Hydrogel Scaffold In Pulp Dentin Complex Regeneration Review Article

by Elline Elline

Submission date: 15-Jul-2021 10:10AM (UTC+0700)
Submission ID: 1619790319
File name: Scaffold_In_Pulp_Dentin_Complex_Regeneration_Review_Article.pdf (2.98M)
Word count: 2992
Character count: 17240

Hydrogel Scaffold In Pulp Dentin Complex Regeneration: Review Article

Elline[1], Kun Ismiyatin[2] Theresia Indah Budhy[3]

[1] Student of Doctoral Program, Faculty of Dental Medicine, Airlangga University, 60132, Surabaya, Indonesia

[2] Conservative Dentistry Department, Faculty of Dental Medicine, Airlangga University, 60132, Surabaya, Indonesia

[3] Department of Imunology, Faculty of Dental Medicine, Airlangga University, 60132, Surabaya, Indonesia

ABSTRACT

Background : *Pulp dentin complex regeneration can be initiated by hydrogel scaffold application in the the pulp using tissue engineering concept and it gives many advantages.* ***Purpose :*** *The purpose of this review is to provide general understanding of current study about hydrogel scaffold as induction of pulp dentin complex regeneration material.* ***Reviews :*** *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.* ***Conclusions:*** *Based on several studies, hydrogel scaffold can be formulated to support dental pulp regeneration using tissue engineering concept. Many favourable condition 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.*

Keywords: *Hydrogel scaffold, pulp dentin complex regeneration*

Correspondence : Kun Ismiyatin, Conservative Dentistry Department, Faculty of Dental Medicine, Airlangga University, 60132, Surabaya Indonesia, ie_elline23@yahoo.co.id , ismiyatinkun@yahoo.com, 087875885511, 085733205778

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 existance 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 existance 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 signalling 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]

REVIEW(S)

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 existance 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 limitate by its lack of control infection such as tunnel defect that can failing to hermetize 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[18,8]. Scaffold is an crucial part provides three dimensional condition mimics natural extraceluler matrix (ECM)[19,20]. 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[21,10,15]. Injectable scaffold can be applied considering the anatomy of the tooth. Eventually, scaffold should be degradable and replaced by new dentin pulp tissue.[19,22]

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.[23] Hydrogel scaffold for pulp dentin complex regeneration can be created from natural and synthetic sources (Table 1) with several criteria.[19,24] 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 has develop 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 can not provide natural or biological characterisation in signalling molecule which needed in cell communication. Composite material is another choice to produce hybrid natural and synthetic injectable biomaterial .[25]

Table 1. Sources of Hydrogel scaffold [19]

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

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 vascularisation. Proper mechanical property of scaffold can stimulates 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 (Fig.1). [24,22]

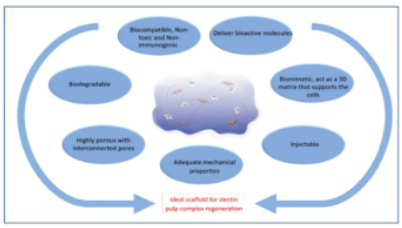

Fig. 1 The Ideal Criteria of Hydrogel Scaffold [24]

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.[26] Hyaluronic acid injectable hydrogel was also potential in supporting dental pulp therapy [17] (Fig 2)

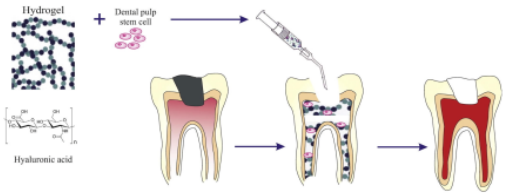

Fig 2. Hyaluronic Acid as regenerative therapy using injectable gel in pulp dentin regeneration [17]

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).[27,20,28] Once applied, scaffold should be degradable after released bioactive molecule to pulp dentin environtment. 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 (Fig.3).[24,29]

