Dante G. Marchesi

Spinal fusions: bone and bone substitutes

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D. G. Marchesi
Department of Orthopaedic Surgery,
Jewish General Hospital, Room-E, 003,
3755 Côte Ste Catherine, Montreal,
H3T 1E2, Canada
e-mail: dante@orl.mcgill.ca

D. G. Marchesi
Division of Orthopaedic Surgery,
McGill University, Montreal, Canada

Abstract Vertebral arthrodesis is one of the most commonly performed, yet incompletely understood, procedures in spinal surgery. Despite major progress in internal fixation techniques, the high rate of non-unions indicates that physiologic, biologic and molecular events that are crucial to this process are not well known. This article will analyze the general biology of bone regeneration, and particularly discuss the

properties and use of various bone graft materials and graft substitutes.

Key words Bone regeneration · Spinal fusion · Bone substitutes · Growth factors

Introduction

The rate of low back surgery has been constantly increasing over the last two decades (by 55% between 1979 and 1990). Lumbar fusion rates have increased even more (by 100% over the same period), and around 200,000 spinal arthrodesis procedures are presently performed each year in North America [42]. Despite modern technologic advances and sophisticated internal fixations, failure to achieve a solid bony union (non-union) occurs in 5–35% of the patients with single-level fusions and more frequently when multiple levels are attempted [18, 23, 65, 67].

The outcome of spinal fusions depends on a complex process influenced primarily by the type of graft material used and on the many local and systemic factors that affect the arthrodesis healing response (Table 1). The biomechanical aspect of the specific type of fusion (i.e., posterolateral intertransverse process, anterior interbody, antero-posterior combined), the location of the arthrodesis itself along the spine, and the efficacy of spinal immobilization after surgery (internal or external) will require special attention. Considerable progress in the technologies of spinal instrumentation have nearly maximized the benefits of mechanical stabilization, but the limiting

Table 1 Factors affecting bone graft healing

Local factors
Biologic
Preparation of recipient site
Vascular supply of soft tissue
Bone graft material (quantity, type, sterilization technique, etc.)
Local bone disease (tumor, marrow infiltrative disease, etc.)
Radiation
Mechanical
Biomechanical stability
Biomechanical loading
Systemic factors
Nutrition
Hormones, growth factors
Drugs
Osteoporosis
Infections
Smoking
Others

step to arthrodesis remains the biologic ability to form osseous consolidation between adjacent vertebral segments.

Recent advances in minimally or less invasive surgical techniques and the potential for biologic regulation or manipulation of bone formation make it important to re-examine our understanding of the biology of bone graft materials and the spinal fusion process. This article will not review the multiplicity of local and systemic factors affecting spinal arthrodesis, but will analyze the general biology of bone regeneration, and particularly discuss the properties and use of various bone graft materials and graft substitutes.

Biology of spinal fusion

The formation of an osseous fusion mass that consolidates adjacent spinal segments is enabled by the bone graft material. The biologic processes affecting bone fusion are:

1. The ability to cause differentiation of an undetermined osteoprogenitor stem cell to an osteogenic cell type (osteinduction)
2. The ability to provide a physical structure or scaffold to support and direct bone formation (osteoconduction), and
3. The ability to provide cells that are, or potentially can be, capable of directly forming bone (osteogenic potential) [7, 47, 59].

The ideal bone graft material possesses the above three distinct properties (osteoconduction, osteoinduction and osteogenesis) with optimal immunological response in the host and without risk of disease transmission.

The osteogenic potential of a graft material directly derives from its cellular content. It must contain viable cells that can form bone (osteogenic precursor cells). These cells participate in the early stages of the healing process to attach the graft to the host bone, and their viability must be ensured during the grafting procedure. Fresh autologous bone and bone marrow are the best known.

Osteoconductivity is the physical property of a graft material that allows the ingrowth of neovasculature and infiltration of osteogenic precursor cells. Appropriate osteoconduction is provided by direct apposition between host bone and implant. Host bone must be viable, the host bone/implant interface must be stabilized (no macromotion) and the implant needs a structure (porosity) allowing new bone ingrowth. Optimal interconnection between pores (connective porosity) and a pore size superior to 100 μm have been demonstrated by biologic studies to be also essential in this process [43].

