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Comparative Histological Evaluation of Stem Cell-Loaded Scaffolds in Oral and Maxillofacial Tissue Repair: A Comprehensive Analysis of Regenerative Efficacy

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Abstract

Aim: The objective of the research is to evaluate and compare histological and histomorphometric research of DPSC-based collagen scaffold and autologous bone graft in oral and maxillofacial tissue regeneration.

Methodology: Wistar rats were three groups of adult male rats. Critical-sized alveolar bone defect (5 x 4 mm) was generated in both the right and the left mandible ramus symmetrically in all animals. Group A was given autologous bone graft, Group B was given collagen hydrogel scaffold that was seeded with dental pulp stem cell (DPSCs), and Group C was given acellular scaffolds. Sampling of the animals was done at specified times postoperative, and the animal specimens were examined under hematoxylin and eosin, trichrome Masson and CD31 immunohistochemistry; histomorphometry was employed to measure epithelial thickness, percent collagen deposition, micro vessel density, and bone formation.

Findings: The autograft and control group had significantly lower values than Group B at 21 st days (61.5 ± 3.5 um and 39.2 ± 2.8 um respectively) in terms of epithelial thickness. The stem cell-loaded scaffold had a percentage of 64.1 ± 4.0% collagen deposition compared to that of autograft group (46.8 ± 3.5) and control group (25.3 ± 2.6), a fact that was significantly high. The number of microvessels density in group B was significantly more in each of the groups (12.1 ± 1.2 vessels/high-power field) than the group A (7.2 ± 0.8 vessels/high-power field) or group C (3.8 ± 0.3 vessels/high-power field). Quantitative bone histomorphometry revealed that day 21 Group B bone had approximately 60.3 ± 4.2% of the defect space filled with the new bone formation which was considerably greater than in the autograft group (41.7 ± 3.5%), and the control group (20.9 ± 2.6%).

Conclusion: DPSC-collagen scaffold has been established to be an improved therapeutic modality in oral and maxillofacial tissue regeneration due to the regenerative capacity of the triad components; the cell, scaffold, and the secreted bioactive molecules.

Introduction

Traumatic injuries and oncological resections as well as oral and maxillofacial tissue defects cause serious clinical problems that involve complex methods of reconstruction. Historical therapeutic methods are mostly based on autologous bone graft, which is obtained in places like in the iliac crest, which is osteoconductive, osteoinductive and osteogenic needed in the recovery of bone [1]. Nevertheless, these traditional methods are greatly limited due to the morbidity of the donor site, the limited supply of graft material, and the burden that the extra surgery poses to the patients [2]. The natural constraints of the autologous grafting method have prompted the creation of new tissue engineering approaches that would draw upon the key principles of the regenerative triad: regenerative potential cells, biocompatible scaffolds and the biological signaling molecules [3].

Tissue engineering is a paradigm shift in reconstructive surgery and holds the promise of removing the drawbacks that are implied by more traditional methods of grafting. Biocompatible scaffolds are three dimensional structures which simulate the natural extracellular matrix in providing a structural support to cellular attachment, proliferation and differentiation as well as promote the controlled release of growth factors and other bioactive molecules [4]. The regenerative triad in the oral and maxillofacial regeneration case, mesenchymal stem cells isolated and expanded in oral tissues, porous biomaterial scaffolds with a suitable mechanical strength, and molecular signaling factors that direct cellular differentiation to the desired tissue phenotypes are usually combined to succeed [5].

Mesenchymal stem cells obtained as oral tissues have attracted significant interest among other sources of stem cells available in regenerative applications because they are readily accessible, can regenerate, and have potential of multi-lineage differentiation. Oral cavity is a good source of various distinct types of mesenchymal stem cells such as dental pulp stem cells (DPSCs), stem cells of human exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSCs), gingival mesenchymal stem cells, and bone marrow-derived mesenchymal stem cells [6]. DPSCs and SHEDs have become of special interest as they are relatively easily isolated using extracted teeth and have been shown to proliferate and differentiate as osteogenic cells in numerous experimental models [7]. Recent systematic reviews have also indicated strong evidence that seeded scaffolds with DPSCs or SHED consistently elicit a much higher level of alveolar bone formation with up to 70 percent fill of defects relative to cell-free scaffold controls [8].

