HHS Public Access

Author manuscript

Spine J. Author manuscript; available in PMC 2015 November 01.

Published in final edited form as:

Spine J. 2014 November 1; 14(11): 2763–2772. doi:10.1016/j.spinee.2014.05.024.

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

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Author disclosures: ***BS:*** Nothing to disclose. ***JZG:*** Nothing to disclose. ***MAM:*** Nothing to disclose. ***SKC:*** Consulting: Stryker (B); Grants: OREF (D, Paid directly to institution). ***JCI:*** Grants: NIH (B). ***SAQ:*** Royalties: Zimmer (B, Paid directly to institution); Consulting: Orthofix (B), Medtronic (B), Stryker (B), Zimmer (B), Speaking/Teaching Arrangements: Medtronic (B), Stryker (B), Scientific Advisory Board/Other Office: MTF (Paid directly to institution), Zimmer SAB (B), Orthofix SAB (B), Pioneer DSMB (B); Grants: CSRS (C, Paid directly to institution).

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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

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 suggested that adding autogenous bone marrow to augment fusion, a process both safe and economical, was worthy of clinical investigation. Cui et al. [26] found that cloned osteoprogenitor cells from the bone marrow, when compared with mixed marrow cells, produced a larger amount of mature osseous tissue at an earlier time point during spine fusion in an athymic rat model. Kai et al. [27] revealed that bone marrow stromal-derived osteoblasts-calcium phosphate ceramic composites may provide an alternative to autogenous graft materials for lumbar spine interbody fusion and that adding bone morphogenetic protein-2 (BMP-2) into the composite may reinforce the biomechanical stiffness of fusion segments. Peterson et al. [28] demonstrated that human-derived bone marrow cells can be infected with BMP-2-containing adenovirus and produce sufficient bone in vivo to fuse the lumbar spine in an athymic rat model. Gupta et al. [29] demonstrated similar fusion rates with osteoprogenitor-enriched graft compared with autograft in an ovine posterolateral lumbar spine fusion model.

More recently, research into adipose tissue as a source of MSCs for use in spine surgery has gained popularity. In contrast to bone marrow, adipose tissue is easily obtained and yields large numbers of MSCs from relatively small amounts of tissue [30]. Miyazaki et al. [31] compared the effectiveness of BMP-2-transfected human MSCs from bone marrow with adipose-derived BMP-2-transfected MSCs in a rat posterolateral fusion model and found similar rates of fusion in both groups. Shen et al. [32] demonstrated the osteoblastic differentiation of rat adipose-derived MSCs when cultured in media with growth and differentiation factor-5. Hsu et al. [33] concluded that adipose-derived MSCs show promise as gene transduction targets for delivery of recombinant proteins such as BMP-2 for the enhancement of spinal fusion in biologically stringent environments.

The current literature evaluating the osteogenic potential of MSCs in animal and in vitro spinal fusion models suggests that MSCs have the ability to produce bone and lead to successful spinal fusion.

Cellular bone matrices

There are currently five commercially available bone graft matrices; Osteocel Plus (NuVasive, San Diego, CA, USA) [34], Trinity Evolution (Orthofix, Lewisville, TX, USA) [35], Cellentra Viable Cell Bone Matrix (VCBM) (Biomet, Warsaw, IN, USA) [36], AlloStem (AlloSource, Centennial, CO, USA) [37], and Ovation (Osiris Therapeutics, Columbia, MD, USA) (Table 1) [38].

Each one of these products is made using proprietary techniques aimed at preserving MSCs. The products are harvested and processed based on the source and living status of the donor. Qualifying donors undergo strict industry-driven screening processes, with standards set to exceed those of the US FDA and American Association of Tissue Banks [2]. The screening

process, reviewed by a licensed physician, includes donor medical and social history, physical examination, and medical record evaluation including autopsy reports, if available. The screening process also includes comprehensive tissue and blood testing and micro-biological testing for bacterial, fungal, and spore contamination [39].

