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RESEARCH ARTICLE

THE ROLE OF BONE MARROW MESENCHYMAL STEM CELLS IN BONE HEALING IN CRANIO-MAXILLOFACIAL BONE DEFECTS : A SYSTEMATIC REVIEW

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ABSTRACT

Objective: The aim of this work was to review the literature about The role of bone marrow mesenchymal stem cells BMSCs in bone healing in cranio-maxillofacial bone defects.
Design: Using related key words, electronic search of English-language papers was conducted on PubMed data-bases in Mars/2016. Studies that assessed the use of bone marrow mesenchymal stem cells BMSCs in bone regeneration in cranio-maxillofacial bone defects in human or animal models were included. The retrieved articles were thoroughly reviewed according to the in vivo experimental model, the cell carrier, the defect type, the method of evaluating and the obtained results.
Results: A total of 24 articles were matched with the inclusion criteria of this study. Six articles were performed on rats, six on rabbits, six on dogs, two on pigs and four on human
Conclusion: According to this review, the majority of the evaluated studies demonstrated positive results regarding the efficiency of bone marrow stem cells for in vivo bone regenerating.

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INTRODUCTION

Stem cells are immature, unspecialized cells that have the potential to develop into many different cell lineages via differentiation (Slack, 2008). There are two primary sources of stem cells: adult stem cells and embryonic stem cells (Takahashi and Yamanaka, 2006; Takahashi *et al*., 2007). Adult stem cells are found in many tissues and organs such as bone marrow, periosteum, muscle, fat, brain, dental pulp, and skin (Zuk *et al*., 2001; McKay, 1997; Gage, 2000; Toma *et al*., 2001; Ding *et al*., 2011; Baddoo *et al*., 2003; Tamaoki *et al*., 2010). Bone marrow (BM) is one of the most sources of mesenchymalstem cells MSCs (Ploemacher *et al*., 1984). In a pioneering study conducted over 30 years ago, Friedenstein*et al* isolated MSCs from bone marrow BM. They named these cells bone marrow stromal cells and demonstrated that, when transplanted, these cells have the ability to form bone, cartilage, adipose (Friedenstein *et al*., 1966; Owen and Friedenstein, 1988). Techniques for the isolation of MSCs from BM range from aspiration and density-gradient centrifugation to simple, direct plating methods (Caterson *et al*., 2002; Hung *et al*., 2002). BMSCs have been extensively studied and demonstrated todifferentiate along osteogenic, chondrogenic, adipogenic, myogenic or non-mesenchymal neurogenic lineages (Pittenger *et al*., 1999; Dezawa *et al*., 2005; Dezawa *et al*., 2004; Egusa *et al*., 2005). Autogenous graft, allogeneic graft, and various alloplastic materials, which have been utilized to reconstruct craniofacial defects have all led to improved clinical outcomes of various degrees. However, these approaches showed inherent limitations, such as insufficient autogenous resources, donor site morbidity, contour irregularities, disease transmission, unpredictable outcome for bone formation, and infection of foreign material (Jackson *et al*., 1986; Oklund *et al*., 1986; Sawin *et al*., 1998; Warren *et al*., 2003). To overcome these limitations, stem cell-based tissue regeneration offers a promising approach to providing anadvanced and reliable therapeutic strategy for craniofacial tissue repair (Miura *et al*., 2006).

Bone marrow as mesenchymal stem cells source is a commonly used for utilization in cell-based regenerative approaches in craniofacial applications (FilhoCerruti *et al*., 2007; Gao *et al*., 2001; Krebsbach *et al*., 1997; Lee *et al*., 2010). The aim of this work was to review the literature about. The role of bone marrow mesenchymal stem cells in bone healing in cranio-maxillofacial bone defects.

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MATERIALS AND METHODS

Review question

This study was conducted to assess the role of bone marrow mesenchymal stem cells in bone healing in cranio-maxillofacial bone defects. Secondarily to review the techniques used in this approach.

