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Review Article

Cellular bone matrices: viable stem cell-containing bone graft substitutes

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Abstract

BACKGROUND CONTEXT: Advances in the field of stem cell technology have stimulated the development and increased use of allogenic bone grafts containing live mesenchymal stem cells (MSCs), also known as cellular bone matrices (CBMs). It is estimated that CBMs comprise greater than 17% of all bone grafts and bone graft substitutes used.

PURPOSE: To critically evaluate CBMs, specifically their technical specifications, existing published data supporting their use, US Food and Drug Administration (FDA) regulation, cost, potential pitfalls, and other aspects pertaining to their use.

STUDY DESIGN: Areview of literature.

METHODS: A series of Ovid, Medline, and Pubmed-National Library of Medicine/National Institutes of Health (www.ncbi.nlm.nih.gov) searches were performed. Only articles in English journals or published with English language translations were included. Level of evidence of the selected articles was assessed. Specific technical information on each CBM was obtained by direct communication from the companies marketing the individual products.

RESULTS: Five different CBMs are currently available for use in spinal fusion surgery. There is a wide variation between the products with regard to the average donor age at harvest, total cellular concentration, percentage of MSCs, shelf life, and cell viability after defrosting. Three retrospective studies evaluating CBMs and fusion have shown fusion rates ranging from 90.2% to 92.3%, and multiple industry-sponsored trials are underway. No independent studies evaluating spinal fusion rates with the use of CBMs exist. All the commercially available CBMs claim to meet the FDA criteria under Section 361, 21 CFR Part 1271, and are not undergoing FDA premarket review. The CBMs claim to provide viable MSCs and are offered at a premium cost. Numerous challenges exist in regard to MSCs' survival, function, osteoblastic potential, and cytokine production once implanted into the intended host.

CONCLUSIONS: Cellular bone matrices may be a promising bone augmentation technology in spinal fusion surgery. Although CBMs appear to be safe for use as bone graft substitutes, their efficacy in spinal fusion surgery remains highly inconclusive. Large, nonindustry sponsored studies evaluating the efficacy of CBMs are required. Without results from such studies, surgeons must be made aware of the potential pitfalls of CBMs in spinal fusion surgery. With the currently available data, there is insufficient evidence to support the use of CBMs as bone graft substitutes in spinal fusion surgery.

Keywords: Cellular bone matrices; Mesenchymal stem cells; Bone graft substitutes; Spinal fusion surgery; Cellular allograft; Osteoprogenitor cells

FDA device/drug status: Not applicable.

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Introduction

Spinal fusion surgery has become an acceptable treatment modality for a range of spinal pathologies, with an estimated 300,000 spinal fusion surgeries performed yearly in the United States [1]. Success of spinal arthrodesis surgery relies on the formation of a solid fusion. Bone graft, in turn, plays a critical role in the formation of the fusion mass. Autograft, most commonly from iliac crest, has historically been the gold standard for bony augmentation in spinal arthrodesis surgery. Autograft contains osteogenic, osteoconductive, and osteoinductive elements essential for the formation of new bone; it is readily available, low-cost, and presents no concerns with regard to tissue compatibility and disease transmission. However, quality of autograft is highly variable and is influenced by age, metabolic abnormalities, and smoking [2]. In addition, numerous complications have been reported with iliac crest autograft harvest [3–6], leading to the development and increased use of bone graft substitutes, graft extenders, and osteobiologic materials. Advances in the field of stem cell technology have stimulated the development and increased use of allogenic bone grafts containing live mesenchymal stem cells (MSCs), also known as cellular bone matrices (CBMs). It is estimated that CBMs comprise greater than 17% of all bone grafts and bone graft substitutes used [2]. This review aims to critically evaluate these novel products, specifically their technical specifications, existing published data supporting their use, US Food and Drug Administration (FDA) regulation, cost, potential pitfalls, and other aspects pertaining to their use.

Methods

A series of Ovid, Medline, and Pubmed-National Library of Medicine/National Institutes of Health (www.ncbi.nlm.nih.gov) searches were performed with time frame of 1970 to 2013. Only articles in English journals or published with English translations were included. Search keywords included: ''cellular bone matrices,'' ''mesenchymal stem cells,'' ''spinal fusion,'' ''bone graft substitutes.'' Level of evidence (I–V) was assessed for each included article according to the published criteria [7]. The strength of recommendation and overall body of evidence with respect to the use of CBMs in spinal fusion surgery was determined on the basis of percepts outlined by the Grades of Recommendation Assessment, Development and Evaluation working group and recommendations made by the Agency for Healthcare Research and Quality [8,9]. Specific technical information on each CBM was obtained by direct communication with the companies marketing the individual products.

Results

MSCs

Mesenchymal stem cells were first discovered in 1966 by Friedenstein et al. [10] in the bone marrow, where they were observed to develop into fibroblast colony-forming cells. Mesenchymal stem cells are adult stem cells that have the capability to self-renew. Mesenchymal stem cells cultured ex vivo have been shown to replicate up to 38 times before undergoing degeneration [11]. They are multipotent cells giving rise to all the cells of the mesoderm, including bone, cartilage, fat, nerve, muscle, tendon, and mature stromal cell lineages [12]. Their differentiation is dependent on both intrinsic and extrinsic factors in their local environment and on neighboring cells [13]. In contrast to embryonic stem cells, MSCs and other adult stem cells have a more limited differentiation potential. In the process of development from embryonic to adult stem cells, MSCs lose differentiation potential and increase in specialization.

Most MSCs are isolated from bone marrow; however, they can be isolated from placenta, umbilical cord blood, connective tissue, skin, synovial fluid, fat, and teeth [14]. Bone marrow contains two types of stem cells: MSCs and hematopoietic stem cells. Mesenchymal stem cells make up only 0.001% to 0.01% of all nucleated bone marrow cells [15]. The highest concentration of MSCs is found in the pelvic girdle and vertebral bodies [16]. It is estimated that an aspiration of iliac crest bone marrow contains between one and five MSCs per 500,000 nucleated cells [17,18].

Mesenchymal stem cells are characterized by special immunological properties. They do not express the human leukocyte antigen Class II molecules, essential for the activation of the cellular immune response, or the accessory molecules (CD40, CD80, and CD86) necessary for T-cell activation and immune system recognition in vitro. [19–21]. Mesenchymal stem cells have been shown to possess autocrine and paracrine functions, essential for lineage progression and differentiation [15,22,23]. They secrete bioactive factors that inhibit fibrosis and apoptosis, which in turn decreases the local immune function, limits the field of injury, enhances angiogenesis, and stimulates division and differentiation of surrounding stem cells [22,24].

In the skeletal system, MSCs are the osteogenic cells required for bone repair, remodeling, and maturation. Under the right circumstances (appropriate spatial organization, density, mechanical forces, bioactive nutrients, and cytokines), MSCs differentiate into osteoblasts that subsequently serve to make new bone [13,23]. It is this naturally occurring potential that has been exploited for therapeutic use in the clinical setting.

MSCs and bony fusion

A total of 61 studies were identified evaluating the use of MSCs in bony fusion, 37 of which evaluated the use of MSCs in spinal fusion. Curylo et al. [25] showed that in cases in which inadequate amount of autogenous bone graft is present, addition of bone marrow aspirate to the fusion bed may facilitate greater bone formation and successful posterolateral spinal fusion in a rabbit model. Their results