International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: SJIF: 5.995
Available Online at www.journalijcar.org
Volume 7; Issue 1(F); January 2018; Page No. 9150-9153
DOI: http://dx.doi.org/10.24327/ijcar.2018.9153.1500

Research Article

STEM CELL BASED TISSUE-ENGINEERING APPROACHES IN CLEFT ALVEOLUS: A SYSTEMATIC REVIEW

Deborah Sybil., Kaleem Fatima and Sneh Lata Gupta

Department of Oral and Maxiilofacial Surgery, Faculty of Denistry, Jamia Millia Islamia MaulanaMohd. Ali Jauhar Marg New Delhi – 110025

A R T I C L E I N F O

Article History:
Received 12th October, 2017
Received in revised form 16th November, 2017
Accepted 26th December, 2017
Published online 28th January, 2018

Key words:
Alveolar bone graft, Tissue engineering, stem cell, bone regeneration.

A B S T R A C T

Alveolar bone grafting is an essential part of treatment concept in cleft lip and palate patients. Autogenous bone grafts are considered the gold standard treatment for human alveolar cleft defects. Alternative techniques like demineralized bone matrix, allogenic or xenogenic grafts and alloplasts have not produced comparable results. With the advent of cell culturing and tissue engineering, several attempts have been made to find engineered bone solutions for cleft alveolus. In this systemic review, we have reviewed articles and discussed the role of stem cell based approaches to bone regeneration in cleft alveolar defects.

INTRODUCTION

The prevalence of cleft lip with or without cleft palate is about 1 per 700 live births in humans and thereby the most common congenital craniofacial anomaly (Vanderas, 1987). Seventy five percent of all cleft lip and palate variations are accompanied by osseous defects of the alveolar bone (Bertz, 1981). An essential part of therapy concept of alveolar cleft is bone grafting before the eruption of permanent canine in the stage of mixed dentition (Horswell *et al*, 2003). This secondary osteoplasty stabilizes the dental arch, creates sufficient bone site for the erupting permanent teeth, closes oronasal fistulae and supports the surrounding soft tissue and the nasal alar base (Bergland *et al*, 1986). The currently established material for alveolar osteoplasty is autogenous iliac bone graft because it contains living immune compatible bone cells and has strong osteogenic properties (Freihofer *et al*,1993). Nevertheless, bone grafting from iliac crest is associated with disadvantages such as donor site morbidity, limited availability and post-operative temporary mobility impairment (Ochs,1996). These drawbacks have led to the search for alternatives, e.g. alternative donor sites for autogenous bone grafts, allogenic bio materials or tissue engineered bone grafts. An alternative for autogenous and allogenic grafts could be the creation of artificial tissue constructs by tissue engineering. These bone grafts are composed of osteogenic cells, an osteoconductive three-dimensional scaffold and osteoinductive growth factors.Tissue engineered osteogenic material comprising of osteogenic cells, a scaffold and growth factors have yielded predictable results (Strietzel, 2006). In this review we have discussed the role of stem cells in the reconstruction of alveolar cleft defects.

Corresponding author:* **Deborah Sybil
Department of Oral and Maxiilofacial Surgery, Faculty of Denistry, Jamia Millia Islamia MaulanaMohd. Ali Jauhar Marg New Delhi – 110025

MATERIALS AND METHODS

Study design

Studies which used stem cells for cleft alveolar reconstruction in humans were included in this review. Studies which used other tissue engineering methods for cleft osteoplasty such as scaffolds with or without growth factors or growth factors alone were not included. Additionally experiments on animal and review articles were excluded.

Search strategy

An electronic search of literature in PubMed was carried out in December 2017, limited to English-language and human studies using a combination of following key words: stem cell, cleft alveolus, tissue engineering, cleft osteoplasty, alveolar cleft, engineered bone. No publication year limitation was applied. A total of 23 search results were returned. Primary selection of titles and abstracts was based on inclusion criteria and full texts of all eligible studies were obtained and reviewed by the authors. Manual search of the references of the eligible articles was done to obtain articles which met the inclusion criteria. (Figure 1)

necessary biological stimulus for bone regeneration in the cleft area (Khojasteh *et al*,2015). With the progress in cell culturing and time engineering it is obviously of interest to use these