Search strategy

An electronic search of papers was conducted in PUBMED databases including English-language papers published until Mars 2016 by using following key words separately and in combination: bone marrow Mesenchymal stem cells, bone regeneration, cranio-maxillofacial bone defect, cranio-maxillofacial reconstruction and tissue engineering. In addition the references of the searched articles were evaluated for other related studies.

Study selection

All studies that investigated the role of bone marrow mesenchymal stem cells in bone healing in cranio-maxillofacial bone defects were included in this review. Titles and abstracts were retrieved and assessed independently as to their relevance to the desired subject. Duplicate articles were identified and removed, Subsequently, full texts of relevant papers were assessed for data extraction.

Data extraction

Data regarding the animal model, evaluated site, the cell carrier, the method of evaluating, the duration of the study, and the reporting results of each study were extracted from the articles.

RESULTS

The initial search resulted in 11897 articles. Following the screening of the titles, abstracts and full texts, 24 papers formed the basis of this systematic review.

Rat

According to inclusion criteria 6 articles used rats as an animal model were evaluated in this study(Akita *et al*., 2004; Kim *et al*., 2007; Castano-Izquierdo *et al*., 2007; Khojasteh *et al*., 2008; Agacayak *et al*., 2012; Allais *et al*., 2015). In 2 of these articles the authors used human bone marrow-derived mesenchymal stem cells hMSCs (Akita *et al*., 2004; Kim *et al*., 2007). Cranial bone defects were used to evaluate the role of BMSCs in bone healing in allof these studies (Table 1). Akita *et al*. (2004) used dual-energy x-ray absorptiometry for bone mineral density BMD. An analysis of a 4-mm cranial defect in nude rats that had received human bone MSCs treated with BMP-2 and basic fibroblast growth factor was compared with MSCs alone using a Gelfoam carrier. Four weeks after surgery, BMD was significantly greater for the first group, although no statistically significant difference was reported from specimens harvested 8 weeks later. Kim *et al*. (2007) observed positive results when treated the cranial defects with MSCs and bone morphogenic protein-2 (BMP-2) carried on acrylated hyaluronic acid (HA) as a scaffold. 84% bone formation was reported 4 weeks after the operationin an 8-mm calvarial defect. No inflammatory response to the xenogenic transplant of MSCs was reported. In another study, isolated rat BMSCs were cultured for 4, 10, and 16 days in an osteogenicmedium. Cells were then loaded on titanium fiber mesh and scaffolds were implanted into 8-mm rat calvarial defects. The largest amount of bone formation was noted in the group receiving BMSCs cultured for 4 days (Castano-Izquierdo *et al*., 2007). Other studies concluded that adding BMSCs alone or with PRP to the synthetic bone substitute are more effective in inducing new bone formation (osteogenesis) than the use of platelet rich plasma combined with synthetic bone substitute in cranial critical size defects (Khojasteh*et al*.,2008; Agacayak *et al*., 2012). However Allias *et al*. (2015) found that the use BMSCs in conjunction with calcium phosphate resulted in a similar behavior in the process of bone repair in critical size defects, when compared with autogenous bone graft.

