SYSTEMATIC REVIEW

Reorienting goals in endodontic therapy: Pulp revitalisation, on the brink of a paradigm shift

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Abstract

Objective: To assess literature related to the various aspects of dental pulp tissue engineering, its myriad protocols, inclusive of adjuvant surgeries, and to summarise the testing methodologies of pulp vitality.

Methods: The multidisciplinary systematic review was conducted at the Army Medical College, Rawalpindi, the National University of Medical Sciences, Rawalpindi, and HITEC Dental College, Taxilla, Pakistan, and comprised literature search on PubMed, Scopus, MEDLINE, Cochrane and Science Direct databases related to articles about 'revitalisation', 'revascularisation', 'dental pulp' and 'regeneration' published from January 2017 to January 2020.

Result: Of the 5,986 articles found through search, 14(0.23%) studies were selected; 8(57.1%) clinical trials, 1(7.1%) case series, and 5(35.7%) case reports with platelet concentrates. All the studies (100%) had observed standard clinical treatment procedures for canal disinfection. Current strategies of pulpal regeneration reported commendable success. Histological analysis of clinical trials is essential to ensure confirmatory evidence of quality of revitalisation

Conclusion: The assessment of the impact of oral factors and a long-term follow up are required to produce a definitive understanding of the phenomenon.

Keywords: Dental pulp, Revitalisation, Regeneration, Revascularisation (JPMA 71: 2589; 2021)

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Introduction

Dental caries is one of the most prevalent diseases, affecting the orofacial complex parallel to the periodontal disease globally. Unfortunately, quite often there is pulpal inflammation, with or without exposure of pulp, leading to a need of endodontic intervention. Pulpal inflammation ultimately leads to necrosis of dental pulp.[1] This necrotic tissue still lodged in the pulp chamber offers a favourable environment for bacterial proliferation, which leads to periapical infections and resorption of apical tooth structure.[1] Absence of hydration provided by the pulp causes reduction in the resilience of the coronal portion of the dental hard tissue[2] and makes teeth brittle which ultimately manifests into chipping or fracture of the coronal tooth upon subjection to masticatory stresses. This is both an aesthetic and functional dilemma.

Current therapies are only oriented conservatively and do not enhance the chance of complete recovery or repair. With time, complete failure of restorative or endodontic therapy is unavoidable. This suggests that treatment options are only improving quality of life (QOL) and reducing the speed of progression of the disease, but ultimately a prosthesis, such as crown, bridge or implant, is inevitable.[3] Conclusively, any effort in the conventional therapies is frequently futile when seen in the long run. In the moderns era, focus is oriented on replication of human tissue by tissue engineering and guided tissue regeneration approaches.[4] Development of pulp in an otherwise devoid pulp chamber can shine a path to revitalisation of teeth with either infected or inflamed pulps.

Over the last 2 years, endodontists have reported commendable successes in the area of canal disinfection, an established success in partial pulpotomy, revascularisation, apexification and apexogenesis which has made pulp revitalisation an approachable milestone in oral rehabilitation in the world today. This opens new doors to a whole new array of therapeutic options in trauma control measures for exposed, necrosed or traumatised tooth pulps.[5]

The current systematic review was planned to study the various aspects of dental pulp tissue engineering cell and auto graft and adjuvant alloplastic material to bridge defects, and their relative success of multiple strategies relative to presence or absence of apex closure, age of patient and technique employed.

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Method

The systematic review was conducted at the Army Medical College (AMC), Rawalpindi, the National University of Medical Sciences, Rawalpindi, and HITEC Dental College, Taxilla, Pakistan, and comprised literature search on PubMed, Scopus, MEDLINE, Cochrane and Science Direct databases related to articles about 'revitalisation', 'revascularisation', 'dental pulp' and 'regeneration' published from January 2017 to January 2020. Torabinejad's study from 2011 is also added to playing a pioneer role.[6]

Extraction of articles was done on January 14, 2020. Of the total articles identified, the studies included were those with in-vivo humans results, those with introduction of human graft materials into the canal chambers, those with teeth recommended for pulpectomy, those with identification of apex either open or closed, those with immature teeth, those with mature teeth, those with platelet-rich plasma (PRP) or platelet-rich fibrin (PRF) or blood clot, and those with auto transplantation of teeth.