Osteoinduction is the process by which some factors or substances stimulate the undetermined osteoprogenitor stem cell (responding cells) to induce the osteoblastic pathway and to differentiate into an osteogenic cell type. Osteoinductive properties have been found in demineralized bone matrix (DBM) and different morphogenetic proteins (BMP, TGF- β , PDGF, EGF, etc) (Fig. 1).

Fig. 1 Biology of spinal fusion

Autogenous bone graft

Autogenous bone contains all of these three properties allowing bone fusion, and it is considered as the gold standard among graft materials, against which all others are compared. Corticocancellous bone, usually harvested from the iliac crest, has been the most common and most successful graft material in spinal fusion surgery. It is thought to contain both determined and inducible osteogenic precursor cells (osteogenic property), non collagenous bone matrix proteins including growth factors (osteoinductive property), and bone mineral and collagen (osteoconductive property) [54, 55]. Autogenous bone also has the advantage of being non-immunogenic and non-pathogenic.

Cancellous bone contains greater osteogenic potential because of the large number of surviving cells in the marrow, and is favorable to vascular ingrowth and exposure of inductive proteins because of the large trabecular surface area and interconnected spaces. Cortical bone offers greater mechanical strength as compared with cancellous bone, but it is less effective. There is less or no marrow, and consequently fewer osteogenic cells; its structure is less favorable for new bone formation and is more resistant to vascular ingrowth and remodeling [59].

The failure rate of autogenous bone graft arthrodesis has been reported to be higher than 30% in some series and, although progress in spinal instrumentation has decreased this rate of sequela, the incidence of non-union has remained unacceptably high [23, 67]. Moreover, the morbidity related to harvesting bone graft from the iliac crest for lumbar spinal fusion can sometimes be more problematic than the primary surgical procedure itself [4]. Major complications such as pelvic fractures, vascular injuries and deep infection have been reported in as many as 9% of patients, while minor complications including chronic donor site pain and superficial infection have been observed in 25% of the cases [20, 25, 46, 68, 77]. The most common minor complication is the alteration in sensation over the donor site area, manifested as chronic pain, hyperesthesia, dysesthesia or diminished sensitivity in the cutaneous nerve territory. The quantity of bone available from the iliac crest, the increased operative time, the blood loss and the possible need for transfusion are additional problems to be considered. For all these reasons, more and more attention has been directed in these recent years to the development and use of bone graft substitutes or extenders.

Allograft

Allograft has historically been the most common substitute for autogenous bone. It is highly osteoconductive, weakly osteoinductive, and not osteogenic, because cells do not survive transplantation [54]. For these reasons, there has been concern over whether allograft can reliably produce spinal fusion. Allografts may be available in a reasonable quantity and are quite versatile, in that the shape, contour, and mineral density of the graft can be defined by the specific portion of the skeleton that is used and the machining that is performed.

Major concern exists among clinicians as well as the public about the possibility of infectious disease transmission, despite meticulous screening and serologic testing of the donor [14, 15]. Allografts are processed and preserved in ways that affect the osteoinductive and osteoconductive capacity of the material as well as its immunogenicity [1, 10, 11, 35, 45, 57]. Preservation is obtained by either freezing or freeze-drying, both of which allow extended storage but reduce the immunogenicity of the graft, may alter its mechanical strength, and leave the worrisome risk of viral disease transmission [15, 57]. Further sterilization with high-dose gamma irradiation or ethylene oxide gas is used, but both methods may further reduce osteoinductivity. Ethylene oxide sterilization is believed by most clinicians to prevent viral infection. However, studies have shown that the gas fails to penetrate cortical bone [58]. Furthermore, several sterilization methods have been investigated, including ethylene oxide, irradiation, hydrochloric acid decalcification, dimethyl sulfoxide, and

freeze drying, for their ability to destroy the feline leukemia virus in the donor bone. All methods of sterilization failed to eliminate the virus. This is a significant finding, because the feline leukemia virus is a retrovirus similar to human immunodeficiency virus [75].

Animal models have been used to compare allograft with autograft in anterior and posterior spinal fusion [70]. Slower fusion rate, greater graft resorption and increased infection rate were observed. For these reasons, there has been limited clinical interest in the use of allograft alone as a substitute for autogenous bone.