Osteocel Plus, Trinity Evolution, and Cellentra VCBM are harvested from a single donor's cadaveric bone within 72 hours of death [39]. Once the initial donor evaluation is complete, the processing stage begins with the isolation of cancellous bone chips and milling and demineralization of the donor's cortical bone. The samples undergo selective immunodepletion to remove the hematopoietic cell lineages from the cancellous bone [40]. They are combined with a cryoprotectant and frozen at −70°C to −80°C, at which temperature their approximate shelf life is 18 to 60 months depending on the product [39,41]. The total cellular concentration ranges from greater than 250,000 cells per cc in both Trinity Evolution and Cellentra VCBM to 3,000,000 cells/cc in Osteocel Plus [39,42,43]. The percentage of MSCs per cc of product is unknown for Cellentra VCBM, is 0.004% (1,000 MSCs per 250,000 total cells) for Trinity evolution, and is 68% for Osteocel Plus [39,42] (Table 1). All three products are coupled with a demineralized bone or cancellous bone chip carrier.

AlloStem is produced by harvesting MSCs from cadaveric adipose tissue, combined with partially demineralized cancellous bone. Following the initial donor evaluation, 2000 cc of adipose tissue from a cadaveric abdomen are collected. The adipose tissue is rinsed using a phosphate-buffered saline solution and mixed with collagenase that digests the collagen tissue of the adipose cells. The solution then undergoes centrifugation, separating it into adipose, fluid, and stromal vascular fraction (SVF) layers [44]. The SVF consists of preadipocytes, MSCs, endothelial progenitor cells, T and B cells, mast cells, and adipose tissue macrophages [45]. The SVF layer is seeded into demineralized bone grafts and incubated for 36 hours, allowing MSCs to adhere to the demineralized bone. The product is thoroughly rinsed to remove all other cells and unwanted antibiotics after which cryopreservative is added and the finalized product is stored at −80°C, at which temperature its shelf life is 60 months [37,44]. The total cellular concentration of AlloStem is 66,255 cells/cc, all of which are claimed to be MSCs (100% MSC concentration) [37,46] (Table 1).

Ovation is the only product that uses a live donor, harvesting cells from the chorion layer of the placenta. The average age of the donor is unknown; however, Osiris Therapeutics claims that since the MSCs are derived from the placenta, the age of the donor is zero. The manufacturing process and steps undertaken to isolate the tissue and produce the final marketed product are proprietary and as such, Osiris Therapeutics chooses not to disclose them. The company claims that Ovation is a whole tissue product that is minimally manipulated and contains MSCs in addition to extracellular matrix, growth factors, and fibroblasts that are known to produce biologically active growth factors in the native tissue. Osiris Therapeutics claims that Ovation contains at least 400,000 cells/cc, with 1 of every 10,000 cells (0.0001%) being an MSC [31,35]. They recommend storing their product between −85°C and −75°C, at which temperature the shelf life is 24 months [35] (Table 1).

Samples from all of the five abovementioned CBMs are tested postcryopreservation to ensure sterility, cell count, viability, and osteogenic and osteoinductive potential. A licensed physician clears the products for market release after a final clearance.

Once ready for use, the products must be thawed, decanted, and placed in sterile saline. There is a variation in the cell viability time after defrosting, ranging from up to 1 hour in Ovation to up to 6 hours in Osteocel Plus (Table 1). These times are dependent on the proper decanting of the cryoprecipitant from the CBMs and immediate placement in sterile saline. If timely decanting isn't achieved and the cells are defrosted in the cryoprecipitant, the cell viability post defrosting is reduced by 50% in Cellentra VCBM [43].

FDA regulation

The Center for Biologics Evaluation and Research, one of the seven centers within the FDA, is responsible for the regulation of many biologically derived products, including blood intended for transfusion, blood components and derivatives, vaccines and allergenic extracts, and cell, tissue, and gene therapy products [47]. The FDA chooses to regulate tissues under the legal authority of Section 361 of the Public Health Service (PHS) Act that authorizes the Surgeon General, with the approval of the Secretary, Department of Health and Human Services, to make and enforce such regulations as judged necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the United States or from state to state [48]. Stem cells are regulated by Center for Biologics Evaluation and Research as human cells, tissues, and cellular- and tissue-based products (HCT/Ps). Human cells, tissues, and cellular- and tissue-based products are articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. The FDA has a risk-based approach to the regulation of HCT/Ps and under the authority of Section 361 of the PHS Act, the FDA established regulations for all HCT/Ps to prevent the transmission of communicable disease. Title 21, Code of Federal Regulations, Part 1271 (21 CFR Part 1271) sets out the criteria that form the foundation of the FDA's tiered, risk-based approach to regulating HCT/Ps. The regulations in 21 CFR Part 1271.10 identify the criteria for regulation solely under Section 361, prevention of transmission of communicable diseases. If all of the criteria in 21 CFR Part 1271.10 are met then no premarket review (application to FDA) is required. To satisfy these criteria, an HCT/P must be no more than minimally manipulated (related to nature and degree of processing); intended for homologous use only (the product performs the same basic function in the donor as in the recipient); and not combined with another article (with some limited exceptions); and the HCT/P does not have a systemic effect and is not dependent on the metabolic activity of living cells for its primary function, or if it does, the HCT/P is intended for autologous use or use by a first- or second-degree blood relative [48]. If the HCT/Ps do not meet all of the criteria of 21 CFR Section 1271.10, they must also be regulated under Section 351 of the PHS Act and/or the Federal Food, Drug, and Cosmetic Act as drugs, devices, and/or biological products and would require premarket approval [48].

