Hydrogel Scaffold in Pulp Dentin Complex Regeneration

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Abstract

Pulp dentin complex regeneration can be initiated by hydrogel scaffold application in the pulp using tissue engineering concept and it gives many advantages. Excavation in deep dental caries, dental trauma, and iatrogenic reasons are several causes of dental pulp exposure that can affect the pulp vitality. It is crucial to maintain the pulp vitality because it can support the tooth survival by avoiding endodontic treatment which affect the resistance of tooth structure. Pulp vitality can be preserved by inducing pulp regeneration using appropriate material. New approach in endodontic regeneration is using tissue engineering concept with hydrogel scaffold, stem cells and growth factors mechanism. Hydrogel scaffold as three-dimensional media can provide cell homing process in pulp dentin complex and may support adhesion of stem cells to differentiate and initiate growth factors release. Based on several studies, hydrogel scaffold can be formulated to support dental pulp regeneration using tissue engineering concept. Many favorable conditions can be achieved such as acts as delivery drug factor with easy injectable application in tooth and it has a lot of potential in dental pulp tissue regeneration treatment.

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Introduction

Deep dental caries removal, dental trauma, and iatrogenic reasons are several causes of dental pulp exposure that can cause loss of dental pulp vitality.[1] Maintaining pulp vitality is important because it can preserves homeostasis, durability and help rescuing many of teeth due to fracture teeth because of failed endodontics treatment [2,3]. One of approaches in pulp dentin complex regeneration treatment is vital pulp therapy.[4] Pulp exposure can stimulates regeneration because existence of progenitor mesenchymal cells and mild inflammation to induce protective mechanism of dental pulp. [1,5,4]

In advances biotechnology, regeneration has been leaded to the application tissue engineering concept in pulp dentin complex therapy with three elements, scaffold, stem cell and growth factor. [6,7] The existence of scaffold provides three dimensional condition which cells can adhere, proliferate, migrate and differentiate and it will optimize pulp regeneration [2,8]. Suitable scaffold induces biological signaling pathway from progenitor [9] and injectable hydrogel scaffold has been develop widely for pulp regeneration, because it can easily applied to the specific area with minimal invasive technique. [10,11]

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Review

Pulp Dentin Complex Regeneration

Regeneration of pulp dentin complex can be achieved by preserving pulp vitality. In many cases, there is crucial need to do some clinical intervention such as vital pulp therapy treatment. The mechanism of tissue regeneration initiates by existence of pluripotent stem cell roles which migrate, proliferate and differentiate into odontoblast like cells and replaces damage odontoblast in the healthy pulp site. Stem cell also supports angiogenic factor release to provide pulp tissue regeneration response and

bioactive scaffold becomes extracellular matrix.[12,13,14,15]. Success in vital pulp treatment can be marked by healing response, such as the restore of structure and function of dentin pulp tissue characterization. [9,2] Current material is limited by its lack of infection control such as tunnel defect that can fail to form hermetic seal against infection. As a new approach, injectable hydrogel scaffold can be used to support cell homing process and it is potential to be used as vital pulp therapy material[15], inducing dentin pulp regeneration and it supports pulp recovery.[16,17]

Scaffold

Three main elements in tissue engineering in pulp regeneration are cells, bioactive molecules or growth factors and scaffolds[8,18,19,20]. Scaffold is an crucial part provides three dimensional condition mimics natural extracellular matrix (ECM)[21,22]. Ideal scaffold should be biocompatible, biodegradable, and mimics the composition of the natural dentin pulp tissue so it provides framework to support cell attachment, proliferation, migration and differentiation of odontoblast cell and performed formation of dentin like tissue[23,10,15]. Injectable scaffold can be applied considering the anatomy of the tooth. Eventually, scaffold should be degradable and replaced by new dentin pulp tissue.[19,24]

Hydrogel Scaffold

The latest review shows the application of injectable hydrogel scaffolds and progenitor cells gives potential result in dentin pulp complex regeneration. The beneficial of hydrogel is it can control scaffold viscosity and porosity.[25] Hydrogel scaffold for pulp dentin complex regeneration can be created from natural and synthetic sources (Table 1) with several criteria.[19,26] Natural sources have advantages in supporting cell adhesion and its mechanism, usually biocompatible and degradable. It will not cause inflammation or severe immune response. The limitation is the transmission of microorganism and the production has many kinds of quality. Synthetic sources had developed in biomaterial too. It can be produced in large amount with good and controlled mechanical property, microelements, degradation, and also avoids microorganism transmission risk. The limitation is in it cannot provide natural or biological characterization in signaling molecule which needed in cell communication. Composite material is another choice to produce hybrid natural and synthetic injectable biomaterial .[27]

Hydrogels	
Natural	**Synthetic**
Alginate, Chitosan, Collagen, Fibrin Hydroxyapatite, Proteoglycans decellularized, demineralized bovine bone	Gelatin methacrylate (Ge1MA) PEG Self-assembling peptides (SAP) Emdogain

Table 1. Sources of Hydrogel scaffold.