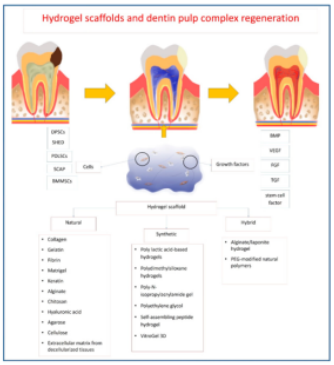

Fig 3. Diagram of mechanism and source of hydrogel scaffold in pulp dentin complex regeneration [24]

Studies of Hydrogel Scaffold in Pulp Dentin Regeneration

There are several reviews which support hydrogel scaffold for dentin pulp regeneration. Abbass *et al*., 2020 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 (Table 2)

Table 2. Hydrogels And Dentin Pulp Complex Regeneration [24]

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 promotes cell binding, as media of delivery bioactive molecules, and promotes celluler mechanism with stem cells.
Concluding remark	Creating formula for hydrogel scaffold requires many criteria and it has been an active research. It has a high potential possibility for replace the conventional endodontic treatment

Hassanzadeh *et al*., 2021 performed the development of injectable hybrid hydrogel nanohydroxyapatite and collagen scaffold for hard tissue engineering application. The result showed in table 3 (Table 3).

Table 3. Injectable Nanohydroxyapatite and collagen scaffold [21]

Analysis	Remarks
Chemical analysis	Nanohydroxyapatite and Collagen could be formulated into poly (ξ-caprolactone) PCL-PEG (Polyethylen 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 lymphosite 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 4. Injectable Keratin hydrogel is also suggested as pulp therapy biomaterial [30]

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
Microstructure ,swelling ratio and contact angle	Interconnected porous in microstructure, swelling ratio wer stabil 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

DISCUSSION

Preserving pulp vitality is important to provide pulp dentin complex regeneration. Tissue regeneration initiates by existance 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 toxixity, biocompatibility, easy to manufacture, prepare and it was crosslinked to bioactive material in improving property of scaffold with economically cost and easy application. [31] Several studies has shown that creating formula for hydrogel scaffold needs many criteria and has potential possibility for replace the conventional endodontic treatment .[24] 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. [21,30]

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

ACKNOWLEDGEMENT

Author Contributions: Authors E. has contributed in original draft preparation writing—Review & Editing; also contributed by funding acquisition, Author : K.I., T.I.B have contributed in supervision and review editing. All authors have read and agreed to the published version of the manuscript.

Funding: We acknowledge financial support by Airlangga University

Conflicts of Interest: The authors declare no conflict of interest.

REFERENCES

1. Morotomi T, Washio A, Kitamura C. Current and future options for dental pulp therapy. Japanese Dental Science Review. 2019 Nov;55(1):5–11.
2. Moussa DG, Aparicio C. Present and future of tissue engineering scaffolds for dentin-pulp complex regeneration. J Tissue Eng Regen Med. 2018 Dec 17;term.2769.

3. Jones TD, Kefi A, Sun S, Cho M, Alapati SB. An Optimized Injectable Hydrogel Scaffold Supports Human Dental Pulp Stem Cell Viability and Spreading. Advances in Medicine. 2016;2016:1–8.

4. Machado MAAM, Stafuzza TC, Vitor LLR, da Costa SA, da Costa SM, Neto NL, et al. Pulp repair response after the use of a dentin-pulp biostimulation membrane (BBio) in primary teeth: study protocol for a randomized clinical trial. Trials. 2020 Dec;21(1):874.

5. Shah D, Lynd T, Ho D, Chen J, Vines J, Jung H-D, et al. Pulp–Dentin Tissue Healing Response: A Discussion of Current Biomedical Approaches. JCM. 2020 Feb 5;9(2):434.

6. Jang J-H, Moon J-H, Kim SG, Kim S-Y. Pulp regeneration with hemostatic matrices as a scaffold in an immature tooth minipig model. Sci Rep. 2020 Dec;10(1):12536.

7. Sancilio S, Gallorini M, Di Nisio C, Marsich E, Di Pietro R, Schweikl H, et al. Alginate/Hydroxyapatite-Based Nanocomposite Scaffolds for Bone Tissue Engineering Improve Dental Pulp Biomineralization and Differentiation. Stem Cells Int. 2018 Aug 2;2018:1–13.

