REVIEW ARTICLE

The Implication of Stem Cells in Direct Pulp Capping: Where Do We Stand?

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Abstract

Direct pulp capping has been established as a more conservative alternative to root canal therapy, especially in case of an iatrogenic or traumatic exposure of the dental pulp. However, recent literature focuses on regeneration therapies to develop a physiological dentin barrier. The process of tissue regeneration through stem cell therapy involves a complex interaction between stem cells, growth factors and scaffolds known as the 'tissue engineering triad'. Recent advancements in stem cell therapy focus on the re programming of stem cells, development of scaffolds and enhancement of the regenerative potential of these stem cells, using appropriate growth factors and transfer media. This article provides a summary of the current evidence regarding the use of stem cell therapy in direct pulp capping. The sources of stem cells, types of scaffolds and growth factors have been described in detail along with the limitations and future prospects.

Keywords: Tissue Engineering, Stem Cell, Transplantation, Dentin, Iatrogenic Disease.

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Introduction

An exposure of the dental pulp may occur as a result of trauma, caries, or due to an iatrogenic cause 1 This breach in the dentin-pulp complex leads to inflammation of the pulp, which can progress to pulp necrosis and apical periodontitis.2 Root canal therapy is indicated to arrest the inflammatory process and the treated tooth often requires an additional coronal restoration.[1,2] A more conservative alternative is the management of pulp exposures through Direct Pulp Capping (DPC).[3] The objective of this procedure is to seal the exposed pulp from bacterial infiltration and facilitate the formation of a hard tissue barrier over the exposure site, thereby maintaining the vitality of the pulp tissue.[2,3] As a result, DPC provides a more conservative alternative to root canal treatment.[1]

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Ideally, the material used for DPC should be biocompatible, anti-bacterial and provide an adequate seal.[3] Considering this, Calcium Hydroxide was most commonly used to seal the exposed dental pulp, however, there were frequent reports of 'tunnel defects' in the newly formed dentin barrier when Calcium Hydroxide was used, moreover, the Calcium Hydroxide dissolved with time.[4] Recent use of Calcium Silicate cements in dentistry has led to the use of Mineral Trioxide Aggregate (MTA) as an alternative which reportedly provides an improved seal and stability over a longer period of time.5 However, MTA has a higher cost with crucial handling properties and can also lead to tooth discoloration.[5] Another biocompatible material in dentistry is Biodentine, which requires a shorter setting time (12 minutes), with less reports of discolouration. However, despite these advancements, a recent systematic review has reported success rates for DPC with MTA to be 81% at 5 years and 86% for Biodentine at 2 years.[6] Naturally, compared to the high success of endodontic treatment (86-93%), improving the predictability of DPC is an important goal in current literature.[7]

Considering the challenges of restorative techniques with DPC, recent literature focuses on the development of regenerative techniques to biologically generate a hard tissue barrier.[8] These can be done through the process of 'cell homing' or via 'stem cell transplantation'.[8] The process of cell homing refers to the use of signaling molecules to allow the recruitment, proliferation, migration and differentiation of cells at the site of injury, which then allows tissue regeneration.[8] On the contrary, stem cell transplantation is a process by which stem cells are isolated, cultured, programmed and transplanted to the affected site.[9] Thereafter, if a suitable environment is provided through an appropriate scaffold and growth factors, the stem cells can differentiate further and eventually allow tissue regeneration.8 Although stem cell induced odontogenesis is a promising area for future development, currently there is limited evidence regarding the effectiveness of stem cell regeneration in direct pulp capping. Therefore, this review aims to provide a comprehensive understanding of stem cell therapy and compile the current available evidence on

the use of stem cell therapy in direct pulp capping.