Rabbit

Using the rabbit model, four studies evaluated BMSCs-related bone regeneration in cranial bone defects and two in mandible (Liu *et al*., 2007; Lee *et al*., 2008; Kim *et al*., 2015; Jiang *et al*., 2012; Saad *et al*., 2015; Alfotawei *et al*., 2014) (Table 2). One study performed a successful augmentation in a 6-mm defect using cellular and acellular 3-dimensional polylactide co-glycolide (PLG) with polyethylene glycol (PEG) and BMP-2 scaffold and compared its efficacy with a PLG scaffold. Twelve weeks postoperatively, histomorphometric analysis demonstrated the largest percentage of bone formation using the 3-dimensional PLG-PEG-BMP-2 construct and rabbit BMSCs, the cellular PLG group showed a larger amount of bone regeneration compared with its acellular counterpart (Liu *et al*., 2007). Another study with a similar design compared the effectiveness of 2 other scaffolds (macroporous bi- phasic calcium phosphate and autologous fibrin glue as cell delivery systems. Qualitative microscopic examination of specimens collected 8 weeks after surgery showed autologous fibrin glue to be the better carrier of rabbit BMSCs (Lee *et al*., 2008). Kim *et al*. (2015) used BCP and BMP-2 in combination with BMSCs and evaluated their osteogenic therapeutic efficacy by using a calvarial defect, their results indicated that the combination of BCP, rhBMP-2, and MSCs synergistically enhances osteogenic potential during the early healing period. Jiang *et al*. (2012) investigated the feasibility of using PRP as a scaffold to carry bone marrow stromal cells (BMSCs) whether they induced with dexamethasone or not, after eight weeks, substantial bone regeneration was observed at the calvarial defect restored with PRP incorporating the induced BMSCs comparable with the whole blood incorporating BMSCs, whether the BMSCs. Two studies used beta-Tricalcium Phosphate (β-TCP) as scaffold in combination with BMSCs in mandibular defects, the first one by Saad *et al*. (2015) Their results revealed that the BM-MSCs endowed b-TCP scaffold with a better and more rapid bone regenerating potential in Critical-sized defects (10 × 15 mm), whereas the results of the second study showed that The addition of BMSCs to the biodegradable b-TCP scaffold did not improve reconstruction of 20 mm-long mandibular defect (Alfotawei *et al*., 2014).

Table 1. Rat studies

Authors	Defect	BMSCS	Scaffold	Growth factor	Method of evaluation	Time of evaluation
Akita *et al*. 2004	Cranial bone	(hMSCs)	Gelatin sponge	(BMP-2)- (bFGF)	Histology,radiologyimmunohistochemstry	2, 4, 8 weeks
Castano-Izquierdo *et al*. 2007	Cranial bone	Femur-tibia	Sintered titanium fiber meshes	-	histomorphometry	4 weeks
Kim *et al*. 2007	Cranial bone	hMSCs	hyaluronic acid-based hydrogel	BMP-2	Histology, immunohistochemstry	4 weeks
Khojasteh *et al*. 2008	Cranial bone	tibia	(Bio-Oss)	PRP	Histology, Histomitry, Immunohistochemistry	6 weeks
Agacayak *et al*. 2012	Cranial bone	Femur- tibia	BCP	PRP	Histology, immunohistochemistry	2, 8, 12 weeks
Allais *et al*.2015	Cranial bone	Tibia- femur	Calciumphosphate	-	Histology,histomorphometry	30,60 days

Table 2. Rabbit studies

Authors	Defect	BMSCS	Scaffold	Growth factor	Method of evaluation	Time of evaluation
LIU *et al*. 2007	Cranial bone	ilium	3-dimensional PLG-PEG	BMP-2	Histology, radiology Histomorphometry	4, 8, and 12 weeks
Lee *et al* 2008	Cranial bone	ilium	Fibrin Glue- BCP		Histology, radiology	2, 1 and3 months
Jiang *et al*. 2012	Cranial bone	tibia	(PRP)	-	Histology, radiology	8 weeks
Alfotawei *et al*. 2014	Mandibular bone	ilium	β-TCP	-	Histology, radiology biomechanical testing	4, 8 and 12 weeks
Kim *et al*. 2015	Crania bone	ilium	BCP	rhBMP-2	Histology, radiology	2or8 weeks
Saad *et al*. 2015	Mandibular bone	femur	β-TCP		Histology, radiology Histomorphometry	2, 4, 12, and 24 weeks

Table 3. Dog studies

Authors	Defect	BMSCS	Scaffold	Growth factor	Method of evaluation	Time of evaluation
Yamada *et al*. 2004	mandible	Ilium	PRP	-	Histology, Histomitry, radiology	2,4,8 weeks
Ito *et al*. 2006	peri-implantdefects	Ilium	PRPFibrin glue		Histology, Histomorphometry,	2, 4, 8 weeks
Yuan *et al*. 2007	mandible	Ilium	β-TCP scaffolds	-	Radiology, histology biomechanical analysis	4 weeks32 weeks
Jafarian *et al*. 2008	mandible	humerus	HA/TCP(Bio-Oss)	-	Histology, Histomorphometry, Immunohistochemistry	6 weeks
Ribeiro *et al*. 2012	peri-implantdefects	Ilium	BD 3DScaffold Composite	-	Histology	3 months
YU *et al*. 2014	Sinus Floor Augmentation	Ilium	Bio-Oss	-	Histology, Radiology, Histomorphometry	12 weeks