8. Kwon Y-S, Kim H-J, Hwang Y-C, Rosa V, Yu M-K, Min K-S. Effects of Epigallocatechin Gallate, an Antibacterial Cross-linking Agent, on Proliferation and Differentiation of Human Dental Pulp Cells Cultured in Collagen Scaffolds. Journal of Endodontics. 2017 Feb;43(2):289–96.

9. Alshehadat SA, Thu HA, Hamid SSA, Nurul AA, Rani SA, Ahmad A. Scaff olds for dental pulp tissue regeneration: A review. IDJAR. 2016;2(1):1–12.

10. Fukushima KA, Marques MM, Tedesco TK, Carvalho GL, Gonçalves F, Caballero-Flores H, et al. Screening of hydrogel-based scaffolds for dental pulp regeneration—A systematic review. Archives of Oral Biology. 2019 Feb;98:182–94.

11. Creasey S, Sammon C, Le Maitre C. Hydroxyapatite nanoparticle injectable hydrogel scaffold to support osteogenic differentiation of human mesenchymal stem cells. eCM. 2016 Jul 5;32:1–23.

12. Shah D, Lynd T, Ho D, Chen J, Vines J, Jung H-D, et al. Pulp–Dentin Tissue Healing Response: A Discussion of Current Biomedical Approaches. JCM. 2020 Feb 5;9(2):434.

13. Okamoto M, Matsumoto S, Sugiyama A, Kanie K, Watanabe M, Huang H, et al. Performance of a Biodegradable Composite with Hydroxyapatite as a Scaffold in Pulp Tissue Repair. Polymers. 2020 Apr 17;12(4):937.

14. Gorin C, Rochefort GY, Bascetin R, Ying H, Lesieur J, Sadoine J, et al. Priming Dental Pulp Stem Cells With Fibroblast Growth Factor-2 Increases Angiogenesis of Implanted Tissue-Engineered Constructs Through Hepatocyte Growth Factor and Vascular Endothelial Growth Factor Secretion: FGF-2 Priming Enhances Angiogenesis by DPSCs. STEM CELLS Translational Medicine. 2016 Mar;5(3):392–404.

15. Haugen HJ, Basu P, Sukul M, Mano JF, Reseland JE. Injectable Biomaterials for Dental Tissue Regeneration. Int J Mol Sci. 2020;34.

16. Njeh A, Uzunoğlu E, Ardila-Osorio H, Simon S, Berdal A, Kellermann O, et al. Reactionary and reparative dentin formation after pulp capping: Hydrogel vs. Dycal. Evid-based endod. 2016 Dec;1(1):3.

17. Ahmadian E, Eftekhari A, Dizaj SM, Sharifi S, Mokhtarpour M, Nasibova AN, et al. The effect of hyaluronic acid hydrogels on dental pulp stem cells behavior. International Journal of Biological Macromolecules. 2019 Nov;140:245–54.

18. Tsai S-W, Huang S-S, Yu W-X, Hsu Y-W, Hsu F-Y. Collagen Scaffolds Containing Hydroxyapatite-CaO Fiber Fragments for Bone Tissue Engineering. Polymers. 2020 May 20;12(5):1174.

19. Karakaya I, Ulusoy N, Department of Restorative Dentistry, Faculty of Dentistry, Near East University, Mersin 10, Turkey. Basics of dentin-pulp tissue engineering. AIMS Bioengineering. 2018;5(3):162–78.

20. Proksch S. Scaffold Materials and Dental Stem Cells in Dental Tissue Regeneration. Curr Oral Health Rep. 2018;14.

21. Hassanzadeh A, Ashrafihelan J, Salehi R, Rahbarghazi R, Firouzamandi M, Ahmadi M, et al. Development and biocompatibility of the injectable collagen/nano-hydroxyapatite scaffolds as *in situ* forming hydrogel for the hard tissue engineering application. Artificial Cells, Nanomedicine, and Biotechnology. 2021 Jan 1;49(1):136–46.