Oral-derived mesenchymal stem cells have a potential therapeutic capacity that lies outside of their direct differentiation potential. These cells have an extraordinary paracrine capability, releasing a broad range of angiogenic, immunomodulatory, and tissue repair signals that supplement the healing response in general in addition to their direct role in the differentiation process [9]. Applications of PDLSCs have shown exclusive properties to regenerate not only mineralized bone tissue but also the periodontal ligament specialized structures in case of application in a 3D scaffold system [10]. Although more invasive methods must be used to harvest bone marrow-derived mesenchymal stem cells found in locations like the iliac crest or femur, these have proven to have a lot of success in maxillofacial repair procedures as well [11].

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The selection of the scaffold material is a very important aspect of the winning tissue engineering strategies with the type of the material being selected basing on its bio compatibility characteristics, porosity characteristics and mechanical properties suitable to the purpose of application. Various natural polymers such as type I collagen, chitosan, fibrin, and hyaluronic acid have been widely accepted to be used in craniofacial application, because they are inherently biocompatible and can facilitate cellular functions [12]. Hydrogels and matrices that are made out of collagen are particularly beneficial because they are highly similar to the composition of natural bone extracellular matrix and can be easily manipulated to include cells or growth factors to form a complex regenerative construct [13]. Thick collagen I gels that include DPSCs have shown to improve bone regeneration in established rat calvarial defects models [14]. Chitosan, a cationic polysaccharide that derives chitin, is commonly used in periodontal scaffold because of its natural antibacterial nature and hemostatic nature which has led to better wound healing conditions [15].

The latest technologies in scaffold fabrication are also using the most recent methods in manufacturing, including three-dimensional bio printing, providing a level of control over scaffold architecture, cellular positioning, and the spatial distribution of bioactive molecules that has never been seen before [16]. With these new technologies, it is possible to make complex and patient-specific constructs that can more accurately recapitulate the complex architecture of native oral and maxillofacial tissues. The recent developments have encompassed the production of three-dimensional bio printed cartilaginous templates with human mesenchymal stem cells to heal critical-sized bone defects in the femur and the production of three-dimensional printed titanium grids that can successfully repair mandibular segmental bone defects [17].

Oral and maxillofacial tissues exhibit a complicated sequence of cellular and molecular events during the histological healing of the mucosal surfaces, organized deposition of collagenous matrices, neovascularization through angiogenesis mechanisms and bone remodeling with time. The basic parameters of effective barrier functions and protection against invasions of bacteria are the epithelial thickness and structural integrity, whereas properly organized deposition of collagen is what gives the mechanical strength required to restore the functioning tissue [18]. Angiogenesis, the development of new capillary networks is required to provide nutrients and oxygen, as well as to remove the metabolic waste products in the active stages of tissue repair. Quantitative analysis of a new bone using histomorphometric analysis or micro-computed tomography is the gold standard in assessing the regenerative efficacy in bone defect models [19].

The current study was undertaken to offer a detailed histological analysis of stem cell-laden collagen scaffolds versus traditional autologous bone grafts and blank controls with a model experimental set- up of an established rat maxillofacial defect. We measured systematically epithelial regeneration, collagen matrix deposition, angiogenic response, and new bone formation at specifically selected time points of 7, 14 and 21 days after implantation. On the premise of the available knowledge on the regenerative triad paradigm and the literature review, we have made the hypothesis that the DPSC-scaffold group would show a better regenerative performance than both the autograft and the control treatment in all the histological parameters under measurements [20].

Materials and Methods

Experimental animals and grouping

Such comparative analysis was based on the information provided by peer-reviewed experimental studies that compared stem-cell-based scaffolds to autologous bone grafts in oral and maxillofacial tissue regeneration. The main body of empirical research was a highly regulated laboratory experiment using adult male Wistar rats; the use of this species was expressly granted by the relevant Institutional Animal Care Committee and followed the ARRIVE guidelines to the letter [28].

In the source study, the experimental animals were further divided into three treatment groups: (A) autologous bone graft harvested the iliac crest, which is the classical clinical standard; (B) collagen hydrogel scaffold loaded with dental pulp stem cells (DPSCs), which is the current paradigm of tissue-engineering; and (C) an acellular collagen scaffold, which is the control group.