Studies excluded were those with ex-vivo experimentation, those with in-vitro experimentation, those with only alloplastic materials as scaffolding materials, those with cell homing as a strategy for pulp resurrection, those with pulpotomies indicated, those with teeth having developmental defects, and those conducted before January 2017.

Results

Of the 5,986 articles found, 14(0.23%) were selected and reviewed (Figure 1). Overall, 8(57.1%) were clinical trials, 1(7.1%) was a case series featuring revitalisation following auto transplantation, and 5(35.7%) were case reports with platelet concentrates (Table 1).

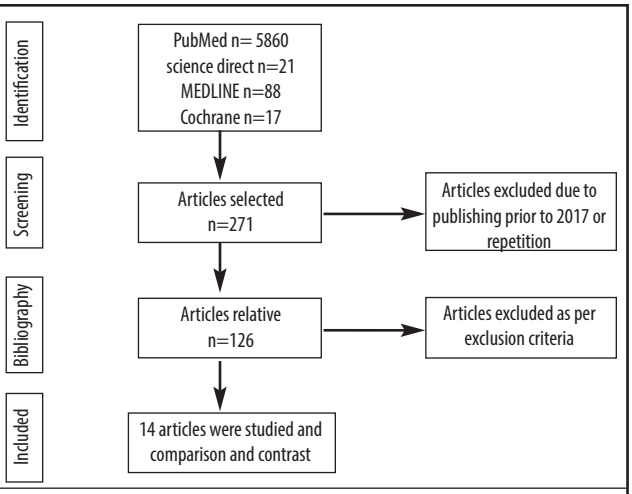

Figure: Study flow-chart.

Discussion

All (100%) studies included for review observed standard clinical treatment procedures for canal disinfection.[7-19] The choice of material for the procedures employed varied (Table 2). Nageh M et al. presented evidence that increasing the canal space in order to accommodate a greater volume of PRF is also an important factor in the success of pulp revitalisation.[11]

Back in 2016, a case report presented a case of mandibular molar with an open apex which was revitalised. During the one-year follow-up, positive pulp testing and resolution of apical lesion were observed, suggesting vitalisation and apexification with the use of PRP.[18] Histological analysis and clinical trials are still required to further study the dental pulp revitalisation process to suggest the effective reorganisation of pulp tissue.[19] Bio scaffold employed successfully is PRP in a human tooth which is used for a mandibular tooth with open apex. The biocompatibility of PRP is what makes it a safe choice because it will not elicit an immune reaction; but PRP cannot be acquired in a chair-side setup, putting its feasibility into question.[19] Previously, auto-graft materials, such as scaffold-free human tissue spheroids, were also seen to be bio-effective when seeded with umbilical vein tissue, but the problem in such a case will be high cost and ethical dilemmas attached to acquiring umbilical tissue relative to other two bio-scaffolds such as PRP or clinical-grade auto collagen.[20]

PRP or PRF?

Teeth with closed apices: Six of the studies reviewed addressed teeth that had received growth till the point of apical closure. All studies indicated the superiority of PRF over PRP, with one confirming it further by presenting a statistically significant improvement in the PRF group.[13] A study confirmed the importance of cannal shapping in order to increase volume of PRF in the pulp chamber.[11]

In another clinical trial, five patients were subjected to removal of inflamed pulp tissue followed by implantation of mobilised dental pulp stem cells on 1st, 10th and 12th week post-pulpectomy. The uninfected pulp was extracted from upper 3rd molars for dental pulp stem cells for implantation after pulp vitality testing. The patients' follow-up revealed a positive response after 4 weeks in four out of five cases. The result was comparable with preclinical findings in dogs that pulp tissue was regenerated in 70-80% of the total volume of the root canal with nerve extension to dentin within 4 weeks.[21] It has been suggested that the regenerated tissue could transmit sensory signals by Aδ (A-delta) fibres perceived as pain by electric stimuli.[22] Widening of periodontal ligament space at 12 weeks and periapical radiolucency at 24 weeks were

Table-1: Summary of procedures and outcomes.