Table 4. Pig studies

Authors	Defect	BMSCS	Scaffold	Growth factor	Method of evaluation	Time of evaluation
Abukawa *et al*. 2006	Mandible	ilium	poly-DL-lactic-coglycolic acid	-	Radiology, Histology	6 weeks
Pieri *et al*. 2009	mandible	Illium	fluorohydroxyapatite (FHA) scaffold	PRP	Histology, Histomorphometry	3-month

Table 5. Human studies

Authors	Defect	BMSCS	Scaffold	Growth factor	Method of evaluation	Time of evaluation
Shayesteh *et al*. 2008	Sinus augmentation	Ilium	HA/TCP	-	Histology, radiology	3 and 12 months
Ueda *et al*. 2008	Sinus augmentation	Ilium	PRP	-	Clinically, radiology	4 to 8 months
Yamada *et al*. 2008	Sinus augmentation	Ilium	PRP	-	Clinically, radiology	3, 6, 12, and 24 months
Kaigler *et al*. 2013	localized craniofacial bone defects	Ilium	Gelfoam®	-	Clinically, radiology	6 or 12weeks

Dogs

To review the dog as animal model 6 articles were selected using the inclusion criteria (Yamada *et al*., 2004; Ribeiro *et al*., 2012). Histomorphometric analysis in Yamada *et al*. study (2004) revealed that a 36.8% partial bone fill was observed after 4 weeks with the application of dog BMSC/PRP in a 10-mm defect. This result showed no significant difference from the control group, which received aparticulateautograft. Eight weeks postoperatively there was a significant increase in bone formation nmaximizing at 61.4%. Adding fibrin glue to this combination, another study treated a 10-mm mandibulardefect with simultaneous implant placement and reported 43% and 53% bone-to-implant contact 4 and8 weeks later, respectively, which were higher than in groups that had been left untreated or had received cellular or cellular fibrin without PRP (19% and 29%vs 22% and 25% vs 32% and 42%, respectively) (Ito *et al*., 2006). Sixweeks after delivering dog BMSCs with hydroxyapatite (HA)-TCP or Bio-Oss in a through-and-through10-mm mandibular defect, Jafarian *et al*. (2008) reported 65.78% or 50.31% of new bone formation, respectively. The use of plain scaffolds was accompaniedby significantly less bone regeneration (44.90% and 36.83%, respectively). Another study was carried out in a dog mandibular defect and compared the efficacy of BMSCs/β -TCP with autogenous bone graft in conducting bone regeneration in a30-mm defect. Using dual-energy x-ray absorptiometry, BMD of newly formed bone was recorded 32weeks later. The results indicated an acceptable regenerationin the test group (0.55 g/cm2), which wassignificantly greater than with the acellular scaffold(0.19 g/cm2) but not as great as with the autogenousbone graft (0.87 g/cm2) (2007). Yu *et al*. compare the potential of tissue-engineered bone derived from bone marrow mesenchymal stem cells (BMMSCs) and periodontal ligament stem cells (PDLSCs) seeded in Bio-Oss for maxillary sinus augmentation. The osteogenic capacity was greater when mesenchymal stem cells were used from two sources than Bio-Oss alone. (Yu *et al*., 2014) finally Riberio *et al*. investigated the effect of bone marrow-derived cells associated with guided bone regeneration in the treatment of dehiscence bone defects around dental implants. Histometric analyses demonstrated that cell-based bone tissue engineering provided favourable results for bone regeneration in periimplantar bone defects, although the combined approach, using membrane and cells, seems to be more relevant, especially in terms of bone regeneration in the region of the implant threads (Ribeiro *et al*., 2012)