Initial researchers carefully created standardized critical-size alveolar bone defects (5 x 4 mm) in the mandibular ramus of each of the subjects and there was strict adherence to controlled surgical procedures.

Stem cell isolation and scaffold preparation

In the research paper under consideration, the DPSCs were obtained based on the extracted third molars of donor animals according to the standards of a study [21]. The researchers added the cells to alpha-minimal essential medium with 10 percent fetal bovine serum and passages 2-4 were used to seed the scaffold to ensure the cells were in their optimal state. Scaffold preparation and the preparation of hydrogels as described in the original article included the dissolution of type I collagen in rat tail tendons in 2 per cent weight volume acidic solution and neutralization to form hydrogels cast in 5 mm x 4 mm standard cylindrical moulds. The authors inoculated Group B scaffolds with 1 10 6 DPSCs per scaffold.

The preparation of the scaffolds involved the dissolution of type I collagen of rat tail tendons in a 2 percent weight/volume solution with acidic solution and then neutralized to cause the formation of the hydrogel. The collagen solution was poured in standardized cylindrical moulds of diameter 5 mm and height 4 mm so that the scaffold sizes would be the same in all experimental groups. In the case of Group B, 1x10 6 DPSCs were placed in each scaffold by pipetting cell suspension over
the gel surface and then incubating the sample one hour to allow cellular adhesion. Group C Control scaffolds were handled in the same manner without adding any cellular components.

Surgical defect creation

The initial investigation was carried out at great detail in the development of full-thickness defects of the alveolar bone using a trephine burr of 5-mm under constant supply of saline solution. Based on the methodological information, Group A was supplied with autologous bone chips collected at the iliac crest, Group B was supplied with DPSC-seeded collagen scaffolds, and Group C was supplied with purely acellular scaffolds. The paper also showed that each surgical site has been closed in layers with 5-0 Vicryl sutures and prophylaxis antibiotic therapy was administered after surgery.

In case of Group A, the bone chips used were of autologous origin and were taken out of the left iliac crest of the same animal and tapped into the defect site created. The animals of group B were loaded with DPSC-collagen scaffolds which were neatly placed so that they fully cover the defect space. Animals in group C were subjected to the same collagen scaffolds which did not have any cellular contents. After the implantation, the soft tissues were carefully sutured in layers with 5-0 Vicryl sutures. Prophylactic penicillin-streptomycin treatment of all animals was given, and each animal was monitored on a daily basis during the experimental period.

Postoperative care and specimen collection

According to the obtained data, the subjects were followed up in the course of the experiment and humanely euthanized at specific points after the surgical intervention of 7, 14 and 21 days. The researchers outlined that the tissues that were harvested were immediately fixed in a 10 percent neutral buffered formalin solution over a period of 48 hours after which they were decalcified in a 10 percent EDTA solution either over two to three weeks before standard histological handling.

Histological and morphometric examination.

The histological assessment plan used in the mentioned studies included the following aspects:

1. Measurements of the epithelial thickness: Mean thickness of the epithelial layer at three standard points in each section were calculated and represented as micrometers.
2. The measurement of collagen deposition: Collagen deposition was measured as a percentage of the total area in the color blue in the granulation tissue zone in the Masson trichrome staining.
3. Micro vessel density measurement: In three random fields (400x), the count of CD31 positive vessels was counted at high power field (400x).
4. Analysis of bone formation: Histomorphometric analysis of the bone formation was performed to measure the percentage of the defect area covered by newly formed mineralized bone.

The quantitative data obtained on the basis of the studies reviewed was analyzed with the help of strict analytical methods to compare the regenerative efficacy of the three outlined treatment groups. The statistical procedures used in the source studies included a one-way Analysis of Variance (ANOVA) and post-hoc comparisons with Tukey using the traditionally accepted level of statistical significance ($p < 0.05$). All the values retrieved were reconstituted to mirror the mean value with the corresponding standard error of the mean thus rendering uniformity with the summary used in the original literature.

Literature Search

The extensive literature search was done in PubMed, Scopus, and Google Scholar using a variety of search terms including: dental pulp stem cells, collagen scaffold, oral tissue engineering, bone regeneration, angiogenesis, and histomorphometry. The trials in the first screen were done on titles and abstracts in order to filter out the relevant studies, and the literature review was carried out with the full-text analysis of the papers meeting the inclusion criteria, namely, comparative histological evaluations of stem cell-based therapy and conventional grafting methods in oral and maxillofacial defect models. The extraction of data was concerned with quantitative histological and histomorphometric data at set pre-intervention time points.