Hydrogel scaffold materials uses for pulp dentin complex regeneration should be biocompatible and easy to applicate, it can be sterilized, setting in time, injectable in certain area and economically cost. Biodegradation rate is also important because it has roles in replacing scaffold with new tissue, interconnected pores provide cellular migration, nutrient and vascularization. Proper mechanical property of scaffold can stimulate cell activity and mechanical loading, which can be increased by crosslinking it with other composite material. Hydrogel scaffold should also be solid in neutral pH or physiological temperature to avoid cellular destruction (Figure 1). [26,24]

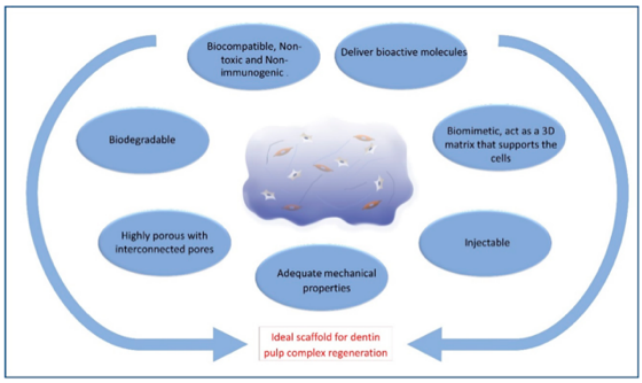

Figure 1. The Ideal Criteria of Hydrogel Scaffold.

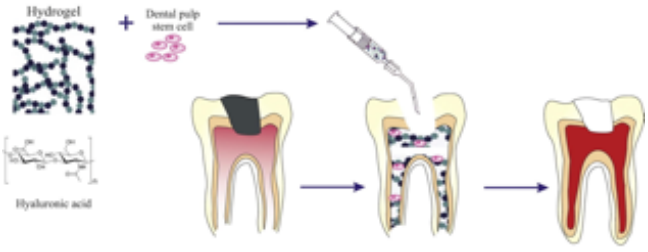

Figure 2. Hyaluronic Acid as regenerative therapy using injectable gel in pulp dentin regeneration.

According to Yan *et al* 2016, injectable composite gel alginate and hydroxyapatite gelatin microsphere scaffold could be crosslinked and encapsulated by tetracycline hydrochloride, with hydroxyapatite as calcium source. The result showed that it could improve mechanical property of scaffold , reduced weight loss , stable in gelation time, swelling ratio, and it facilitated drug release to its microenvironment.[28] Hyaluronic acid injectable hydrogel was also potential in supporting dental pulp therapy. [17] (Figure 2)

Mechanism of Hydrogel Scaffold in Pulp Dentin Complex Regeneration

Hydrogel scaffold is applicated in pulp chamber, it can be used as carriers of drug or bioactive material delivery such as antibiotics to support VEGF, FGF or stem cell factor release. It also support stem or progenitor cell attachment with highly odontogenic ability such as Dental Pulp Stem Cells (DPSCs).[29,20,30] Once applied, scaffold should be degradable after released bioactive molecule to pulp dentin environment. There are several hydrogel material and polymers which are important to make a gel form, that can support in pulp dentin complex regeneration. The scheme shown by figure 3 (Figure 3).[26,31]

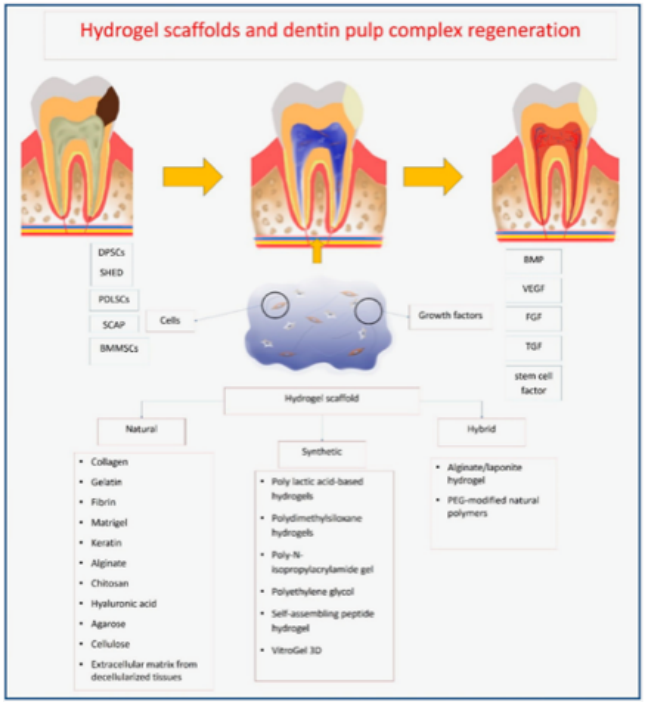

Figure 3. Diagram of mechanism and source of hydrogel scaffold in pulp dentin complex regeneration.

