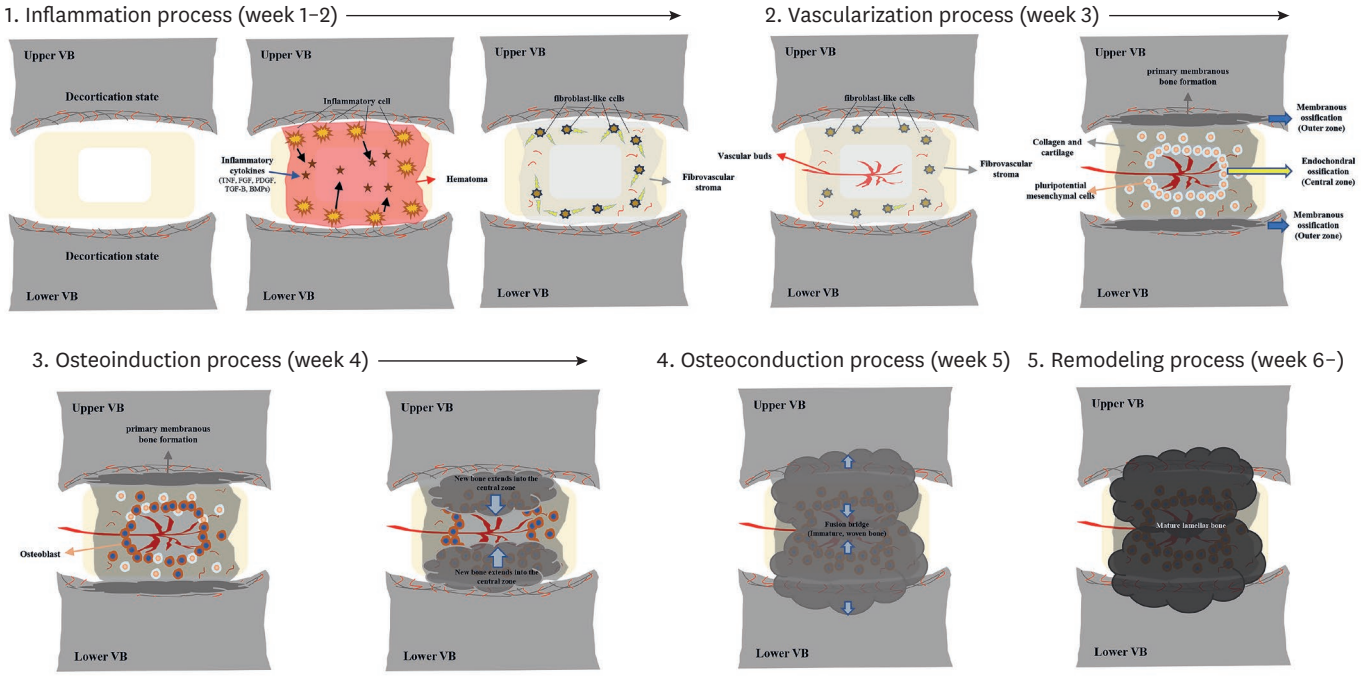

FIGURE 1. Process of spine fusion.
VB: no description, TNF: tumor necrosis factor, FGF: fibroblast growth factor, PDGF: platelet-derived growth factor, TGF-β: transforming growth factor beta, BMP: bone morphogenetic protein.

BONE GRAFT SUBSTITUTES

Bone graft substitutes assist in successful fusion through the following mechanisms: osteogenesis, osteoinduction, and osteoconduction. Osteogenesis is process of providing active cells (such as osteoblasts and osteoprogenitor cells) that can differentiate into cells capable of creating bone, depending on osteoprogenitor stem cells. Osteogenic grafts that include autografts can provide such cells. Osteoinduction involves providing factors that stimulate the growth of new bone and can includes BMP, demineralized bone matrix (DBM), autografts, or allografts. Osteoconduction entails providing a scaffold or structure that allows new bone to grow and includes materials such as autografts, allografts, ceramics, and DBM (**TABLE 1**).[12,15,19,32]

TABLE 1. Bone graft substitutes properties

Graft material	Osteogenesis	Osteoinduction	Osteoconduction
Autograft	2	2	2
Allograft	0	2	2
BMA	3	2	0
BMP	0	3	0
DBM	0	2	1
Ceramic			
β-TCP	0	0	2
Hydroxyapatite	0	0	1
Injectable CP cement	0	0	1

Data from reference [12,15,19,32]; sore range 0 (none) to 3 (excellent).
BMA: bone marrow aspirate, BMP: bone morphogenetic protein, DBM: demineralized bone matrix, β-TCP: β-tricalcium phosphate, CP: calcium phosphate.

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Autografts

An autograft, which is local bone or harvested bone, is commonly used because it has all three properties of osteogenesis, osteoinduction, and osteoconduction, and thus includes osteoblasts, bone matrix, BMPs, and bone graft factors.[6,22] Additionally, autografts are cost-effective and do not carry any risk of disease transmission when compared with other bone graft substitutes. Many studies have reported relatively high fusion rates ranging from 40 to 100% with autografts.[14,29,36,39] However, these fusion rates can vary significantly depending on the surgeon's technique, use of instrument, amount of graft volume, and endplate preparation. Unlike BMP, autograft transplanted into soft tissue does not form bone because the level of transforming growth factor-beta is relatively low in the autograft. Therefore, several studies have questioned the osteoinduction ability of autografts.[22] If a large amount of autograft cannot be obtained, harvesting is performed. The representative harvest location is the iliac crest. However, the harvesting procedure is associated with well-documented complications and morbidity, including infection, lateral femoral cutaneous nerve injury, fractures, hematomas, and donor site pain.[1,45] Donor site pain is a particularly common issue, with several studies reporting rates as high as 60%, although the general consensus is that this is typically around 25%.[13,14,26,42]