Table 1 Summary of articles reviewed

S.No	Author	Type of study	Number of patients	Control used	Cells	Growth factor	Scaffold	Results
1.	Hibi et al 2006	CR	1	-	BM aspirate	PRP	-	Bone fill=79.1%
2	Michael Gimbel et al 2007	CS (21T, 48C)	69	1BG	BM aspirate of anterior iliac crest	-	Resorbable collagen matrix	Donor site morbidity least in test group
3	Pradel et al 2008	CR	1	-	Autogeous osteoblasts from maxilla	-	Resorbable bovine collagen matrix(osteovit)	Complete bony closure of cleft and spontaneous eruption of canine in right place happened
4	Hossein Behnia et al 2009	CR	2	-	BM aspirate of posterior iliac crest	-	Osteoset(calcium sulfate) + Demineralized bone matrix	Bone fill=34.5% and 25.6%
5	Winnie Pradel Gunter Lauer 2012	CS	8 (4C , 4T)	IBG	Autogenous osteoblasts from maxilla	-	Bovine collagen matrix	Cell group=40.9% IBG group=36.6%
6	Hossein Behnia et al 2012	CR	3 (4 sites)	-	Human MSC from posterior iliac BM aspirate	PDGF	Hydroxyapatite and Tricalcium phosphate scaffold	Bone fill= 51.3%
7	Stonko P et al 2013	CR	1	-	BM aspirate	Hydroxyapatite + PRP	Resorbable collagen membrane	Successful bone formation

CS- case series, C- control T-test, IBG-iliac bone graft, CR-case report, MSC-mesenchymal stem cells, BM-bone marrow, PRP-platelet rich plasma, PDGF- Platelet derived growth factor.

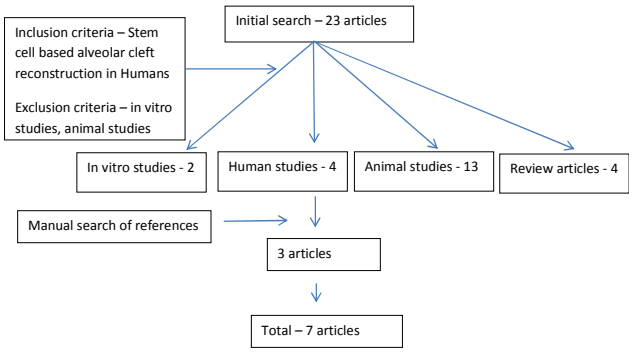

Figure 1 Search strategy

RESULTS

Of the 23 articles obtained from the search engine, 13 were on experiments done on animals, 4 articles were reviews and 2 were in vitro studies. 4 articles met the inclusion criteria. Manual search of the references of the 4 eligible articles was done which yielded 3 more articles which met the inclusion criteria. Finally 7 articles have been reviewed by the authors. (Table 1)

DISCUSSION

Along with being the most common congenital deformity, cleft lip palate and alveolus patients have various concerns, both functional and esthetics. Lack of bone in the alveolus causes unerupted teeth, loss of dental continuity, retarded maxillary growth, constricted maxillary arch, malocclusion, difficulty in mastication leading to poor nutritional status and poor oral hygiene (Vecchiatini *et al*,2009). Cleft patients also face esthetic problems due to depressed nasal bridge, deformed alar cartilage, widened nasal sil, deviated columella, missing teeth leading to unaesthetic smiles, poor self esteem, discouraging these patients from taking up jobs involving public speaking or interaction (Le *et al*, 2009). Restoring the bony defect in cleft patients requires a combination of osteogenic, osteoconductive and osteoinductive potentials to regenerate bone in an area where it is congenitally missing. Apart from autogenous bone, none of the other currently available grafts provide the new techniques in treatment of patients with cleft deformity. Additionally, the use of stem cells produces less donor site morbidity, reduces length of hospital stay and reduces overall cost of the procedure (Gimbel *et al*,2007). Tissue engineered bone consisting of a biomaterial seeded with autogenous cells in combination with growth factors has been successfully used in treating cysts or for augmentation of the alveolar ridge and for sinus floor elevation in rehabilitation of completely or partially edentulous jaws (Pradel*et al*,2012).

Cell source

Two major kinds of cells can be used- undiffentiated mesenchymal stem cells (UMSC) and diffentiated osteoblastic precursor cells. Literature suggests that UMSC enhance bone formation as compared to the differentiated cells. The use of bone marrow stem cells for bone regeneration is currently a popular practice. Their multilineage diffentiation potential, their relative availability in terms of cell harvesting and their capacity to undergo extensive replication without a loss of that multipotential capacity make them on attractive cell source for cell- based approaches (Lieberman *et al*,2002). All the studies we reviewed used mesenchymal stem cells of bone marrow aspirates from iliac crest except both the studies of PradelW. (2008, 2012) where the authors used autogenous osteoblasts from a maxillary biopsy. Harvesting cells from maxilla further reduces donor site morbidity as this can be done during previous lip or palate surgeries and cryopreserved (Pradel*et al*, 2008). This is an advantage in cleft patients as it reduces an additional surgery for harvesting cells. This is an important advantage in cleft patients as they need to undergo further surgeries for secondary correction of lip/nasal esthetics and suffer for many years with residual deformity and recurrent fistulas (Stanko *et al*, 2013).