The HCT/Ps regulated solely under Section 361 of the PHS Act include bone (including demineralized bone), ligaments, tendons, fascia, cartilage, ocular tissue (cornea and sclera),

skin, arteries and veins (except umbilical veins), pericardium, amniotic membrane (when used alone, without added cells for ocular repair), dura mater, heart valve allografts, semen, oocytes, embryos, and hematopoietic stem/progenitor cells derived from peripheral and cord blood [48].

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 [34–38]. However, all of these products are composed of MSCs derived from freshly procured cadaveric bone marrow, cadaveric adipose tissue, or chorion layer of the pacenta.

An FDA inspection of Osiris Therapeutics in early 2013 revealed that Ovation did not meet all of the criteria in 21 CFR 1271.10 and therefore, was not regulated solely under Section 361 of the PHS Act. The FDA found that the manufacturing process significantly altered the original relevant characteristics of the tissue, relating to the tissue's utility for reconstruction, repair, or replacement and that the product was dependent on the metabolic activity of living cells for its primary function. As such, the FDA advised Osiris Therapeutics that to lawfully market Ovation it must obtain a valid biologics license that is granted only after a showing of safety and efficacy for the product's intended use [49]. Osiris Therapeutics will continue producing Ovation for a limited time at which point it will be discontinued and replaced by a new product OvationOS, a CBM harvested from cadaveric bone.

At the current time, the FDA has not approved any stem cell-based products for use other than cord blood-derived hematopoietic progenitor cells (blood forming stem cells) for certain blood cancers and some inherited metabolic and immune system disorders [50].

Safety

Since the currently marketed CBMs are bypassing FDA premarket review, they are not required to undergo clinical trials to establish their safety. Bypassing FDA premarket review can only be achieved under current regulations if CBMs can prevent transmission of communicable diseases. As such, they undergo rigorous screening tests that exceed those required by the FDA and American Association of Tissue Banks [2]. There is currently no published literature on adverse events associated with the use of CBMs. There is currently an ongoing prospective, randomized trial evaluating the safety of MSCs and spinal fusion, comparing the spinal fusion obtained after instrumentation and the use of MSCs with the current gold standard iliac crest bone graft. The findings of this trial are expected to become available in June 2016 [51].

The current widespread use of CBMs in the clinical setting and the lack of reported adverse events associated with their use appear to suggest that CBMs are safe for use as bone graft substitutes in spinal fusion surgery, however their safety has not been established by way of clinical trials.

Cost

All of the currently available CBMs comprise demineralized bone and MSCs, except for Ovation that comes in a liquid form and is added to a carrier of choice. Osteocel Plus,

Trinity Evolution, Cellentra VCBM, and AlloStem are sold in 1, 5, 10, and 15 cc packages. Allostem is also available in two different sized strips. Ovation is sold in 0.3 and 1.0 cc vials.

Cellular bone matrices are sold at a premium price that is comparable with, or exceeds, the price of InFuse (Medtronic Sofamor Danek, Memphis, TN, USA). Cellular bone matrices range in price from $460 to $7,150 (0.3–15 cc) compared with InFuse that ranges from $876 to $5,408 (XXSmall 0.7 ccLarge 8 cc) and allograft and demineralized bone matrices that range from $119 to $1,927 (0.5–90 cc) (Table 2) [52].

