CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
http://doi.org/10.5281/zenodo.2632666

Available online at: http://www.iajps.com *Review Article*

EFFICIENCY OF USING DENTAL PULP STEM CELLS IN PULP REGENERATION TREATMENT

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Article Received: February 2019 **Accepted:** March 2019 **Published:** April 2019

Abstract:

Infection of the dental pulp will cause inflammation and at some point, tissue necrosis which is dealt with traditionally by pulpectomy and root canal treatment. Advances in regenerative medicine and tissue engineering together with the introduction of new sources of stem cells have resulted in the opportunity of pulp tissue regeneration. In this review we discuss about stem cell sources and their usage in medicine and specifically in dental field. We conducted a literature review of articles published up to 2018, in following databases; PubMed, and Embase overviewing the dental pulp stem cells in pulp regeneration treatment. It is essential to recognize that endodontic therapy of teeth with necrotic pulp using stem cells as well as appropriate biomaterials lead to pulp regeneration. Nevertheless, feasibility of stem cell transplantation to therapy sites together with its cost might be challenges for medical use of such methods. Scafolds and biomaterials supply a purposeful strategy to far better include stem cells and development factors in addition to regulated rate of regeneration. As a result, we recommend future studies to concentrate on providing a clear guideline for appropriate as well as better features of biomaterials to be made use of in regenerative endodontics.

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Please cite this article in press Faisal Mubarak Hussain Al Qahtani et al., ***Efficiency of Using Dental Pulp Stem Cells in Pulp Regeneration Treatment.,*** *Indo Am. J. P. Sci, 2019; 06(04).*

INTRODUCTION:

Since Kakehashi et al. reported that bacteria triggered pulpitis in their mouse experiment in 1965, endodontic therapy has created with the goal of the full removal of bacteria from the root canal [1]. It was thought that, when revealed to bacteria, the dental pulp would come under a state of irreversible pulpitis that could never ever be recovered to the regular state and that the development of inflammation would certainly lead to death. Therefore, the dental pulp tissues that are harmed due to bacterial intrusion or dental trauma should be eliminated. The traditional root canal therapy focuses on three-dimensional mechanical preparation, disinfection, and the limited sealing of the root canal space to totally get rid of the dental pulp and bacteria in the root canal and prevent reinfection. Nonetheless, this treatment is only an action targeted at fixing as opposed to true healing/regeneration. Hence, lots of researches have been carried out in the field of dental endodontics with the purpose of pulp regeneration.

Two techniques have been embarked on for dental pulp-dentin complex regrowth. The very first approach is the revascularization procedure. Numerous case reports have found scientific success complying with revascularization treatments, as an example, no signs and no periapical lesions [2], [3]. Nonetheless, the histological monitorings from animal experiments have revealed that the tissues created in the root canal do not reflect the regeneration of pulp-dentin however are instead formed of periodontal tissues, such as cementum, periodontal ligament, and bone [3]. The revascularization procedure has its own clinical advantages in the therapy of premature teeth; however, it does not lead to pulp-dentin complex regeneration in truth sense.

The 2nd method for regenerating the dental pulp-dentin complex is the transplantation of mesenchymal stem cells into endodontically treated canals. In the last few years, numerous stem cells have been isolated from the oral cavity. In 2000, Gronthos et al. separated dental pulp stem cells (DPSCs) from human 3rd molars for the first time, and these DPSCs were identified as extremely proliferative cells with self-renewal multidifferentiation characteristics in vitro [4]. The dental pulp is vascularized and characterized by innervated loose connective tissue that contains heterogeneous cell populaces [4]. Because of the complexity of pulpal tissues, no generally approved procedures or cell types are currently available to examine pulp regeneration. Nonetheless, a consensus exists relating to the significance of neural and vascular reinnervation for effective pulp regeneration [2]. DPSCs that show pluripotent mesenchymal stem cell qualities can be quickly isolated from teeth [5]. For that reason, the strong angiogenic and neurogenic possibilities of DPSCs have drawn in much interest in the research of pulp regeneration [5].

Infection of the dental pulp will cause inflammation and at some point, tissue necrosis which is dealt with traditionally by pulpectomy and root canal treatment. Advances in regenerative medicine and tissue engineering together with the introduction of new sources of stem cells have resulted in the opportunity of pulp tissue regeneration. In this review we discuss about stem cell sources and their usage in medicine and specifically in dental field.

