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Tissue Engineering Options For Cleft And Surgical Cases – Changes and challenges- A Mini review

Dental Science

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ABSTRACT

Clefts of the lip and palate are the most prevalent congenital craniofacial birth defects in humans. The developing field of tissue engineering is considered for the management of clefts of the lip and palate along with wide bony defects in surgical orthognathic cases. Although the current approaches for the treatment of the cleft of the lip and palate include surgery and bone grafts; however, there are limitations associated with these therapies. Tissue engineering strategies particularly, alveolar bone engineering and soft tissue engineering, may provide clinicians with new alternatives. A tissue engineering approach may be a useful alternative for the treatment of cleft palates as it mitigates the concerns of donor site morbidity as well as provides additional options of growth factors delivery.

KEYWORDS:

cleft lip and palate, tissue engineering, bone grafts, growth factors

Introduction: The reconstruction of alveolar defects is well established, with the most widely accepted approach being secondary alveolar cleft osteoplasty in the mixed dentition phase with autologous bone grafting.The source material for most of the bone grafts has been particulate bone marrow harvested from the anterior iliac crest, and this represents the standard material with which other materials from the rib, mandible, calvarium and tibia are compared. Donor site morbidity is an important factor in deciding the site for harvesting cancellous bone. Allogenic and xenogenic materials can eliminate this concern but not the risk of disease transmission. Osteoinductive agents such as recombinant human bone morphogenetic protein-2 can solve these problems. Recently tissue engineering has become available as a regenerative treatment for bone defects, however, little has been reported on the application of tissue engineering for regeneration of cleft defect tissues.[1]

Tissue engineering strategies: The field of tissue engineering aims to restore function to or replace damaged or diseased tissues through the application of tissue engineering and biologic principles. These principles include the selection and manipulation of cells, design of scaffold matrices, and identification and use of pertinent biologic signaling molecules. The intended outcome of any implanted tissue engineered construct is a new tissue that is structurally and functionally into the surrounding host tissue. Repair of the bony defects continues to remain a challenging part of many reconstructive procedures. Currently the gold standard for grafting of bone defects is the use of autogenous bone. To avoid morbidity at the donor site or if large amounts of autogenous bone are necessary, bone substitution materials can be used.[2] The reconstruction of alveolar cleft defects is well established with the most widely accepted approach being secondary alveolar cleft osteolplasty in mixed dentition phase.3In conventional methods, autogenous bone grafting has become an essential step in treating the patients with alveolar clefts, and allows the placement of dental implants for the missing teeth in the final stages of the treatment.4 it also assist in preventing the maxillary segmental collapse, particulary in patients with bilateral clefts. Secondary grafting consistently produces trabecular bone to unify the maxilla and provides odontogenic support. Its high success rate makes it the preferred approach in most of the centers.[5]

1. Alveolar cleft osteoplasty using tissue engineered osteogenic material (TEOM): The use of tissue engineered osteogenic material comprising platelet – rich plasma and autologous mesenchymal stem cells isolated, expanded and induced to osteogenic potential in bone augmentation procedures as a replacement for autologous bone grafts, offers predictable results with minimal donor site morbidity. Use of tissue- engineered osteogenic material (TEOM), comprising autologous mesenchymal stem cells (MSCs) and platelet rich plasma(PRP) in bone augmentation procedures as a replacement for autologous bone grafts, offers predictable results with minimal donor site morbidity. Cells, cytokines and a matrix are three prerequisites for the tissue engineering and MSCs, PRP compounds are applied in the present TEOM.[6-9] The PRP contains not only fibrinogen that forms a fibrin network acting as a matrix but also chemical substances such as platelet derived growth factor, transforming growth factor beta, vascular endothelial growth factor and insulin like growth factor. These factors contribute to cellular proliferation, matrix formation, collagen synthesis, osteoid production, and other processes that accelerate tissue regeneration. TEOM regenerated the bone in the alveolar cleft defect without donor-site morbidity resulting from the autologous bone graft. Grafted bone remodels new bone due to apposition following resorption. As the bone regenerated in the cleft defect, the ingrowing bone seemed to accompany the roots of not only the canine but also the lateral and supernumerary incisors, which consequently approximated and erupted. Bone regeneration with the TEOM may therefore have helped to induce teeth to reposition properly in the horizontal and vertical planes. Younger patients have more MSCs and their harvesting, isolation and cryopreservation allows TEOM to be supplied repeatedly when needed. This repeatability will facilitate the sequential treatments of cleft patients in the future.