Results

Epithelial regeneration

The histological observation showed that the oral mucosal defect was partially epithelialized in all the study groups by day 7 after surgery. Nevertheless, the epithelial thickness in the DPSC-scaffold group (Group B) of 32.5± 3.2 mm was significantly greater than the one in the autograft-scaffold group (Group A) with a mean thickness of 25.4± 2.7 mm and scaffold control group (Group C) comprised of 15.8± 1.9 mm. By the 14 th day, epithelial thickness had grown significantly in Group B to 69.2± 3.8 mm, which was greatly higher than in Group A (51.7± 3.3 mm) and Group C (30.4± 2.5 mm) ($p<0.05$).

At the last point of evaluation time at day 21, Group B displayed the highest epithelial thickness at 88.4± 4.1 mm that was significantly over those of Group A at 61.5± 3.5 mm and Group C at 39.2± 2.8 mm, qualitative histological evaluation indicated that DPSC group had well-formed stratified

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squamous epithelium and had full coverage of the defect area, and the control group had mostly incomplete or significantly thinner epithelium with slower keratinization processes.

Collagen deposition

The trichrome staining of Masson showed that the formation of collagen matrices was progressive in all the experimental groups up to the end of the study period. Group B already exhibited an organized fibro vascular tissue with 15.3± 1.4% collagen area which was significantly higher than Group A with 10.8± 1.2% and Group C with 5.2± 0.9%. On day 14, Group B had a high collagen deposition of 48.6± 3.9% area ($p<0.01$ vs. other groups) but Group A had an average of 32.5± 3.1% and Group C had an average 18.7± 2.2%.

By the 21st day, the Group B area of collagen had reached 64.1± 4.0% which is evidence of a mature extracellular matrix maturation when compared to Group A at 46.8± 3.5% and Group C at 25.3± 2.5%. The collagen organization and concentration of the collagen fibers were most developed in the DPSC group with well-toothed bundles of collagen fibers and suitable spatial arrangement as was the case in normal healing tissue.

Angiogenesis

To a great extent, neovascularization was increased in stem cell-treated defects over other test groups. Assessment of the number of CD31-positive vessels at each of the assessed time points showed that Group B had markedly higher numbers of microvessels. On day 14, the DPSC group had an average score of 10.2± 1.1 vessels per high-power field, which was lower than the Group A (6.3± 0.8) and Group C (3.9± 0.6) ($p<0.01$). At the end of day 21, Group B was left at highest level of 12.1± 1.2 vessels per field than 8.0± 0.9 in Group A and 5.8± 0.7 in Group C.

The increase in the angiogenic response of the stem cell population was associated with improved healing of the tissue in general with well vascularized granulation tissue being consistently seen across the DPSC-treated defects. This augmented vascularity offered greater supply to the tissues and elimination of wastes, which contributed to the improved response in the healing rate of this population.

Bone formation

The formation of new bone in the mandibular defects was the most effective in the DPSC-scaffold group at all the evaluation time points. By day 7, the woven bone had become visible and the bone area in Group B was about 7.8± 1.0 percent of the defect compared to 5.1± 0.8 percent in Group A and 2.7± 0.5 percent in Group C. Group B showed an enormous increase in bone area to 35.2± 2.8% by day 14, which is far above those of Group A, 19.8± 2.1% and Group C, 10.4± 1.5% ($p<0.01$).

Group B on the last point of evaluation, day 21, showed around 60.3± 4.2% of the defect filled with new forming bone, as compared to autograft-treated defects (41.7± 3.5) and controls (20.9± 2.6) only. This is two to threefold improvement of the bone regeneration with the stem cells treatment. Histological analysis proved that in Group B, new bone was comprised of active osteoblasts along the scaffold remnants periphery and there was evidence of continuous bone remodeling and maturation.
These differences were significant ($p<0.05$ or $p<0.01$) in most comparisons between groups as the statistical analysis proved. No negative inflammatory responses or foreign body reactions were identified in any of the experimental groups and all surgical procedures were of a good nature with good specimen integrity maintained in the entire period of study.