Methodology and Study Selection

Online database PubMed and Cochrane were searched for all publications related to DPC with a combination of the following key words: 'stem cells' or 'stem cell therapy' and 'dentinogenesis' or 'dentin barrier' or direct pulp cap' or 'odontoblast'. Thereafter, the following inclusion and exclusion criteria were applied:

Inclusion criteria

1. Publications in English language
2. Studies which performed stem cell transplantation on an iatrogenically exposed dental pulp of animal or human teeth
3. Studies which reported dentinogenesis or dentin bridge formation as the outcome
4. Type of publications (randomized or non-randomized clinical trials, randomized or non-randomized animal studies)
5. Studies with the presence of a control group

Exclusion criteria:

1. Publications addressing general applications of stem cell therapy
2. Studies reporting outcomes such as pulp regeneration, periodontal tissue regeneration
3. The studies which assessed dentinogenesis or differentiation of stem cells after subcutaneous implantation instead of direct application on the exposed dental pulp
4. Review articles or case reports

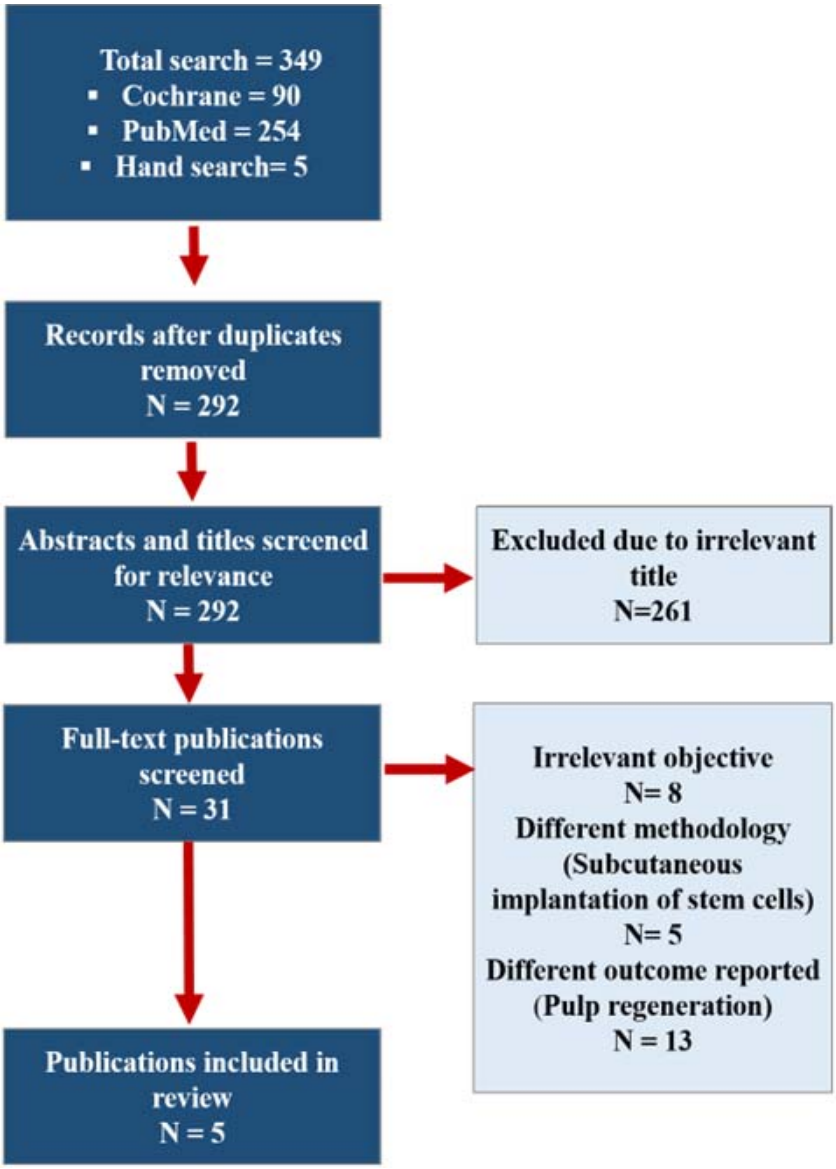

Figure: Literature Search .