Allografts

An allograft is a bone extender commonly used in spine fusion surgery.[22,45] Allografts are produced by two different manufacturing processes that yield fresh-frozen or freeze-dried material. Fresh-frozen allografts contain BMPs and consequently have a better fusion rate than freeze-dried grafts, although the risk of disease transmission is greater. Freeze-dried allografts lose immune cells during the processing process, and the fusion rate subsequently decreases because of destruction of BMP, an osteogenic factor, and damage to mechanical integrity; however, the risk of disease transmission is minimized.[15,37] Currently, freeze-dried allografts are predominantly used. In a recent meta-analysis study, the fusion rate of allograft in spine surgery was reported to be approximately 87.8%.[43] However, allograft bone quality varies depending on donor age, sex, and harvesting site. In particular, even within a single donor, bone strength varies by up to 20% depending on the harvesting site.[34] Allografts can also cause low-level inflammatory reactions, which are initially strong inflammatory reactions that delay the vascularization and osteoinduction processes, and this immune response may induce nonunion.[15,18]

DBM

DBM is a bone substitute derived from human cadaver bone through acid extraction. DBM comprises a matrix that includes noncollagenous proteins, collagen fibers, and BMP, as well as a carrier material. The effectiveness of DBM can vary based on the carrier material and matrix composition.[22] Additionally, because of the proprietary nature of the demineralization process, the technology behind DBM has not been publicly disclosed, and the process has no regulatory governance. Consequently, different DBM products can exhibit significant differences in the actual BMP concentration within them[22]; furthermore, the BMP concentration in DBM products can be up to 10^{6}% lower than that in commercial BMP products.[25] When comparing fusion rates, for instance, in lumbar interbody fusion, between DBM with hydroxyapatite and autograft, these demonstrated comparable fusion rates at 76.5% and 77.8%, respectively, 1 year after surgery.[20] In single level instrumented posterolateral lumbar fusion, the 2-year fusion rates of Grafton (local bone) DBM and iliac crest bone graft (ICBG) confirmed by computed tomography were statistically similar at 86% and 92%, respectively.[29] DBM is rarely used alone because it does not produce a strong

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enough response to provide reliable bone fusion when compared with cell-containing graft material. Therefore, DBM is used as a graft extender.[44,45]

Ceramics

Marine coral has a similar microporous structure to bone and was proposed as a bone graft substitute; the word ceramic itself originated from the word coral.[8,23] Ceramic ingredients include calcium sulfate, calcium phosphate, hydroxyapatite, and mixtures of these, which are similar to those of coral.[16,27,45] Ceramics have several advantages over existing bone graft substitutes as these are easily obtained in large quantities with low production costs and no risk of disease transmission. Additionally, the porosity or pore size of the graft can be designed as desired.[22] However, the disadvantages of ceramic components include limitations in shear and compression strength.[23] Ceramics are mainly known to play a role in osteoconduction,[45] but recent studies have reported a role in osteoinduction. Although the mechanism is unclear, ceramics have been suggested to help mesenchymal stem cells differentiate into osteoblasts by promoting macrophage chemokine release and suppressing proinflammatory cytokines release.[7,16] Ceramics can be broadly divided into noninjectable and injectable ceramics. Noninjectable ceramics include calcium sulfate, a-tricalcium phosphate, b-tricalcium phosphate, and hydroxyapatite, and injectable ceramics include calcium phosphate cement. Noninjectable ceramics can be further divided according to the resorption rate, which is determined by the porosity of the ceramic.[10] The ceramic creates a microenvironment rich in calcium phosphate, stimulating the resorption of osteoclasts and subsequently stimulating osteoblasts to grow new bone within the absorbed implant. Less porous ceramic is absorbed before complete bone ingrowth is achieved.[18] b-tricalcium phosphate and hydroxyapatite have good porosity and are generally absorbed slowly, but calcium sulfate and a-tricalcium phosphate have poor porosity and are absorbed quickly (1–3 months). Calcium sulfate or a-tricalcium phosphate are considered as ceramic bone substitutes but are not recommended because of their low osteoconduction ability that is caused by their rapid resorption rate.[6] Calcium phosphate cement is a mix of inorganic calcium and phosphate that hardens at low temperatures through a crystallization reaction and slowly transforms into bone over 3–4 years. A study using calcium phosphate cement as a substitute for polymethyl methacrylate during vertebroplasty showed increased washout tendency and low flexural and shear resistance due to resorption and fragmentation of the cement, so the routine use of this during vertebroplasty was not recommended.[2] The overall fusion rate of ceramic products in lumbar fusion is approximately 86.4%, and mixing ceramic products with local autograft shows a higher fusion rate.[33] In a randomized controlled trial of 62 patients who underwent one-level instrumented posterolateral lumbar spine fusion with ICBG or b-tricalcium phosphate and local autograft, both groups achieved 100% fusion on x-ray 3 years after surgery.[11] Additionally, in a prospective, randomized trial of 62 patients who received fusion with ICBG or hydroxyapatite for lumbar stenosis, 100% fusion was achieved in all groups 1 year after surgery.[30]

CONCLUSION

As the population ages, the number of patients with osteoporosis is increasing among both men and women, producing a rise in the incidence of spine fractures ranging from low to high energy trauma. Consequently, a growing number of patients also require fusion surgery. However, once the decision for fusion surgery is made, achieving successful fusion becomes the paramount objective. To address this, numerous bone graft substitutes have been

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introduced for surgical use. The advantages and disadvantages of each bone graft substitute must be considered to select an appropriate one tailored to the circumstances of both the patient and the medical team.

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