Literature evaluating CBMs and spine surgery

A total of 37 studies evaluating the use of MSCs in spine surgery were identified using our search criteria. Of those, 21 were animal studies, 11 were review articles on MSC technology in spine surgery, and 2 were in vitro studies. Only three studies were identified that evaluated the use of CBMs in humans.

There are multiple ongoing industry-sponsored clinical trials evaluating the efficacy of Osteocel Plus and Trinity Evolution in spinal fusion surgery, the results of which are currently not publically available [53–59]. There are currently only three published studies reporting fusion rates using CBMs. Kerr et al. [60] retrospectively reviewed 52 consecutive patients who underwent lumbar fusion surgery with Osteocel (first generation CBM from NuVasive, San Diego, CA, USA) at one and two contiguous levels and found that solid arthrodesis was achieved in 92.3% of patients using a combination of plain radiographs and computed tomography scans. Ammerman et al. [61] retrospectively reviewed 23 patients who underwent minimally invasive transforaminal lumbar interbody fusion with Osteocel Plus and found that at 12 months, 91.3% of the patients underwent successful fusion based on plain radiographs. Tohmeh et al. [62] examined the 12-month clinical and radiographic outcomes of 40 patients who underwent an extreme lateral interbody fusion with Osteocel Plus and observed a 90.2% fusion rate using a combination of plain radiographs and computed tomography scans. Two of the published works did not disclose whether they had conflicts of interest [60,61] and one study was industry sponsored [62]. Although the results reported in the aforementioned published works appear to be equivalent if not superior to the accepted rates of spinal fusion using iliac crest autograft, no such conclusion can be made without supportive evidence from large, randomized controlled trials. At this time, no randomized controlled studies evaluating the efficacy of CBMs in spinal fusion surgery exist.

Based on the percepts outlined by the Grades of Recommendation Assessment, Development and Evaluation working group and the recommendations made by the Agency for Healthcare Research and Quality, the quality of evidence supporting the use of CBMs as bone graft substitutes in spinal fusion surgery is deemed to be insufficient, indicating that evidence is either unavailable or does not permit a conclusion.

Potential pitfalls of CBMs in spinal fusion

The capacity for bone formation at a particular site is directly proportional to the number of osteoblasts available, which in turn is directly proportional to the number and concentration

of MSCs that enter and commit to the osteogenic differentiation pathway. Hernigou et al. [63] showed that bone marrow aspirates containing less than 1,500 MSCs/cc were ineffective for the treatment of tibial nonunion, suggesting that this is the minimal MSC concentration for bony healing in this setting. Cuomo et al. [64] compared the osteogenic potential of human bone marrow aspirate (mean concentration of 1,010 MSCs/cc) with that of human MSC-enriched bone marrow aspirate (mean concentration of 6,150 MSC/cc) in a critically sized rat femoral defect model and concluded that neither aspirates resulted in reliable healing of the bone defects. Minamide et al. [65] compared the efficacy of cultured bone marrow cells with that of BMP in a rabbit posterolateral fusion model and described fusion rates of 57% in the autograft group, 100% in the BMP-hydroxyapatite (HA) group, 0% in the low-marrow-HA group, and 71% in the high-marrow-HA group. In their study, there was a 100-fold difference between the amounts of bone marrow cells in the low-marrow (1 million cells) versus high-marrow (100 million cells) groups. The authors remained uncertain of the minimum threshold concentration of cultured stem cells required to generate a 100% fusion rate. One of the key differences in the CBMs currently available is the wide variation in the total amount of cells and concentration of MSCs in each product. There is a 45-fold difference in total cellular concentration between Osteocel Plus (3,000,000 cells/cc) and AlloStem (66,255 cells/cc) and a 51,000-fold difference in the concentration of MSCs between Osteocel Plus (2,040,000 MSCs/cc) and Ovation (40 MSCs/cc) (Table 1).

An important distinction between the commercially available CBMs is the tissue of origin of the MSCs (Table 1). Adult stem cells, such as MSCs, are considered to be developmentally committed. As such, they are restricted to produce specific lineages, namely those from the tissue in which the stem cells reside [66]. As the research in the field of stem cell technology expands, we are increasingly learning that MSCs can be distinguished at the level of cytokine production and gene expression profile based on their tissue of origin [67]. Ragni et al. [68], studying the adipogenic potential in human MSCs, concluded that MSCs show a different degree of phenotypic plasticity depending on the source tissue, which should be taken into consideration for the selection of the most appropriate MSC type for specific tissue regeneration purposes. Studies do exist describing osteoblastic differentiation of both adipose- and placenta-derived MSCs in ex vivo culture media [32,69–71], however, no evidence exists that these cells have the ability to undergo osteoblastic differentiation once implanted into an in vivo human fusion bed.