The screening and selection of articles was carried out in two phases, an initial screening followed by a full-text evaluation. Authors (MD and ZH) screened the titles and abstracts independently and a full-text reading was only carried out at this stage if the title or abstract was ambiguous. In the second phase, the full-text articles of the shortlisted studies were assessed according to the aforementioned inclusion/exclusion criteria. A third author (RO) was consulted if a disagreement was encountered. Although a systematic review could not be carried out due to the limited studies available, a PRISMA flowchart was still followed for a more standardized reporting of the available evidence, as shown in Figure 1. As a result, only 5 animal studies were found to be relevant to the objective of this study, the characteristics

Table: Characteristics of Studies Using Stem Cells as a Direct Pulp Capping Agent

S #	Study;(year)	Model; Sample Size	Groups	Stem Cell Type;Scaffold Type	Time of Assessment	Outcome(s) Assessed	Results
1	Farzad et al.[20]; (2022); Vet Res Forum	Randomized controlled Animal Study;39 Dog Teeth;(n=13 each group)	ProRoot MTAhydroxyapatite/collagen hybrid scaffoldBMSCs +hydroxyapatite/collagen hybrid scaffold	Stem Cell: BMSC (Dog ileac crest)Scaffold: Hydroxyapatite/collagen hybrid	At 3 months	Dentine bridge (formation + quality)Inflammation	The efficacy of MTA for calcified bridge formation was higher than hybrid scaffold group and BMSC group
2	Sarra et al.[28]; (2021); Tissue and Cell	Randomized controlled Animal Study; 20 Wistar rats; (n=10 each group)	Pro Root MTAH-DPSC CM + MTA	Stem Cell: DPSC (human)Scaffold: MTA	At 5, 7, 10, 14, 21 days	Dentin bridge (formation +quality)Pulp vitality	The conditioned medium improved the organization of the newly formed hard tissue
3	Amin LE et al.[27];(2021);Austral Endod J	Randomized controlled Animal Study 72 male Wistar rats; (n=12 each group)	BiodentineCaOhBMSC + Biodentin	Stem Cell: BMSC (Rat femur)Scaffold: Biodentin	At 1 week, 3 weeks, 5 weeks	Dentin bridgeInflammationPulp vitality	BMDSCs + biodentine substantially reduced inflammatory reaction and necrotic tissue while promoting calcified tissue formation
4	Abdelaz P. et al.[26]; (2019); Brazilian Dent J	Non- Randomized controlled Animal Study 24 teeth from 3 Mongrel Dogs; (n=12 each group)	Calcium Hydroxide (Dycal)DPSC	Stem Cell: DPSC (Mongrel Dogs)Scaffold: MTA	At 3 months	Dentine bridge (formation + quality)Pulp vitality	Significant differences in the calcium and phosphorous wt, % in the reparative dentin of calcium hydroxide treated group
5	Sueyama et al [29]; (2017); J Endodon	Non- Randomized controlled Animal Study 40 Wistar rats; (n=8 each group)	1.PLLA scaffolds with MSCs and ECs, 2.Implanted scaffolds with MSCs, 3.Implanted acellular scaffolds 4.No implantation 5.Sound teeth	Stem Cell: MSC (Rat bone marrow) Scaffold: Hydrogel made scaffold; Porous PLA	At 14 days	1. Dentin bridge formation	Teeth co-implanted with MSCs and ECs showed pulp healing with complete dentin bridge formation compared to teeth with MSCs alone

BMSC: Bone Marrow Stem Cells, H-DPSC: Human Dental Pulp Stem Cells; CM: Cellular Matrix; MTA: Mineral Trioxide Aggregate; CaOH: Calcium Hydroxide; MSCs: Mesenchymal Stem Cells; EC: Endothelial Cells; PLA: Poly-Lactic Acid

of which have been summarized in Table 1. 5 remaining sections of this article will provide a comprehensive review of core concepts regarding stem cell induced tissue regeneration, to provide a foundation for understanding the current evidence regarding the use of stem cell therapy in direct pulp capping.