Various clinical reports examining the performance of allograft for spinal fusion have been presented in the literature, but only few have been prospectively designed and well conducted. The most favorable data are reported for interbody fusion in the cervical spine. Similar results to autologous graft are presented for one-level arthrodesis, but the union rate drastically drops in multilevel procedures [12, 19, 32, 78, 81]. In the lumbar spine, cortical allograft is generally used for structural support (femoral rings) in combination with autogenous bone graft, showing only rare pseudarthrosis [5, 44]. During recent years, the use of machine-threaded cortical allograft bone dowels or allograft interbody cages obtained from midshaft or diaphyseal bone has gained considerable popularity for anterior lumbar spine arthrodesis. Outcome data using these particular allografts are currently being collected. Several published reports have also addressed the use of allograft alone or mixed with autograft for posterior spinal fusion. When used in instrumented thoracic spine the results are reported as favorable [2, 52]. In the lumbar spine it shows lower fusion rate and higher resorption when compared with autograft [41, 50].

Ceramics and bone substitutes

Because of the previously discussed problems associated with auto- and allograft material, there has been increasing interest in biodegradable osteoconductive ceramic bone graft substitutes, which would be available in unlimited quantity, without donor site complications or infectious risks. For synthetic implants to be useful *in vivo*, they must have certain properties: compatibility with surrounding tissues, chemical stability in body fluids, compatibility of mechanical and physical properties, ability to be produced in functional shapes, ability to withstand the sterilization process, reasonable cost of manufacturing and reliable quality control [6].

The most commonly used ceramics in bone surgery are calcium phosphates, which include hydroxyapatite (HA) and tricalciumphosphate (TCP). They have exclusively osteoconduction properties, and are characterized by a high degree of biocompatibility with host tissue [27, 38]. Ceramics present with a specific porosity, which may be artificially created and act as scaffold for further os-

teoblastic ingrowth. This unnatural pathway of ceramic matrix with poorly interconnected porosity inflicts on the ingrown bone, and retards the normal rate of bone healing and remodeling process required to obtain optimal mechanical strength.

The remodeling process depends on the biodegradability of the ceramic: nonresorbing materials may interfere with remodeling, be the locus of a mechanical stress riser, and impede the accretion of strength of the fusion mass [38]. The various calcium phosphate ceramics differ with regard to their bioresorbability characteristics. Hydroxyapatite is relatively inert and biodegrades poorly, which may hinder remodeling, prolong the strength deficiency of new bone, and leave permanent stress risers in the fusion mass. Conversely, ceramic TCP undergoes biodegradation within the first 4–8 weeks of implantation – possibly too early for optimal fusion mass healing [26]. Biphasic ceramics, where the ratio of HA to TCP can be varied to increase either the mechanical strength or the degree and speed of resorption, are now available [8, 21, 24, 29, 30, 53, 80].

Natural ceramics derived from sea coral are reported to have morphologically better interconnective porosity, and are structurally similar to cancellous bone. Composed of 97% calcium carbonate in the form of aragonite, coral undergoes a thermal reaction where calcium carbonates are transformed into HA. Coral is extremely biocompatible, and has yielded promising results when it has been used to replace or augment autogenous bone graft [13, 17, 31, 36, 37, 38] or as part of a composite with an osteoinductive bone protein [22]. Despite these properties, the poor bioresorbability of the HA remains a significant problem for these natural ceramics as well, resulting in poor bone remodeling. The alteration of the coral processing with a partial thermoreaction, where only 20% of the calcium carbonate is converted into HA, has been recently found to improve its bioresorbability [3, 66].

The efficacy of these different ceramics at obtaining spinal arthrodesis has been studied in animal models and in selective clinical studies. Anterior interbody fusion in the thoracic spine of dogs was analyzed by Emery et al., using autologous tricortical iliac crest graft, HA ceramics, calcium carbonate and a mixture of HA and TCP [24]. Autologous graft still proved to be the most effective material tested in this comparative study. Autologous bone was also significantly better than calcium carbonate ceramics when combined with internal fixation [28].

Posterolateral intertransverse lumbar fusion was analyzed mainly in sheep [29]. Some authors demonstrated better results with autologous bone when compared with different ceramics [3, 8], others found similar results in term of fusion rate when using coral porites (calcium carbonate), a combination of HA and TCP, or resorbable coralline HA [30, 66].