METHODOLOGY:

We conducted a literature review of articles published up to 2018, in following databases; PubMed, and Embase overviewing the dental pulp stem cells in pulp regeneration treatment. We restricted our search to only English published articles with human subjects concerning. More studies were recruited from scanning the bibliography of found studies to have more support evidence.

DISCUSSION:

- **STEM CELLS**

Banking of stem cells

There is an abundant source of adult stem cells in the human exfoliated deciduous teeth (SHED). Current studies have shown that SHED has the capacity to turn into even more kinds of body tissues than other types of stem cells. Researchers have discovered the pulp of exfoliated deciduous teeth to consist of chondrocytes, osteoblasts, adipocytes, and mesenchymal stem cells. All of these cell types hold enormous possibility for the therapeutic treatment of: Neuronal degenerative ailments such as Alzheimer's, Parkinson's, and ALS (Amyotrophic Lateral Sclerosis or Lou Gehrig' Disease); chronic heart conditions such as congestive heart failure and chronic ischemic heart disease; periodontal disease and to grow replacement teeth and bone [6].

Maintaining this premise in mind, the idea of the tooth banking has promoted, and different companies have actually set up tooth banks to tap the potential of this new and cutting-edge strategy for protecting SHED and stem cells from other dental resources [6]. Hence the ultimate key to effective stem cell therapy is to harvest cells and store them securely up until

accident or ailment requires their use. The tooth banking is not very popular, but the trend is catching up, mostly in the developed countries. Likewise, it is now been shown that the primary teeth are a much better source of restorative stem cells for usage in regenerative medication than wisdom teeth, and orthodontically extracted teeth [7].

Dental stem cells isolated from various parts of the teeth are

1. SHED.
2. Adult dental pulp stem cells (DPSC).
3. Stem cells from the apical part of the papilla (SCAP).
4. Stem cells from the dental follicle (DFSC).
5. Periodontal ligament stem cells (PDLSC).
6. Bone marrow derived mesenchymal stem cells (BMSC).

Advantages of SHED banking [7].

1. Provides an autologous transplant for life.
2. Simple and painless procedure.
3. SHED cells are complementary to stem cells from the cord blood.
4. Useful for close relatives of the donor.
5. Not subjected to the same ethical concerns as embryonic stem cells.

A new method to cryopreserve DPSC inside a whole tooth was recommended by Silvia and also partners. They showed the feasible evasion of purification of the cells before cryopreservation as well as decreasing the initial prices and workload of the tooth banking. They further showed that DPSC isolated from laser pierced cryopreserved teeth show mesenchymal stem cells morphology, immune-phenotype, viability and also proliferation rate similar to those of the cells separated from fresh, non cryo-preserved teeth, whereas significant loss of the cell viability and proliferation rate was shown by the cells isolated from teeth cryopreserved without laser piercing [7].

It is essential to keep stem cells that can serve as an essential source of biological components for both fundamental and also sophisticated research projects. There are different stem cell banks, storage spaces that protect and also preserve morally sourced stem cell acquired from various beginnings [8]. Current past has shown worldwide campaigns to resolve administration and also standardization processes for the stem cell research and also banking. The "International Society for Stem Cell Research and also the International Stem Cell Banking Initiative" is just one of the pioneers of this program [9]. These banks also offer to freeze the dental stem cells of baby teeth when the anterior primary tooth is shedding (DPSC is preferred for storage). The tooth is removed by the dental expert as well as well maintained in a special kit given individually from the stem cell bank. This assembly is then moved to their special labs to harvest the dental stem cells and also keep them in their bank for each child confidentially until they are required later for the child himself or a participant of his family. In India, 'Life Cell International', was the initial private sector stem cell banking services began in Bangalore (India) in the year 2009.

Initially, via individual and also corporate techniques, fees for collecting and also saving the stem cells were hardly affordable (approximately 3000 USD); that is why it might not obtain much promo in India [7].

Certified tooth stem cell banks, Worldwide and also in India, made use of for cryopreservation as well as isolation is as follows [6].

1. In Japan, the first tooth bank was established in Hiroshima University and the company was named as ‘Three Brackets’ (Suri Buraketto).
2. BioEden (Austin, Texas), StemSave, and Store-a-Tooth (USA)
3. The Norwegian tooth bank.
4. In India, Stemade Biotech Pvt. Ltd. (Delhi, Chennai, Chandigarh, Pune, and Hyderabad).