Stem Cells and the Tissue Engineering Triad

Mesenchymal stem cells (MSCs) are undifferentiated cells with the potential for regeneration and differentiation into multiple cell types. Broadly, stem cells can be divided into Adult Stem Cells (ASCs) and Embryonic Stem Cells (ESCs).[8] The ASCs are limited in number and have 'multipotent' potential, which allows them to regenerate and differentiate into certain specific cell types, thereby contributing to tissue healing and maintenance.[10,11] On the contrary, ESCs are considered 'pluripotent' and can differentiate into almost all cell lines, depending on the stimulus.[9] However, ESCs are found in the blastocyst stage embryo, whereas ASCs have been isolated from skin, muscle, nerve, bone and dental tissues.[9] As a result of the ease of accessibility of ASCs, recent advancements have led to the development of 'cell plasticity', which

involves the reprogramming of ASCs to produce pluripotent stem cells, which allows them to develop into any cell lineage, depending on the stimulus.[9]

The Bone Marrow Derived Stem Cells (BMSCs) can be isolated from intra oral sites such as the maxilla or mandible; as well as extra oral sites including the iliac crest or femur.[11] Although BMSCs have had uneventful outcomes with regeneration, the process of obtaining and isolating these stem cells is invasive.[12] On the other hand, stem cells of dental origin are easier to access and these include human exfoliated deciduous teeth (SHED), Dental Pulp Stem Cells (DPSCs), gingival mesenchymal stem/progenitor cells (GMSCs), stem/progenitor cells from apical papilla (SCAP), periodontal ligament stem cells (PDLSCs) and dental follicle stem/progenitor cells (DFSCs).[13] Despite the variety of available sources, it is important to consider that successful tissue regeneration is a result of a complex interplay between three main factors: Stem cells, scaffolds and growth factors, also described as the 'Tissue Engineering Triad'10 (Figure 2)