Studies of Hydrogel Scaffold in Pulp Dentin Regeneration

There are several reviews which support hydrogel scaffold for dentin pulp regeneration. Abbass *et al.,* concerned in source of injectable scaffold which has potential in pulp dentin regeneration because it is possible to be injected easily to the pulp and adapt to the pulp contour [26] (Table 2).

Source of Injectable Hydrogel	Remarks
Natural	Source of natural bioactive has several advantages such as biocompatible, biodegradable by enzymes or hydrolysis
Synthetic	Source of synthetic has good mechanical properties, thermal stability and durability compared to natural source.
Hybrid hydrogel	Hybrid hydrogel can promote cell binding, as media of delivery bioactive molecules, and promotes cellular mechanism with stem cells.
Concluding remark	Creating formula for hydrogel scaffold requires many criteria and it has been actively researched. It has a high potential possibility for replace the conventional endodontic treatment

Table 2. Hydrogels and Dentin Pulp Complex Regeneration

Hassanzadeh *et al.,* performed the development of injectable hybrid hydrogel nanohydroxyapatite and collagen scaffold for

hard tissue engineering application[23]. Injectable keratin hydrogel is also suggested as pulp therapy biomaterial.[32] The result showed in Table 3 and Table 4.

Analysis	Remarks
Chemical analysis	Nanohydroxyapatite and Collagen could be formulated into poly (ξ-caprolactone) PCL-PEG (Polyethylene Glycol) -PCL hydrogel
Histology examination	The addition of nanohydroxyapatite and collagen effects in decreasing of biodegradation rate, with minimum inflammation response
Level of CD68 and CD8/CD4 lymphocyte ratio	There are no differences between the addition of nanohydroxyapatite and collagen or not
Gene expression analysis	The expression of the CD31, IL-10 was increased significantly in the addition of nanohydroxyapatite and collagen to PCL-PEG-PCL
Concluding remarks	Injectable PCL-PEG-PCL-Collagen/nanohydroxyapatite was appropriate for advanced research in hard tissue regeneration

Table 3. Injectable Nanohydroxyapatite and collagen scaffold.

Analysis of Characterization	Remarks
Flow characterization	The dynamic elastic and viscous was significantly increase in 15% ,17 and 20% (w/v) gel concentration in minimal essential medium immersion in 10 days
Micro structure, swelling ratio and contact angle	Interconnected porous in microstructure, swelling ratio were stable in 1 hour without significant ratio between 1 to 24 hours, and contact angle in 35.52±7.187
Biocompatibility	In partial pulpotomy site, there was cellular infiltration with mild and moderate inflammation. It performed blood vessel presence and reparative dentinogenesis
Concluding remarks	20% injectable keratin hydrogel was stable, non-toxic and biocompatible to pulp tissue healing. It also performed reparative reaction

Table 4. Injectable Keratin hydrogel is also suggested as pulp therapy biomaterial

Discussion

Preserving pulp vitality is important to provide pulp dentin complex regeneration. Tissue regeneration initiates by the existence of stem cell which differentiates into odontoblast like cells and also supports angiogenic factor release so it performs healing response.[12] As a new approach, hydrogel scaffold is potential to be used as a material inducing dentin pulp regeneration.[15] Many concern to develop natural, synthetic or composite scaffolds using unique material with their polymer to form injectable gels. Hydrogel scaffold being researched for its toxicity, biocompatibility, easy to manufacture, prepare and it was crosslinked to bioactive material in improving property of scaffold with economically cost and easy application. [33,34] Several studies has shown that creating formula for hydrogel scaffold needs many criteria and has potential possibility for replace the conventional endodontic treatment.[26] Injectable PCL-PEG-PCL-Collagen/nanohydroxyapatite was appropriate for hard tissue regeneration, and 20% injectable Keratin hydrogel was non-toxic and biocompatible to pulp tissue healing. [24,33,34]

According to several research before, we can conclude that hydrogel scaffold can support induction dental pulp regeneration using tissue engineering concept and it can be crosslinked with other bioactive material which can increases its properties. Hydrogel scaffold was also used as a delivery drug factor that has a lot of advantages. Further studies about hydrogel scaffold should be performed to explore the potential in dental pulp tissue regeneration treatment and it can support pulp vital therapy treatment in clinical application

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Declaration of Interest

The authors report no conflict of interest.

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