Dental pulp stem cells

In all research studies making use of DPSCs, they isolated the stem cells from human healthy pulp tissue to be made use of in their animal model, generally from orthodontically removed teeth, for example third molars were commonly utilized [10]. Alongi et al. reported that infamed pulp tissue was a suitable source for isolation of DPSCs [11]. In their research study infamed pulp-derived stem cells exposed a capability for regeneration of the dentine-pulp complex, albeit the regrowth was weak compared with the control group where the cells were derived from intact pulps [11]. It has actually additionally been reported that stem cells from a subjected pulp are a lot more vulnerable to diferentiate right into osteoblastic cells instead of dentinogenic cells [12].

Stem cells from apical papilla

As a component of a creating tooth, the stem cells of the apical papilla (SCAP) have a better stem capability [13], [14]. Stem cells of the apical papilla are known for a lot more quick spreading and mineralization, better movement and also telomerase activity than DPSCs [14]. Wang et al. reported

deposition of more uniform dentine-like tissue produced by SCAPs than DPSCs with better similarities to natural dentine [13]. Stem cells of the apical papilla were typically isolated from immature third molars.

Periodontal ligament stem cells

Periodontal ligament stem cells (PDLSCs) have been used to develop PDL (periodontal ligament) in studies trying to restore a new bio-root [15]. They accomplished a bio-root with an ideal PDL tissue using a combination of DPSCs as well as hydroxyapatite, which were covered by a sheet of PDLSCs. These newly produced roots in small pigs had comparable high qualities to all-natural teeth in both mineral element and also biomechanical features however effective outcomes were accomplished in only one-fifth of the samples while titanium implants were 100% successful [15].

Stem cells from human exfoliated deciduous teeth
Stem cells from human exfoliated deciduous teeth (SHED) are another kind of stem cell, which are derived from drawn out deciduous teeth and also are taken into consideration as a non-invasive resource of stem cells [16]. These stem cells have a boosted capacity for osteogenic regeneration and also greater spreading rate compared to DPSCs [14].

Bone marrow derived mesenchymal stem cells

Bone marrow obtained mesenchymal stem cells (BM-MSCs) are one more resource that has actually been used thoroughly in regenerative procedures [17]. Use such cells with a dentine matrix scafold was related to distinction of the stem cells right into polarized odontoblast-like cells with penetrating processes into dentinal tubules [17]. However, harvesting these cells from human resources is an invasive procedure as well as its primary medical application is in orthopedic research study [18]. At the same time, Zhang et al. suggested making use of endogenous BM-MSC for restoring shed tissue after observing its systemic homing to the root canal, powered by application of stromal cell obtained factor-1 (SDF-1), in a subcutaneously transplanted tooth with an origin canal [19].

Adipose-derived stem cells

Hung et al. utilized adipose-derived stem cells (ADSCs) because of their huge population in mammals and higher rate of spreading with comparable outcomes to DPSCs in tooth regeneration [20]. While gathering DPSCs is achieved mostly from the healthy pulp of a tooth, use ADSCs could be more convenient. Murakami et al. reported that in spite of the prevalence of DPSCs, sufficient ADSCs and also bone marrow obtained mesenchymal stem cells could be considered as an option to DPSCs [21].

Umbilical cord mesenchymal stem cells

Umbilical cord mesenchymal stem cells (UCMSC) are available in huge quantities without invasive harvesting processes and also are stored in worldwide stem cell banks [18]. They reported UCMSC capacity for distinction right into odontoblast-like cells and deposition of tough tissue. Notably, these cells are taken into consideration secure as they are safeguarded from viral infections by the placenta, which has a significant medical value [18].

• DPSCs and TISSUE REPAIR

It is known that MSCs are associated with growth, injury healing, as well as cell substitute under both physiological and pathological conditions. These cells have been revealed to be efficient in regenerating periodontal tissue, diabetic critical limb ischemic tissue, bone damage triggered by osteonecrosis, skin lesions triggered by burns, liver, neuronal and also skeletal muscle tissue, as well as blood vessels among other tissues [22]. Regarding DPSCs, their capacity to separate right into odontoblasts was a significant boon for their usage in tooth-tissue engineering, however expanding evidence that these stem cells were likewise efficient in repairing extraoral tissues, for instance, tissues of the musculoskeletal system, because of their similarities to bone marrow-derived MSCs, has caused their currently being recognized as one of the most accessible and also attractive multipotent MSCs, with high rates of growth, for usage in engineering cells and in regenerative medicine [23].