Argo-Gomez E et al, 2019[7]	Nine-year-old patient with multiple horizontal root fractures in 2 upper central incisors	Case report Blood clot and platelet-rich plasma (PRP). Cone beam computer tomography used for analysis 4 years follow up	Both teeth revitalized, however PRP showed greater canal calcification. Calcification of fracture lines after 1 year
Rizk HM et al, 2019[8]	15 cases of immature permanent maxillary central incisors with necrotic pulps using	Human trial Blood clot (BC) and PRP scaffold follow up 3,6,9, & 12 month	100% success in all cases however there is a statistically significant increase in root length in the PRP group
Gaviño Orduña J et al, 2019[9]	Auto transplanted mature mandibular premolar	Case report Fragile fracture apicoectomy and plasma rich in growth factor in socket 2 weeks post-treatment, orthodontic traction was applied 3 year follow up	Pulp testing was positive canal obliteration
Mittal N, Parashar V et al, 2019[10]	Necrotic immature permanent maxillary incisor	Human trial Natural scaffold platelet-rich fibrin (PRF) and artificial scaffolds commercially available collagen, placentrex, and chitosan follow up 3,6 & 12 months	All groups express radicular growth and apical healing however based on these two parameters collagen and PRF showed statistically significant improvement over the others
Ragab RA et al, 2019[11]	22 Necrotic Immature Permanent Anterior teeth age 7-12	Human trials Group A using blood clot only Group B blood clot scaffold with PRF 1 year follow up	Presence of calcific apical and cervical bridges, evidence of root lengthening, apical healing Difference in 2 groups is statistically insignificant
Nageh M et al, 2018[12]	15 necrotic mature permanent teeth	Human trials Introduction of PRF Group 1: untreated Group 2: canal preparation till file 60-80 done. Antibiotic paste filled and glass ionomer cement (GIC)seal made for 3 weeks. After 3 weeks bleeding induced, PRP introduced into blood clot, mineral trioxide aggregate directly place over it and tooth restored with GIC and composite 1 year follow up	Electrical pulp testing shows positive vitality. A statistically significant difference between the 2 groups $P < 0.0001$
Prasad J et al, 2018[13]	14 year old maxillary central incisors. After evacuation old of GP and sealant	Case report Comparision between PRP and PRF Coronal closure with mineral trioxide aggregate and GIC Follow up of 2 years	Similar root lengthening, dentinal wall thickening Apical bridge formation occurs in PRF only
Santhakumar M et al, 2018[14]	40 immature permanent teeth	Human trials Group A PRF gel Group B PRF membrane. 12 months follow up	PRF membrane is easier and less time consuming. similar clinical success. PRF gel gave a better radiographic success.
Shivashankar VY et al, 2017[15]	Sixty patients (6 to 28 years) with necrotic pulp and open apex	Human trial Group A induced bleeding Group B PRF as scaffolding material Group C PRP as the biomaterial	PRP was better than PRF and induced bleeding technique on grounds of periapical healing Statistically insignificant difference in root lengthening and wall thickening.

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Table-1: (*Continued from previous page*)

Alagl A et al, 2017[16]	Thirty non-vital immature permanent teeth	Human trial PRP vs blood clot infused in Scaffold made mineral trioxide aggregate cone-beam computed tomography 12 months follow up	The PRP group shows greater radicular development
Bakhtiar H et al, 2017[17]	4 immature teeth with necrotic pulp	case series With PRF in canal and Bio dentine used for tooth restoration. 12 months follow up	PRF is a successful scaffolding material for pulp regeneration.
Nakashima M et al, 2017[18]	5 mature necrotic teeth aged 20-55 years old	Human trial Implantation of pulp mesenchymal derived dental pulp stem cells 's from uninfected third molars Cone beam tomography Magnetic resonance imaging scans.	Electric pulp testing shows vital pulp in 4/5 teeth. Functional dentine formation in 3/5 teeth 4/5 teeth show MRI similar to normal untreated pulp in healthy teeth
Subash D et al, 2016[19]	1 immature tooth	Case report PRF used with Biodentine scaffold 12 month follow up	Resolution of apical lesion, positive electric pulp testing results
Torabinejad M et al, 2011[6]	Necrotic permanent 2nd molar of 11 year old	Case report PRP was injected into the canal space up to the cementoenamel junction level	Sensitivity tests with cold and an electric pulp test elicited a positive response similar to those found in the first premolar tooth.