22. El Fadhlallah,P.M., Yuliati,A., Soesilawati,P., Pitaloka,P. Biodegradation and Compressive Strength Test of Scaffold with Different Ratio as Bone Tissue Engineering Biomaterial. JIDMR [Internet]. 2018;11 (2). Available from: http://www.jidmr.com

23. Zein N, Harmouch E, Lutz J-C, Fernandez De Grado G, Kuchler-Bopp S, Clauss F, et al. Polymer-Based Instructive Scaffolds for Endodontic Regeneration. Materials. 2019 Jul 24;12(15):2347.

24. Abbass MMS, El-Rashidy AA, Sadek KM, Moshy SE, Radwan IA, Rady D, et al. Hydrogels and Dentin–Pulp Complex Regeneration: From the Benchtop to Clinical Translation. Polymers. 2020 Dec 9;12(12):2935.

25. Chang B, Ahuja N, Ma C, Liu X. Injectable scaffolds: Preparation and application in dental and craniofacial regeneration. Materials Science and Engineering: R: Reports. 2017 Jan;111:1–26.

26. Yan J, Miao Y, Tan H, Zhou T, Ling Z, Chen Y, et al. Injectable alginate/hydroxyapatite gel scaffold combined with gelatin microspheres for drug delivery and bone tissue engineering. Materials Science and Engineering: C. 2016 Jun;63:274–84.

27. Ahmed GM, Abouauf EA, AbuBakr N, Dörfer CE, El-Sayed KF. Tissue Engineering Approaches for Enamel, Dentin, and Pulp Regeneration: An Update. Stem Cells International. 2020 Feb 25;2020:1–15.

28. Tsutsui T. Dental Pulp Stem Cells: Advances to Applications. SCCAA. 2020 Feb;Volume 13:33–42.

29. Raddall G, Mello I, Leung BM. Biomaterials and Scaffold Design Strategies for Regenerative Endodontic Therapy. Front Bioeng Biotechnol. 2019 Nov 15;7:317.

30. Sharma,A. L, Love RM, Ali MA, Sharma A, Macari S, Avadhani A, et al. Healing response of rat pulp treated with an injectable keratin hydrogel. JABFM. 2017;15(3):0–0.

31. Samiei,M., Fathi,M., Barar,J., Fathi,N., Amiryaghoubi,N., Omidi,Y. Bioactive hydrogel-based scaffolds for the regeneration of dental pulp tissue. Journal of Drug Delivery Science and Technology. 2021;64.

Hydrogel Scaffold In Pulp Dentin Complex Regeneration Review Article

ORIGINALITY REPORT

8%	4%	7%	3%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.mdpi.com Internet Source	2%
2	Marwa M. S. Abbass, Aiah A. El-Rashidy, Khadiga M. Sadek, Sara El Moshy et al. "Hydrogels and Dentin–Pulp Complex Regeneration: From the Benchtop to Clinical Translation", Polymers, 2020 Publication	1%
3	Submitted to Universitas Airlangga Student Paper	1%
4	Armin Hassanzadeh, Javad Ashrafihelan, Roya Salehi, Reza Rahbarghazi et al. " Development and biocompatibility of the injectable collagen/nano-hydroxyapatite scaffolds as forming hydrogel for the hard tissue engineering application ", Artificial Cells, Nanomedicine, and Biotechnology, 2021 Publication	1%
5	www.tandfonline.com Internet Source	1%

6	"Endodontic Materials in Clinical Practice", Wiley, 2021 Publication	1 %
7	Moataz El Gezawi, Uta Christine Wölfle, Rasha Haridy, Riham Fliefel, Dalia Kaisarly. "Remineralization, Regeneration, and Repair of Natural Tooth Structure: Influences on the Future of Restorative Dentistry Practice", ACS Biomaterials Science & Engineering, 2019 Publication	<1 %
8	reachwater.org.uk Internet Source	<1 %
9	repository.unair.ac.id Internet Source	<1 %
10	Albuquerque, M. T. P., M. C. Valera, M. Nakashima, J. E. Nor, and M. C. Bottino. "Tissue-engineering-based Strategies for Regenerative Endodontics", Journal of Dental Research, 2014. Publication	<1 %

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		