• PERIODONTAL REGENERATION WITH DPSC

Among one of the most usual chronic transmittable disorders, impacting approximately 90% of the population worldwide, is periodontal disease (PD) [24]. At the periodontal level, repair involves healing an injury also without totally restoring the initial architecture or tissue function. On the other hand, regrowth entails recreating lost or damaged component, to ensure that the original performance is totally restored. The PD type, called periodontitis, appears by the progressive damage of the structures sustaining the teeth and also is a major cause of missing teeth in adults [25]. Therefore, when it comes to periodontitis, periodontal regeneration would certainly entail the full restoration of all the elements of the periodontal ligament, consisting of periodontal and gingival connective tissue, cementum, and alveolar bone, which is an obstacle in medical practice, since when histological tests

showed good regrowth, the new tissues resembled the lost tissues but had various qualities, although, in many cases, regeneration of the periodontal ligament stopped working in between the neoformed tissue and bone cementum [25].

Current regeneration protocols, such as those utilizing autologous bone grafts, allografts, or alloplastic products, additionally have limitations since they normally cause tissue repair but not in true regeneration and can not be made use of in all clinical situations [26]. Thus, these methods, although promising, are far from a clinical certainty. Various other procedures such as the addition of development and distinction elements and anti-inflammatory molecules generated favorable outcomes by inducting periodontal regeneration, however the average half-life of these elements is short, which restricts their use in regenerative therapy [27].

Preclinical research studies have shown that DPSCs, isolated from human third molars and transplanted right into immunodeficient mice and rats, differentiated right into cementoblast-like cells, adipocytes as well as collagen forming cells with the capacity to create material similar to periodontal tissue cement [26]. The expression of STRO-1, CD146, and CD44 has actually been observed in cells involved in periodontal regeneration, and also Du et al. revealed that SDF-1 was an added sign of periodontal tissue regeneration [27].

Researches have actually shown that it is possible to create complex structures such as pulp-dentine, root cementum, and also the periodontal ligament, by transplanting DPSCs right into immunocompromised mice, and that these cells might be associated with the repair processes that happen within periodontal defects produced in rodents. There are additionally reports showing that SHED cells have the ability to stimulate bone development, which increases the opportunity that they could be made use of to induce bone craniofacial bone regeneration [28]. However, although these and also various other experimental animal data supplied clear evidence of the capacity of DPSCs to generate the development of dental tissues, clinical trials using DPSCs have not been commonly reported [30]. D'Aquino et al. reveal that human autologous DPSC/collagen sponge biocomplex implants restore the mandibular bone tissue of patients [32].

Interesting is that medical analysis, performed 3 years after implantation of autologous human DPSC, has shown that performance of oral cavities, mandibles, and also mucosal membranes was typical as well as no alterations were observed; however, a detailed histological research and also a sophisticated in-line holotomography revealed that regenerated tissue from the graft sites was composed of a completely small bone uniformly vascularized and with a high matrix density, instead of a spongy kind that is physiological for the space; thus, the bone restored was entirely various from regular alveolar bone. Authors suggest that this is probably due to the fact that grafted DPSCs do not follow the local signals of the bordering spongy bone [72]. Just recently it was found that pretreatment of DPSCs with valproic acid (VPA), a selective inhibitor of histone deacetylases (HDAC), substantially improves mineralized matrix formation, raising the expression of bone glycoproteins associated with the development of the mineralized matrix and adversely impacting late-stage markers of distinction [29]. This recommends that regulating the response of stem cells to epigenetic modifications might be the key to regeneration with DPSCs, efficiently creating complex structures (a true regeneration), and not just does it bring a tissue that appears like the initial, such as what is accomplished making use of the tissue engineering approaches offered today. Whether, as suggested by Jo et al., application of epigenetic regulators, for instance, HDAC inhibitors, may be valuable for stem cell-based interventions is an issue that is worthy of far more focus in the future [29], [31].

CONCLUSION:

It is essential to recognize that endodontic therapy of teeth with necrotic pulp using stem cells as well as appropriate biomaterials lead to pulp regeneration. Nevertheless, feasibility of stem cell transplantation to therapy sites together with its cost might be challenges for medical use of such methods. Scafolds and biomaterials supply a purposeful strategy to far better include stem cells and development factors in addition to regulated rate of regeneration. As a result, we recommend future studies to concentrate on providing a clear guideline for appropriate as well as better features of biomaterials to be made use of in regenerative endodontics.

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