Another relevant difference between the CBMs is the donor age at the time of graft harvest. The average donor age of the currently available CBMs ranges from 0 to 50 years (Table 1). Muschler et al. [72] investigated the influence of age on human MSC concentration and revealed a significant age-related decline in the number of nucleated cells harvested per aspirate from both man and women ($p=.002$). An average of 1 of every 10,000 bone marrow cells in a newborn is an MSC, a number that decreases to 1 in 250,000 by 30 years and drops further to 1 in 2,000,000 by 80 years. It has also been described that MSCs have a decreased ability to proliferate, differentiate, and mobilize with age [2]. Wu et al. [73] evaluated the effect of age on human adipose-derived stem cells and concluded that infant-derived cells exhibit enhanced angiogenic and osteogenic capabilities compared with older cells. It is evident that donor age plays a critical role on the number, function, osteoblastic potential,

and cytokine production of MSCs. An optimal donor age range for harvest of MSCs used in spinal fusion surgery is currently unknown.

Arguably the most important question regarding CBMs is whether the MSCs within these products are able to survive in the fusion bed posttransplantation. Mesenchymal stem cells hold a considerable promise in bioengineering because of their ability to differentiate into various phenotypes. To date, however, MSCs have not met this promise in part because of their high death rate on transplantation. Toma et al. [74] evaluated the fate of MSCs after their vascular delivery into rat cremaster muscle microcirculation and found that after injection, microvascular plugging with obstruction of flow lead to a microischemia, resulting in loss of 86% of the cells within the first 24 hours. Degano et al. [75] analyzed the bone regenerating capacity of human bone marrow (hBMSC) and adipose tissue (hAMSC) MSCs implanted in a mouse calvarial bone defect and found that at 90 days, 37% of hBMSCs remained alive compared with only 5% of hAMSCs. A likely explanation for this limited cellular survival is that on implantation, MSCs encounter an ischemic environment composed of low oxygen tension and nutrient deprivation [76]. Adequate oxygen tension is crucial in the modulation of cell adhesion, metabolism, proliferation, and differentiation and has a profound effect on cellular survival [77–79]. Potier et al. [80] recently reported that transplanted MSCs subjected to hypoxia exhibited a limited angiogenic factor secretion and persistent down regulation of several osteoblastic markers, affecting their bone-forming potential. Several studies described the efficacy of hyperbaric oxygen therapy in improving bone formation [81–84]; however, a study evaluating the effects of hyperbaric oxygen treatment revealed that it did not enhance the preconditioned MSCs with regard to the success of posterolateral lumbar fusion in a validated rabbit model [85]. A more recent study by Deschepper et al. [86] showed that glucose also plays a critical role in enhancing the ability of human MSCs to survive in a near-anoxic environment.

A key factor in the ability of MSCs to survive posttrans-plantation is their ability to evade the host immune system. In vitro studies have shown that MSCs are able to evade the host immune system through their lack of human leukocyte antigen Type II antigens and accessory surface molecules [19–21]. However, all of these observations were based on in vitro experiments. Niemeyer et al. [87] evaluated the survival of human MSCs from bone marrow and adipose tissue after xenogenic transplantation in immunocompetent mice and discovered that undifferentiated MSCs were candidates for nonautologous cell transplantation, whereas osteogenic-induced MSCs seem to be eliminated by the host's immune system. Evidence regarding the emergence of immunological defense reactions against MSCs is not consistent, and although positive clinical results without significant immunological rejections have been described, reports of relevant immunological responses have been published [88–90]. If it cannot be shown that MSCs within CBMs are able to survive posttransplantation, then CBMs are reduced to the osteoconductive carrier that they are coupled with. This leaves the surgeon to rely on the fusion rates of demineralized bone matrices and bone chips for successful spinal fusion in patients.

The available literature on MSC technology has not yet established that MSCs, when transplanted into the human spinal fusion bed can regenerate by incorporating themselves into the native tissue, surviving and differentiating.