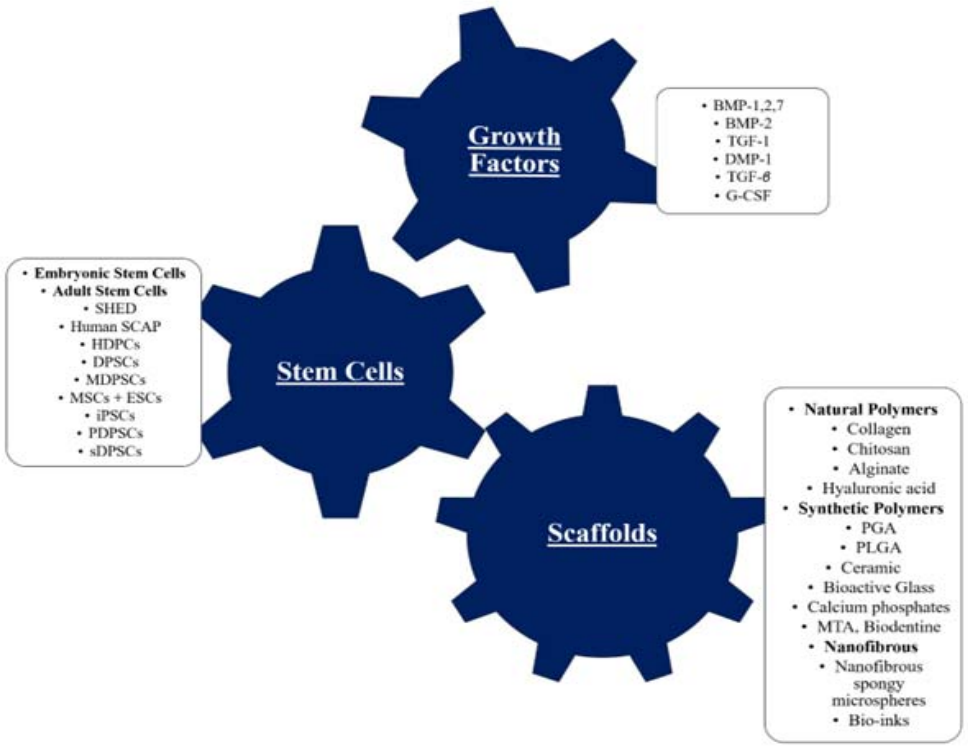

Figure-2: The Tissue Re-engineering Triad

BMP: Bone Morphogenic Protein, TGF: Transforming Growth Factor, DMP: Dentin Matrix Protein, SHED: Stem Cells of human exfoliated deciduous teeth, DPSC: Dental Pulp Stem Cells, GMCS: gingival mesenchymal stem/progenitor cells, SCAP: Stem/progenitor cells from apical papilla, PDLCS: periodontal ligament stem cells and DFSCs: dental follicle stem/progenitor cells, PGA: Poly-glycolic acid, PLGA: Poly-lactic glycolic acid.

The Role of Scaffolds

Despite current advancements in tissue regeneration, the challenge of developing a suitable scaffold for dentin regeneration persists.[14] This is owing to the fact that the dentin matrix is secreted by the odontoblast, a terminally differentiated cell which is challenging to isolate.[13] Ideally, four properties are essential requirements of a scaffold.[15] Firstly, the scaffold must provide a three dimensional construct that outlines the shape of the developing tissue.[10] Second, the scaffold should facilitate the attachment, proliferation and differentiation of the stem cells. Third, a scaffold should provide an open porous network for cell networking to facilitate the cellular interactions required for cell seeding, migration and nutrient transport.[10,15] Fourth, a scaffold should provide a delivery vehicle for growth factors and stem cells.[10] Additionally, scaffolds should be biocompatible, chemically stable, with adequate mechanical strength and controlled degradation.[16] Several natural polymer scaffolds including collagen, chitosan, alginate, peptide-based scaffolds and hyaluronic acid have been implemented, due to their excellent biocompatibility (Figure 2).[16] However, these materials exhibit poor physical properties, with low mechanical stability and unpredictable degradation.[17] Considering this, synthetic polymers were devised with improved physical properties and controlled degradation including polyglycolic acid (PGA), polylactic acid, polylactide-co-glycolide (PLGA).[17] Although the mechanical properties of these materials improved, biocompatibility was a new challenge.

Ceramic based scaffolds including bioactive glass and calcium phosphates have also been used as scaffolds.[18] Calcium phosphate scaffolds are comprised of tricalcium phosphate or

hydroxyapatite which enhance the process of mineralization during dentinogenesis.[18] Moreover, calcium hydroxide, Biodentine and Mineral Trioxide Aggregate (MTA) have also proved to be biocompatible and facilitate cell differentiation and dentinogenesis.[19] A study by Farzad et al. compares the outcomes of MTA pulp capping with pulp capping carried out using BMSCs in a collagen and hydroxyapatite hybrid scaffold.[20] They observed that MTA was comparatively more effective as a direct pulp capping agent, due to the quality of mineralized tissue formed.[20] The quality of mineralized tissue formed is an area that requires improvement and several studies have attributed this to the non-porous macrostructure of the scaffolds, since the structure interferes with cellular interaction and seeding.[14] Kuang et al. and Wang et al. have fabricated Nano Fibrous-Spongy Microspheres (NF-SMS) with an interconnected pore structure and found that these NF-SMS enhanced odontoblast differentiation and proliferation along with providing superior quality of dentin-like tissue, which is a promising area for future development.[21] However, in both the aforementioned studies a subcutaneous implantation of the cultured cells was carried out.[14,21] As evident in Table , there is a great heterogeneity in the type of scaffolds used. Amin et al. used biodentin, Sarra et al. and Abdelaz et al. used MTA, whereas Sueyama et al. and Wang et al. used PLLA scaffolds. Favourable outcomes were reported in the aforementioned studies, however, it is difficult to determine the ideal scaffold for dentinogenesis based on the limited number of studies.[14,21]