Scaffold

An ideal scaffold material is one that resorbs at the same rates new bone formation occurs. If it resorbs too rapidly, it causes contraction of grafted site before new bone is formed, if it resorbs too slowly, it may delay new bone formation (Pradel *et al*,2008). Hossein *et al* in 2009 used a demineralized bone

matrix (DBM) combined with calcium sulphate (Behnia *et al*,2009). DBM has been reported to provide osteoinductive BMPs that signal precursor cells and stimulate bone formation at the defect site. Addition of calcium suphate increases structural strength and prevents early resorption of the DBM. But the authors noted comparatively less bone fill (34.5% and 25.6%) and concluded that DBM was not a suitable scaffold for MSC- induced bone regeneration. Alloplastic biomaterials such as hydroxyapatite and tricalcium phosphate may affect physiological processes such as tooth eruption and jaw development in growing individuals (Pradel *et al*,2012). Additionally alloplasts persist at the defect site and delay or hinder new bone formation. This could be the reason for reduced bone fill seen in the study of Hossein (Behnia*et al*,2012). Non resorbable calcium phosphate ceramics disturb tooth eruption and tooth development by initiating a dense cellular fibrous network at the grafted site (Feinberg *et al*,1989). A resorbable matrix scaffold is thus preferred. Four of the studies we reviewed (Pradel 2008, Pradel 2012, Gimbel 2007, Stonko 2013) used a resorbable collagen matrix as the scaffold. Literature shows that stem cells seeded onto a resorbable collagen matrix sponge has comparable results with autogenous grafting with regard to alveolar bone healing (O'Hara *et al*, 2004).

Growth factor

The role of growth factors in tissue engineered grafts is to provide osteogenic signals and induct osteoprogenitor cells at the defect site. A number of studies have used rhBMP-2 with or without scaffold or cells and have found high rate of success (Khojasteh *et al*,2015). The best result in bone regeneration at cleft defect was reported with the use of rhBMP-2 but the high cost of rhBMP-2 has discouraged its widespread clinical use (Dickenson *et al*,2008). Platelet rich blood substances which are autologous and much cheaper substitute to BMP, have shown to provide various growth factors like platelet derived growth factor, vascular endothelial growth factor, transforming growth factor, insulin-like growth factor, epithelial growth factor and recombinant human basic fibroblast growth factor. Literature shows successful bone formation in cleft defects with the use of platelet rich blood products (Khojasteh*et al*,2015). Three of the articles we reviewed (Hossein 2012, Hibi2006, Stonko2012) have used platelet derived substance as growth factors in their grafts. Hibi *et al* (2006) prepared an injectable gel form of the tissue engineered graft and reported a bone fill of 79.1% in one patient (Hibi *et al*,2006). Such high rate of success can be attributed to better adaptation of the injectable graft at the defect site and proportionally increased number percentage of cells due to absence of particulate scaffold material.

Evaluation Criteria

Most of the studies we reviewed assessed bone formation in terms of percentage fill of defect (Pradel 2012, Hossein 2012, Hossein 2009, Hibi 2006). The study by Pradel(2008) evaluated the success of bone formation by observing natural eruption of permanent tooth into the grafted bone. Stonko*et al* in 2012 showed successful bone formation on computed tomography in adult patient. They did not comment on percentage bone fill of tooth in the cleft site. Contrastingly, the study by Gimbel *et al* (2007) evaluated only the donor site morbidity with tissue engineered graft versus autogenous graft. These authors did not assess the success of bone regeneration at the cleft site. Such varied evaluation criteria makes it difficult to compare the results of each study. There is a need for standard evaluation criteria which measures not only the quantity of bone formed but also quality of bone formed in terms of natural eruption of teeth, orthodontic tooth movement or implant placement at the defect site.

Only 2 out of the 7 studies compared their results with controls (Pradel 2012, Gimbel 2007) of which one did not assess bone formation. The absence of control groups in the articles we reviewed (except Pradel 2012), is the most important criticism of all studies that have used stem cells for alveolar bone grafting. Without a control group, the studies were limited to case reports and case series, making it impossible to reach a consensus regarding the use of MSCs in cleft patients. A higher level of evidance is needed in the form of controlled clinical trials to identify the best approach for using regenerative medicine in cleft alveolar defects with minimal donor site morbidity.

CONCLUSION

Stem cell approaches are a promising step towards regeneration of bone in alveolar cleft defects with reduced or nil donor site morbidity. Further clinical studies are needed preferably with control and test groups to establish their effectiveness and efficiency over conventional methods.

References

Behnia H., Khojasteh A., Soleimani M., Tehranchi A., Khoshzaban A., Keshel SH., Atashi R. Secondary repair of Alveolar clefts using human mesenchymal stem cells. *Oral Surg Oral Med Oral RadiolEndod*. 2009; 108: e1-e6.