Pig

Using the pig as animal model 2 articles which made on mandible met the inclusion criteria (Abukawa *et al*., 2004; Pieri *et al*., 2009). The first study evaluated the role of bone marrow-derived cells seeded into poly-DL-lactic-coglycolic acid scaffolds in bone healing in 2×2 cm bony defects. After 6 weeks the defects appeared to be filled with hard tissue resembling bone, whereas controls were filled with fibrous tissue. Radiographically, the tissue-engineered constructs were uniformly radiodense with bone distributed throughout. The interface between native bone and constructs was indistinct. Complete bone in growth was not observed in control defects (Abukawa *et al*., 2004). The second study tested the effect of the combination of mesenchymalstemcells (MSCs) and platelet-rich plasma (PRP) incorporated into a fluorohydroxyapatite (FHA) scaffold on bone regeneration in cylindrical defects in the edentulous mandibular ridge of minipigs. MSCs-PRP-FHA (45.28%) produced a significantly higher amount of vital bone than PRP-FHA (37.95%), or FHA alone (36.03%). Further, the MSCs-PRP-FHA-treated defects showed a significantly higher percentage of contact between graft particles and newly formed bone compared with PRP-FHA and FHA group (59.23% vs 48.37% and 46.43%, respectively) (Pieri *et al*., 2009).

Human

Four articles used human as model were included in this study for review .The first study used autogenous BMSCs/PRP (with simultaneous implant placement in 6 sinus lifts, 3 maxillary augmentations, and 5 mandibular augmentations). This study reporteda 100% success rate with 2 to 5 years of follow-up for the sinus lift procedure. Despite 4 cases of sinusmucosa perforation during surgery, no major complications were documented. In this study, of 8 cases treated for vertical ridge augmentation, 2 patients demonstrated inadequate bone gain 4.8 months after the operation. The remaining 6 alveolar ridge reconstructions healed uneventfully, with an average increase of 5 mm in vertical bone height (Ueda *et al*., 2008). The second study applied HA-TCP loaded with BMSCs (for 3 cases of unilateral and 4 cases of bilateral sinus augmentation; dental implants were also placed in 6 patients 3 months postoperatively) this study also demonstrated adequate bone augmentation with 41.43% new bone formation and an average bone height of 12 mm. These findings were based on histomorphometric and radiographic analyses 3 months after grafting. Radiographs 12 months postoperatively showed a 10.83-mm bone height increase. Twenty-eight of 30 implants (93%) were reported clinically successful at 6 months (Shayesteh *et al*., 2008).The third study used injectable tissue-engineered bone, along with bone marrow–derived stromal cells (BMDSCs) and platelet-rich plasma as an autologous scaffold, to conduct maxillary sinus floor augmentation by the simultaneous placement of bone graft and dental implants. The height of mineralized tissue at 2 years showed the mean increases of 8.8±1.6mm compared to preoperative values, and no adverse effects and remarkable bone absorption were seen in the 2–6-year follow-up time (Yamada *et al*., 2008). The fourth study is A Randomized, Controlled Feasibility Trial. Twenty-four patients were randomized to receive either guided bone regeneration (GBR) or Tissue repair cells (TRCs) transplantation. Clinical, radiographic, to mographic, and histological measures demonstrated that TRC therapy accelerated alveolar bone regeneration compared to GBR therapy. Additionally, TRC treatment significantly reduced the need for secondary bone grafting at the time of oral implant placement with a fivefold decrease in implant bony dehiscence exposure (residual bone defects) as compared to GBR-treated sites (Kaigler *et al*., 2013).

Conclusion

BMMSCs are one of the most promising adult stem cell populations for tissue repairing and bone regeneration in craniofacial region. However there are many challenges ahead

of us in terms of utilizing bone marrow stem cells in tissue regeneration regarding to, the control of differentiation of stem cells, proper application methods, appropriate scaffold with optimal degradation and osteoconductive surface and combinations of stem cells with growth factors.

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