Clinical data on the use of ceramics alone or combined with autologous bone are limited. Some authors have ad-

vocated the use of ceramics as graft extenders for autologous bone in fusions with long instrumentations for deformities [34, 48, 56]. In a study of 12 adolescent patients, Passati et al. used a combination of HA and TCP with autologous bone, and found all patients to be clinically and radiologically fused. Histologic analysis done on specimens obtained from two of these patients indicated *de novo* bone ingrowth into the ceramic pores. However, these studies have been criticized for their less challenging healing environment, e.g., instrumented posterior thoracic spine in adolescents with scoliosis. A high fusion rate was reported by Thalgott et al. in patients who had undergone cervical spine fusion with interbody cages filled with coral-HA [69].

Although selective data from both animal and clinical studies seem favorable, the role of ceramics implants is still not well defined. Its possible use as a complementary agent in composite form with osteoinductive growth factors is presently under investigation, and is discussed in the next section.

Osteoinductive growth factors

During the last 40 years, mainly through the studies of Marshal Urist, demineralized bone matrix has been shown to induce ingrowth of connective tissue cells and differentiation of cartilage and bone [71, 73]. Advances in protein isolation technology yielded evidence of a series of osteoinductive glycoproteins, including BMP, identified by Urist, TGF- β , PDGF, EGF, etc. Extracts of bone containing these growth factors consistently produced new bone in ectopic sites in animal trials [16, 74].

Clinical tests using purified human BMP extracts were performed on femur and tibia non-unions. When treated with internal fixation and grafted with autograft combined with hBMP, almost all healed with the single procedure [39, 40]. Posterior spinal fusion using the same principles was also performed in five patients with posterior spinal pseudarthrosis, showing an 80% fusion rate [62]. However, human BMP remains a rare and very expensive product. It comprises only 0.1% by weight of all bone protein, and is most abundant in diaphyseal cortical bone. It exists in the extracellular matrix, and is not accessible until the bone matrix has been demineralized [72, 73].

More recently, using molecular cloning technology it has been possible to produce recombinant BMP as a singular molecular species in virtually unlimited quantities and without immunogenetic properties [76]. Thoracic spinal fusion in the dog was used to evaluate the efficacy of partially purified bovine BMP. The BMP/autograft condition had the highest fusion rate (71%) when compared with other conditions [49]. Posterolateral intertransverse lumbar fusion in dogs was also evaluated, showing faster achievement of fusion when using rhBMP-2 [60, 61]. The same procedure in rabbits showed a 100% fusion

rate with the use of rhBMP-2, compared with 42% with autograft [63, 64]. Anterior lumbar interbody fusion in sheep using cylindrical spacers containing rhBMP-2 also demonstrated a 100% fusion rate compared with 33% when using cages with autologous bone [61]. Another similar study done on the thoracic spine found a similar fusion rate (63%). Anterior cervical fusion in goats occurred in 100% of the cases with rhBMP-2 compared with 67% using the cages filled with autologous bone [79].

Because growth factors are signaling peptides for specific physiologic processes that may vary depending on the complexity of species, there is evidence to suggest that osteoinductive agents may demonstrate desirable efficacy in a lower species but not in a higher one, such as more complex animals or humans. For this reason, animal model experiments culminating with primate studies have been recently undertaken, demonstrating that osseous consolidation of adjacent vertebral segments is consistently produced in the presence of some of these factors [8, 33, 51]. The data have been substantial enough to warrant limited and selective investigations in humans [9].

Conclusion

Significant progress in the development of internal spinal fixation has nearly maximized the benefits of mechanical

stabilization. On the other hand, our ability to regulate the biologic processes of bone fusion is only at the beginning. For this reason, enormous clinical attention is being paid toward the biology of bone regeneration and repair. This is mainly directed through the availability of potent osteoinductive growth factors, which can independently initiate the entire cascade of osteogenesis. Different bone substitutes acting as osteoconductive carriers are also demonstrating interesting solutions to achieving arthrodesis. Experimental data from animal series, culminating with primate studies, have demonstrated encouraging results, enough to warrant selective human investigations. Other adjunctive modalities like pulsed electromagnetic fields or low-intensity pulsed ultrasound therapy to enhance skeletal healing have also shown potential efficacy.

It is apparent that biologic manipulation of spinal arthrodesis may ultimately require combined strategies. It is mandatory that each of these exciting and powerful tools continues to be prudently evaluated with sound scientific methods and well-designed, well-controlled and rational clinical studies. The valuable data obtained in this fashion should be primarily used to determine future clinical investigations.

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