Conclusion

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. 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. Furthermore, CBMs come with a premium price because of the claim that the MSCs within them have the ability to produce bone. However, with the current lack of evidence showing that MSCs can survive in a fusion bed posttransplantation, no such claim can be made. With the currently available data, there is no sufficient evidence to support the use of CBMs as bone graft substitutes in spinal fusion surgery.

Acknowledgments

No funding was obtained for this study and no conflicts of interest exist for this study.

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Table 1

Currently available CBMs (all data is shown exactly as reported by the individual companies; no extrapolations have been made)

Product	Osteocel Plus	Trinity Evolution	Cellentra VCBM	AlloStem	Ovation
Manufacturer	NuVasive, Inc. (San Diego, CA, USA)	Orthofix (Lewisville, TX, USA)	Biomet (Warsaw, IN, USA)	AlloSource (Centennial, CO, USA)	Osiris Therapeutics, Inc. (Columbia, MD, USA)
Source of MSCs	Cadaveric bone	Cadaveric bone	Cadaveric bone	Cadaveric adipose tissue	Live donor placenta chorion layer
Average donor age at harvest (y)	18–44	30	n/a	50	n/a
Total cellular concentration (cells/cc)	3,000,000	≥250,000	≥250,000	66,255	≥400,000
MSC Concentration (MSCs/cc)	n/a	≥1,000	n/a	66,255	n/a
% MSCs	68	n/a	n/a	100	0.0001
Storage temperature	−80°C±5°C *−75°C to −45°C	−80°C	≤−70°C	−80°C	−85°C to −75°C
Shelf life (mo)	60 *3	60	18	60	24
Cell viability once defrosted (h)	≤6	≤2	≤4	n/a	≤1
Osteoinductive cytokines	Naturally occurring in bone	Naturally occurring in bone	BMP-2, 4, 7; VEGF; TGF-β; PDGF; IGF-1; FGF	Naturally occurring in bone	BMP-2, 7; PDGF; VEGF; FGF; IGF-1; TGF-β; PIGF
Osteoconductive carrier	Cancellous bone chips	Demineralized bone	Cancellous bone matrix	Demineralized bone	None (product can be added to any carrier)

CBM, cellular bone matrix; VCBM, viable cell bone matrix; n/a, not available; MSC, mesenchymal stem cell; BMP, bone morphogenetic protein; VEGF, vascular endothelial growth factor; TGF, tissue growth factor; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor; PIGF, placental growth factor; FGF, fibroblast growth factor.

Table 2

Prices of CBMs compared with prices of other bone graft substitutes and osteobiologic materials available at our institution

Product	**Price per volume**				
CBM	*0.3 cc*	*1 cc*	*5 cc*	*10 cc*	*15 cc*
Osteocel Plus	n/a	$460	$2,120	$3,520	$5,400
Trinity Evolution	n/a	$540	$2,395	$4,365	$5,455
Cellentra VCBM	n/a	$620	$2,751	$5,009	$6,258
AlloStem	n/a	$540	$2,300	$3,500	n/a
Ovation	$2,700	$7,150	n/a	n/a	n/a
rhBMP-2	*0.7 cc (XXSmall)*	*1.4 cc (XSmall)*	*2.8 cc (Small)*	*5.6 cc (Medium)*	*8.0 cc (Large)*
INFUSE	$876	$1,726	$3,451	$4,893	$5,408
Synthetics	*1 cc*	*5 cc*	*10 cc*	*15 cc*	*30 cc*
Mastergraft Hydroxyapatite+beta-tricalcium phosphate	$127	$357	$643	$810	$1,072
Allograft	*5 cc*	*15 cc*	*30 cc*	*60 cc*	*90 cc*
Cancellous cubes	n/a	$473	$715	n/a	n/a
Cancellous chips	$175	$342	$560	$1,057	$1,617
Cancellous crushed	n/a	$498	$747	$1,325	$1,927
Cortical cancellous chips	n/a	$311	$529	$964	n/a
Cortical cancellous crushed	n/a	$324	$541	n/a	$1,318
DBM	*0.5 cc*	*1 cc*	*2.5 cc*	*5 cc*	*10 cc*
Grafton DBM gel	$119	$216	n/a	$865	$1,320
Grafton DBM putty	$125	$216	$476	$865	$1,342

CBMs, cellular bone matrices; BMP, bone morphogenetic protein; VCBM, viable cell bone matrix; n/a, not available; DBM, demineralized bone matrix.