demonstrated by dental radiographical examination in one of the 5 patients, suggesting that the transplanted pulpal tissue of the tooth, even following regeneration, may end in re-infection and necrosis due to the canal being infected gradually by micro leakage from the apex.[17] Other studies suggested that mesenchymal dental pulp stem cells (MDPSCs) are a superior alternative to colony-derived dental pulp stem cells (DPSCs) in order to initiate larger volume pulp-regenerative procedures while avoiding mineralisation or calcification inside the canal space.[21,23] MDPSCs did not show direct differentiation, but acted as a secretory body. MDPSCs secreted topical factors which resulted in migration and proliferation of nearby cells. At the same time, MDPSCs showed behaviour as a regulator of inflammation causing immunosuppressive and immunomodulatory actions.[24] A study showed that an uninfected teeth with pulp inside can be implanted successfully and vitalised if PRP is used in the socket.[8]

Teeth with open apices: All teeth with open apices were revitalised by blood clot, PRF and PRP. However, use of fibrin scaffolding material is a more convenient choice. Gel form PRF was also used with similar success. Other materials, such as double-setting hyaluronic cement, mineral trioxide aggregate, biodentine, clinical-grade auto collagen and collagen matrix, were all tolerable for the newly budding pulp. Decellularized soft tissues contain collagen type I, type III, or type IV etc. and elastin. In appropriate conditions, even the hydroxyl– groups on the collagen molecule can induce mineralisation[8] as suggested by a study in which follow-up assessed pulp stones and sclerotic dentine formation.[25]

Pulp vitality testing

There are a variety of methods employed in order to evaluate pulp vitality. The methods can be classified as sensitivity testing or sensibility testing methods. Variable confounding factors can still exist in testing from person to person even with the most accurate testing methodology. An example of these confounding factors may be age; for example, increased age and sclerotic dentine can give a false negative to hot or cold just like non-vital pulp[26,27] or it could cause aging-related neurodegenerative changes in the pulp in both the coronal and radicular portion.[27-31]

Methods of testing pulp vitality

Sensitivity testing using electric pulp test (EPT), hot and cold testing: The most convenient method to accomplish chair-side testing is the EPT, and the hot and cold tests. These methods are convenient, cost-effective and good indictors, but do not yield conclusive information about the vitality of pulp. These tests check sensitivity and have up to 10% frequency of false negative results.[32] Other laboratory methods include the following:

Magnetic resonance imaging (MRI): The MRI creates a directional magnetic field or moment that causes odd protons and/or neutrons to spin in a characteristic motion

Table-2: Test-retest reliability using intraclass correlation coefficient (ICC).