Behnia H., Khojasteh A., Soleimani M., Tehranchi A., Atashi R. Repair of alveolar cleft defect with mesenchymal stem cells and platelet derived growth factors. *Journal of Cranio-Maxillo-Facial Surgery* 2012; 40: 2-7.

Bertz JE. Bone grafting of alveolar clefts. *J Oral Surg*.1981; 39: 874-877.

Bergland O., Semb G., Abyholm F. Elimination of the residual alveolar clefts by secondary bone grafting and subsequent orthodontic treatment. *Cleft Palate J.*1986;23:175-205.

Dickenson BP, Ashley RK, Wasson KL, O'hara C, Gabbay J. Heller JB. Reduced morbidity and improved healing with bone morphogenic protein-2 in older patients with alveolar cleft defects. *Plast Reconstruct Surg* 2008; 121: 209-217.

Feinberg S.E., Weisbrode S.E., Heintschel G. Radiographic and histological analysis of tooth eruption through calcium phosphate ceramics in the cat. *Arch. Oral Biol*. 1989; 34: 975-984.

Freihofer HP, Borstlap WA, Kuijpers-Jagtmann AM, Voorsmit RA, Van Damme PA, Heidbuchel KL, Borstlap-Engels VM. Timing and transplant materials for closure of alveolar clefts: A clinical comparison of 296 cases. *J CranioMaxillofac Surg* 1993; 21: 143-48.

Gimbel M., Ashley RK., Sisodia M., Gabbay JS, Wasson KL., Heller J., Wilson L., Kawamoto HK., Bradley JP. Repair of Alveolar Cleft Defects: Reduced Morbidity With Bone Marrow Stem Cells in a Resorbable Matrix. *J CraniofacSurg* 2007; 18: 894-901.

Hibi H., Yamada Y., Ueda M., Endo Y. Alveolar Cleft Osteoplasty using tissue-engineered osteogenic material. Int.J.OralMaxillofac. Surg. 2006; 35: 551-555.

Horswell BB, Henderson JM.Secondary osteoplasty of the alveolar cleft defect. *J Oral MaxillofacSurg* 2003; 61:1082-1090.

Khojasteh A., Kheiri L, Motamedian SR., Nadjmi N. Regenerative medicine in the treatment of alveolar cleft defect: A systemic review of the literature. *Journal of Cranio-Maxillo-Facial Surgery.* 2015: 43: 608-1613.

Le BT., Woo I. Alveolar cleft repair in adults using guided bone regeneration with mineralized allograft for dental implant site development: a report of 2 cases. *J Oral MaxillofacSurg* 2009; 67:1716-1722.

Lieberman JR., Daluiski A., EinhornTA. The role of growth factors in the repair of bone.Biology and clinical applications. *J Bone Joint Surg Am.* 2002; 84-A: 1032-44.

OchsMW. Alveolar cleft bone grafting (part II):secondary bone grafting. *J Oral Maxillofac Surg*. 1996; 54:83-8.

O'Hara C, Sisodia M, Kawamoto HK. Bone marrow stem cells and resorbable collagen matrix heals alveolar cleft defects with reduced morbidity. 73rd Annual Meeting of the American Society of Plastic Surgeons. 2004, Philadelphia, October 9.

Pradel W., Lauer G. Tissue-engineered bone grafts for osteoplasty in patients with cleft alveolus. *Annals of Anatomy* 2012; 192: 545-548.

Pradel W., Tausche E., Gollogly J., Lauer G., Dresden, Penh P. Spontaneous tooth eruption after alveolar cleft osteoplasty using tissue-engineered bone:a case report: *Oral Surg Oral Med Oral Pathol Oral RadiolEndod* 2008; 105: 440-4.

Stanko P, Mracna J. Stebel A, Usakova V, Smrekova M, VojtassakJ. Mesenchymal stem cells- a promising perspective in the orofacial cleft surgery. *BratislLekListy* 2013: 114: 50-52.

Strietzel F.P. Tissue-engineered bone for lateral alveolar ridge augmentation: a case report. *Int. J.Oral Maxillofac. Implants* 2006; 21:131-135.

VanderasAP. Incidence of cleft lip, cleft palate, and cleft lip and palate among races: a review. *Cleft Palate J*.1987; 24: 216-25.

Vecchiatini R, Mobilio N, Raimondi F, Catapano S, CaluraG.Implant-prosthetic rehabilitation for a patient with monolateral cleft lip and palate: a clinical report. *Quintessence Int*.2009; 40:445-447.

How to cite this article:

Deborah Sybil., Kaleem Fatima and Sneh Lata Gupta (2018) 'Stem Cell Based Tissue-Engineering Approaches in Cleft Alveolus: A Systematic Review ', *International Journal of Current Advanced Research,* 07(1), pp. 9150-9153.
DOI: http://dx.doi.org/10.24327/ijcar.2018.9153.1500

****