A. Use of human mesenchymal stem cells for secondary repair of alveolar clefts: [10,11] Mesenchymal stem cells which can be isolated from the marrow cavity as well as from the trabecular compartment, have been shown to have the ability to form new bone when transplanted. Bone marrow aspirated with resorbable collagen matrix reported to have reduced morbidity in repair of alveolar cleft defects. Bone substitution materials can be combined with vital cells such as MSCs to increase bone formation. Bone tissue engineering requires at least living osteoprogenitor cells or osteoblast –like cells in combination with suitable scaffolds for effective bone formtion. The use of MSCs for bone regeneration is currently becoming a popular practice. Their multilineage differential potential, their relative availability in terms of cell harvesting, and their capacity to undergo extensive replication without loosing their multipotential capacity make them an attractive cell source for cell based therapeutic approaches. Several experiments have demonstrated that MSCs can be induced to transform into osteoblasts. However directing these cells into osteogenic differentiation is still a major obstacle.

B. Using mesenchymal stem cells and platelet derived growth factors:[12] With the advent of invivo tissue engineering methods, mesenchymal stromal cells and osteoprogenitor cells were also considered as a possible treatment solution since they were capable of increasing the number of potentially osteogenic cells. Bone marrow aspirate soaked in absorbable collagen sponge was reported as an alternative method for the closure of the human alveolar clefts. Mesenchymal stem cells (MSCc) loaded on biphasic hydroxyapatite/ tricalcium phosphate (HA/TCP) showed enhancement of the bone regeneration in dog mandible defects. The MSCs loaded on biphasic calcium phosphate scaffolds revealed more bone formation than scaffold carried on PRP when combined with MSCs, the carrying capabilities and ectopic bone formation potency of biphasic bone substitutes were also reported to be more than natural bovine derived bone mineral . Lack of xenogenic growth factors such as foetal calf serum in the in vitro culture of human MSCs might have a weakening effect on bone formation. Combination of growth factors with human derived MSCs may strengthen these cells and encourage the clinical use of MSCs.

C. Perspectives and challenges of using plasma rich in growth factors in regenerative medicine:[13-15] Developing the strategies that promote tissue regeneration is the current effort of many scientific and clinical institutions worldwide and it has become also the fuel to promote the field of regenerative medicine. This new area of research deals with the development and application of innovative medical therapies focused on healing damaged tissues or regenerating the injured organs. The technology of plasma rich in growth favors (PRGF-Endoret) is an evolution of the pioneering approach developed by Eduardo Anitua to promote bone and soft tissue regeneration. Upon activation with calcium chloride or autologous thrombin, platlets pour out their growth factor content to the local milieu. In addition, the fibrinogen present in the plasma is cleaved to form fibrin and then crosslinked with factor XIII a, creating a three dimensional fibrin scaffold that retains part of the released protein content, maintains the regenerative space and serves as matrix for endogenous ells. Further advances in the field have enabled the development of therapeutic formulations that can be easily prepared, handled in the clinical setting.

From the therapeutic point of view, there are two major processes related with the potential of this technology. First is the release of hundreds of proteins and growth factors from the platelets that actively stimulate tissue regeneration. This pool of factors is added to the biologically active molecules already present in human plasma. Second is the formation of a three dimensional fibrin matrix that retains and later releases part of the growth factors, and which also acts as temporal nesting scaffold for the cells.

Therapeutic clinical applications in oral and maxillofacial surgery: The ability to properly formulate the platelets and growth factors in novel formulations has stimulated the research and use of this type of preparations in a wide range of medical fields including dentistry, oral implantology, ulcer treatments, eye disorders and ophthalmology among others. The use of autologous platelet rich products for tissue regeneration purposes represents a major advance in the concept of personalized medicine. The rationale of using plasma rich in growth factors is derived from the hypothesis that such preparation will increase the local concentration of growth factors, it will provide a temporal cell maintaining fibrin scaffold and thereby will activate the endogenous tissue regeneration machinery. Platelet rich preparations have been shown to be safe and effective in many different therapeutic applications. Nevertheless more intense research is needed to understand the molecular mechanisms that drive the different biological effects and to explore new potential therapeutic indications of platelet and plasma based technologies.

Conclusion: Tissue engineering strategies for cleft palate and surgical cases promise to deliver improvements in a way that bone defects such as cleft plalates are repaired. Although autologous bone is presently the preferred material for grafting procedures to repair a cleft palate by providing a scaffold on which bone cells can proliferate, thereby providing a reservoir of skeletal stem and progenitor cells that can form new bone. However autologous bone supplies are limited and procurement procedures can induce donor site pain and morbidity and can lead to anatomical and functional complications. Therefore the field of tissue engineering challenges these complications by providing an insight into alternative procedures which aim to restore function to or replace the damaged or diseased tissue through the application of engineering and biologic principles thus bringing about a change in the conventional approach in a practical and acceptable form.

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