Authors	Intracanal medicaments and procedures			
	irrigation	Antibiotic	Canal shaping	Cavity sealing materials
Argo-Gomez E et al, 2019[6]	NaOCl*	Minocycline Metronidazole Ciprofloxacin	EDTA**	Mineral trioxide aggregate glass ionomer cement
Rizk HM et al, 2019[8]	NaOCl*	Minocycline Metronidazole Ciprofloxacin	Filing 40-90 with k file	Collagen matrix Mineral trioxide aggregate Fuji 2 glass ionomer cement Resin Composite
Gaviño Orduña J et al, 2019[9]	Case of auto transplantation root canal procedure is not required aseptically socket assistance to revitalise pulp			
Mittal N, Parashar V et al, 2019[10]	NaOCl*	Metronidazole Ciprofloxacin	EDTA**	Placentax Collagen glass ionomer cement
Ragab RA et al, 2019[11]	NaOCl*	Metronidazole Ciprofloxacin	EDTA**	mineral trioxide aggregate glass ionomer cement
Nageh M et al, 2018[12]	NaOCl*	Metronidazole Ciprofloxacin	Manual Filing 60-80 k file	mineral trioxide aggregate glass ionomer cement
Prasad J et al, 2018[13]	NaOCl*	Metronidazole Ciprofloxacin	EDTA**	mineral trioxide aggregate glass ionomer cement
Santhakumar M et al, 2018[14]	NaOCl*	Minocycline Metronidazole Ciprofloxacin	EDTA**	mineral trioxide aggregate glass ionomer cement
Shivashankar VY et al, 2017[15]	NaOCl*	Minocycline Metronidazole Ciprofloxacin	propylene glycol and macrogol ointment	mineral trioxide aggregate glass ionomer cement
Alagl A et al, 2017[16]	NaOCl*	Cefaclor Metronidazole Ciprofloxacin	EDTA**	mineral trioxide aggregate
Bakhtiar H et al, 2017[17]	NaOCl	Cefaclor Metronidazole Ciprofloxacin	EDTA**	glass ionomer cement Composite resin
Nakashima M et al, 2017[18]	NaOCl* H_2O_2***	Minocycline levofloxacin	Instrumentation avoided	Double setting hyaluronic cement Composite Clinical grade auto collagen glass ionomer cement Poly carboxylate cement temporary crowns
Subash D et al, 2016[19]	NaOCl* H_2O_2***	Minocycline Metronidazole Ciprofloxacin	mesial canals up to ProTaper F3 file	Cotton pellet Cavit
Torabinejad M et al, 2011[6]	NaOCl* H_2O_2***	Minocycline Metronidazole Ciprofloxacin	Instrumentation avoided	mineral trioxide aggregate Cavit

*Sodium hypochlorite; ** Ethylenediaminetetraacetic acid; ****hydrogen peroxide

as the magnetic field goes across them. This notion is similar within all the atoms with odd number of neutrons or protons. This creates a resonate frequency within the medium that is read and presented by the machine.[33] This energy signature of revitalised tooth is compared with normal vital teeth in order to access tooth vitality.

Laser doppler flowmetry: This technique depends on the doppler principle. Movement or flow of red blood cells scatters or spreads the incident light from the laser diode. This scatter indicates the flow of blood. The output signal flux can be the product of red cell concentration and relative velocity of motion.[34] Laser flowmetry is a dependable method to analyse circulatory status in teeth.[35]

Pulse oximetry: Pulse oximetry has recently made its way to dentistry and can be introduced as a chair-side method. Pulsatile changes in the in absorption of red and infrared light absorbed by a vessel bed is calibrated in order to access oxygen saturation and in-term circulatory status.[36] None of the above studies showed calibration because it is a very unreliable method.[37]

Future Recommendations

There is a need to further study the impact of oral factors, and the significance of long-term effect of alloplastic biomaterials used should also be assessed with relationship to their release kinetics, dissolution behaviour and plasticisation along with its effect on the pulp. There is a

need for more extensive clinical trials with a larger sample categorised by age, ethnicity, gender and behavioural habits. A long-term understanding of the significance of materials used for coronal and apical seal also require a purpose-built assessment system in order to ensure the sterility of the de novo pulp tissue.

Conclusion

There is reasonable amount of evidence that pulp regeneration can be achieved via tissue engineering with PRP and PRF, which are successful methods with apical surgeries and in cases of transplantations,

Regenerated dental pulp tissue should exhibit angiogenesis, morphological and histological coherence/similarity to natural pulp along with generation of new innervation and odontoblasts to produce dentine, and only a histological examination can truly explain the nature of the de novo tissue.

Current strategies of pulpal regeneration have shown commendable success, but larger clinical trials are required to produce a definitive understanding.

Inorganic scaffolds -- ceramics and glasses -- are oxides, or contain oxides, and are highly reactive, or, alternatively, highly soluble. Decellularised scaffolds are not inert. A long-term follow-up of the effect of such materials needs to be done.

Standardisation of methods used to assess pulp vitality and grading is essential to quantify success in pulp revitalisation.

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