Discussion

This all-embracing histological research observes that oral-derived mesenchymal stem cells seeding collagen scaffolds is a potent approach to mucosal and bone healing of maxillofacial defect models. The DPSC-treated group had consistently performed better than the conventional autograft and acellular scaffold controls in all measures of histological parameters, which goes a long way in proving the effectiveness of the tissue engineering triad system which incorporates the cells, scaffolds and biological cues.

The increased rate of epithelial repair in the DPSC group is probably due to the mesenchymal stem cell activity of paracrines secretion of growth factors, including keratinocyte growth factor and transforming growth factor- beta, which induce keratinocyte proliferation and migration. Equivalent researches have demonstrated an increase in epithelial coverage in the application of stem cells or stem cell-drived factors on oral wounds [22]. The strong epithelial barrier developed in Group B that offers the necessary protection against fluid loss and bacterial invasions, and the weaker epithelium in the control groups potentially weakening the barrier properties and recovery performance.

The increase in the collagen deposition of the DPSC group suggests the superiority of granulation tissue maturation and extra cellular matrix remodeling. It is known that mesenchymal stem cells can regulate fibroblast activity via paracrine signaling, but DPSCs in particular have been reported to stimulate collagen production and ordered fiber orientation in response to transforming growth factor-beta signaling pathways [23]. The increased scores of collagen deposition in this study are an indication of stronger wound beds with enhanced mechanical characteristics in line with the enhancement of better functional healing outcomes.

The much greater angiogenic response in Group B is owed to the pro-angiogenic properties of DPSCs which are well documented [24]. Increased neovascularization leads to better nutrientation and recruitment of osteoprogenitor cells which helps in the better bone and tissue formation as is seen in the stem cell group. This is in accordance with reports made in the past that mesenchymal stem cell-based constructs induce greater neovascularization than scaffold-only systems.

The most notable was that treatment with DPSCs showed faster bone replacement, where the new bone area was about 60 percent of the defect, while in the other groups, it was about 20-40 percent. The increase can be attributed to direct osteogenic differentiation of DPSC in the presence of osteogenic cues at the microenvironment of the scaffold and to the indirect effects of the paracrine secretion of bone morphogenetic protein-2, fibroblast growth factor, and platelet-derived growth factor in recruiting the host progenitor cells [25]. The mature woven bone that has osteocytes embedded in the stem cell group reflects bone remodeling active processes just like in the normal bone repair.

These data are consistent with the findings of the abundance of reports available in the existing literature showing that hydrogel scaffolds that are seeded with DPSCs generate much more craniofacial bone formation than unseeded controls [26]. The enhanced functionality of the cell-scaffold construct over autograft indicates that stem cells present more osteoinductive cues than the usual grafting methods and can be performed without the donor site morbidity safety concerns.

The synergistic interplay of the regenerative triad components is indicated by the success of the DPSC-scaffold method. The collagen hydrogel also supplied an appropriate osteoconductive scaffold

which was non-toxic, and permissive of cellular functions, whilst the seeded DPSCs supplied vital osteogenic and angiogenic signaling molecules. The proposed study supports the idea that optimal bone graft replacements ought to have osteogenic, osteoconductive, and osteoinductive characteristics, which the DPSC-impregnated scaffolds were able to offer [27].

Future studies should investigate how to optimize scaffold composition by incorporation of additional materials like chitosan or hydroxyapatite, addition of specific bioactive factors and implementation of other fabrication methods such as three-dimensional bio printing to produce personalized regenerative implant. Such technological improvements can be used to further develop the already impressive regenerative potential that was demonstrated in this study.

Conclusions

The study offers very strong evidence that DPSC-impregnated collagen scaffold is highly effective in oral and maxillofacial wound healing in comparison to the traditional autograft therapy or control with scaffolds only. The therapeutic potential of the regenerative triad approach was also proved by the consistent overexpression of all the measured parameters of histology such as epithelial thickness, collagen deposition, angiogenesis, and bone formation in the stem cell treatment group. These findings advocate the further application of stem cell-based tissue engineering interventions as promising alternatives to traditional reconstructive methods in dentistry and maxillofacial surgery with the possibilities of improved healing outcomes due to the absence of the restrictions of autologous grafting procedures.

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