Growth factors and Signalling Molecules

Growth factors play a critical role in tissue generation by binding to stem cell membrane receptors and inducing cell proliferation, induction, differentiation and mineralization.[16,22] Naturally, growth factors are essential in the process of dentinogenesis for direct pulp capping.[13] These growth factors include Bone Morphogenic Proteins 2, 4, 7 (BMP2,4,7), Dentin Matrix Protein-1 (DMP-1), Transforming growth factor Beta-1 (TGF-1) and Fibroblast Growth Factor-2 (FGF-2).[23,24] The differentiation of dental pulp stem cells to odontoblasts is controlled by BMP-2, whereas TGF-β can stimulate the differentiation of odontoblast-like cells. Moreover, platelet derived growth factor enhances the proliferation of odontoblasts.[23, 24]

Outcomes of Direct Pulp Capping

In the European Society of Endodontology (ESE) position statement, it is suggested that the outcomes of direct pulp capping be assessed according to clinical and radiographic criteria.[25] The clinical parameters include absence of pain, swelling, mobility, discolouration and soft tissue parameters. Radiographically, a successful outcome is the presence of a dentin bridge, continued root development and absence of periapical pathosis.[6, 25] Since most of the studies carrying out DPC with stem cells were performed on animal models, a direct assessment of the clinical parameters was not possible. However, another important factor evaluated in the literature is the presence of the dentin bridge, along with the quality of the mineralized tissue. This was reported through an elemental analysis of the percentage weight of calcium and phosphorous by Abdelaz et al., who found that the mineral content and composition of dentin formed by DPSC showed no difference when compared to physiological dentin.[26] Similarly, Wang et al. observed that a combination of BMP and dexamethasone improved the quality of mineralized tissue.[21] Moreover, Amin et al. noticed that a combination of BMSC with Biodentin reduced the inflammatory tissue response when compared to Biodentin alone, along with improving the quality of calcified tissue[27] (Table). It is noteworthy that although recent guidelines suggest that a follow-up period of 6 months should be considered to assess the outcome of direct pulp capping, this was not reported in most studies. The longest follow-up period reported was of 3 months by Faraz et al. and Abdulaz et al., which was followed by 5 weeks, as reported by Amin et al., 21 days by Sarra et al. and 14 days by Sueyama et al.[20,26-8] Naturally, this makes the long term prognosis of this treatment modality questionable.

Limitations and Future Directions

Although most studies did follow a standardized methodology, there are still several grey areas in the literature that warrant further research. Regarding stem cells, there is great heterogeneity in the type of stem cells used in the available literature. Moreover, the concentration of the stem cells required for successful dentin regeneration remains unaccounted for, which is why the translational value of these studies remains questionable. Furthermore, the heterogeneity in the type of scaffolds, growth factors and culture media that has been reported in the literature further adds to the ambiguity. A majority of the reported studies compare stem cell therapy in DPC with other pulp capping materials such as MTA or Biodentine, which provides vital information regarding the ability of stem cells to induce mineralized tissue formation.[26-28] However, future research should compare the use of different growth factors and scaffolds to allow a better understanding for the ideal environment that can favour

dentinogenesis.[20,26-28] Moreover, the storage media, time of storage and transport of the recruited stem cell shows great variation, making it difficult to develop a standardised treatment protocol. [20, 26-28] Therefore, more studies with a more standardised protocol, presence of control groups and longer follow-up periods should be carried out to improve the quality of evidence.

Conclusion

The use of stem cells in direct pulp capping has shown promising results in animal models in several studies. However, due to the heterogeneity in data the true potential of stem cells in direct pulp capping requires further investigation. Moreover, the cost effectiveness, ethical concerns and applicability of these results to human teeth requires further investigation.

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Conflict of Interest: None to declare.

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