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Pulp Revascularization: A Boon for Future Therapy in Young Permanent Teeth.

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Abstract

Introduction: Pulp revascularization can be a favourable treatment option for permanent teeth with damaged pulp since it allows the continuous development of root and thicker walls which is in contrast with other treatment options. It requires minimum instrumentation and since the blood clot acts as a biological scaffold the formation of a good quality of blood clot is important. The three important components which are essential for pulp revascularization are stem cells, scaffolds and growth factors. Stem cells help in pulp revascularization due to their various unique properties/advantages like tissue specificity, anti-inflammatory potential.

Objectives: This review concentrates not only on the beneficial effects of pulp revascularization but also on the role of various other factors that influence and makes it a success like stem cells, growthfactors, scaffolds.

Materials and Methods: This review paper was written using original research articles, reviews, and case studies that were published in online databases like PubMed, Google Scholar and books like Cohen's Pathways of the Pulp 12th Edition.

Results: This review gives an acknowledgement of pulp revascularization in terms of its basic principle, process, role of stem cells and scaffolds and its comparison with other treatment options along with its disadvantages.

Keywords: Dentin, Growth factors, Pulp, Regeneration, Revascularization, Scaffolds.

Introduction

The dental pulp is a unique organ made up of soft connective tissue and a variety of specialised cells including, fibroblasts, blood vessel cells, neural cells, defence cells, dentin producing cells, progenitor cells, and ecm (extracellular matrix), which is made up of fibrillar proteins and ground material[1]. To secrete dentin is the basic function of pulp-dentin complex, but it's clear that it is capable of adapting responding defensively to different types of stimuli for maintaining its existence. The pulp preserves the dentin via self-defensive and homeostatic systems once tooth development gets complete[2]. Intense and severe stimuli like accidental trauma, iatrogenic causes, dental caries cause irreversible damage to the dental pulp which cause the two most wide spread diseases like pulpal and periapical diseases[3]. There are two different ways in which pulp disease typically manifests, the first one is, when the preservation of vitality is the key concern when the tooth pulp is still alive and potentially inflammatory. The plan of treatment is to encourage the remodelling of the underlying connective tissue and locally regenerate new dentin. Considering the second plot, pulp is absolutely lost due to tissue and cell decay that is brought on by enormous inflammation and infection. As a result, the pulp canal system is left without any living tissue which is typically severely infected. The goal in this situation is to attempting to generate new vital connective tissue, that resembles the tooth pulp ideally.

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How to cite the article: Gharat MG, Patil A, Yadav P, Jain AK, Mali S, Singh S. Pulp Revascularization: A Boon For Future Therapy In Young Permanent Teeth. Oral Maxillofac Pathol J 2024; 15(1). Page number 109-113.

Source of support: Nil

Conflict of interest: None

Knowledge of tooth mineralization moreover biological behaviour of the pulp-dentin complex has greatly increased as a result of considerable advancements in the area of managing dental caries[2]. The first attempt to revascularize the pulp tissue was conducted by Nygaard Ostby in 1961[4]. Revascularization operations are a gain over other techniques of treatment that result in short roots and thin, fragile root canal walls, even if the results are still somewhat unexpected and dental treatment for these teeth is difficult. When these don't

produce the desired outcome, they also keep space for other treatment options in addition to extraction[5].

Important stem cells and their propertiesThe important stem cells in pulp revascularization are DPSCs, SHEDs, PDLSCs, SCAPs, HERs which have properties like specificity of tissue, increased proliferation, differentiation, regeneration, etc. Pertaining to the uniqueness and capacity of progenitor cell types in the tooth pulp, there is still much to learn. A crucial step in regeneration would probably include the mobilisation of body's own stem cells, and the idea of cell homing presents intriguing possibilities[2]. It is known, in particular, that endothelial cells and DPSCs interact in order to regulate each other's functions. DPSCs have lately been discovered as a possible promise in the field of tissue regeneration[8] (Figs 1, 2, 3 and Table 1),

Growth factors for pulp revascularization:-

Table 2(12)

Scaffolds in pulp revascularization- Scaffolds are three-dimensional (3D) porous solid biomaterials designed. Some of the important scaffolds are:-

Blood clot- Lacks GFs and has less cytokines than PRP (Platelet Rich Plasma) and PRF (Platelet-Rich Fibrin), also clot formation occurs at a rate that's equivalent to the body's natural clotting along with slower healing time in comparison to PRP and PRF

PRP- There are fewer cytokines compared to PRF and thrombin is added to cause fibrinogen to become fibrin leads to a dramatic activation and quick polymerization in PRP resulting in an extensive monofilament network with low cytokine concentration. Slower recovery than with PRP. Limited regeneration of dentine and bone. Prior to actual cell ingrowth, morphogens are released to their highest levels. As a result, fewer signalling molecules are left for osteoblasts and odontoblasts in the surrounding tissues, BMSC (Bone mesenchymal Stem Cells) development is inhibited, and fibrin matrix is more vulnerable to washout in surgical settings.

PRF- Cytokine concentration at its highest level. A flexible three-dimensional fibrin network that promotes cytokine entanglement and cellular motility can be formed through slow physiological polymerization. Stronger and more robust fibrin matrix, faster and more effective healing kinetics than PRP, growth factor releases that peaks at 14 days, which corresponds to the growth pattern of the periapical tissues, BMSC proliferation and differentiation[9].

Bioactive ceramics- Both osteoblast development and differentiation have been shown to be improved by bioactive ce-

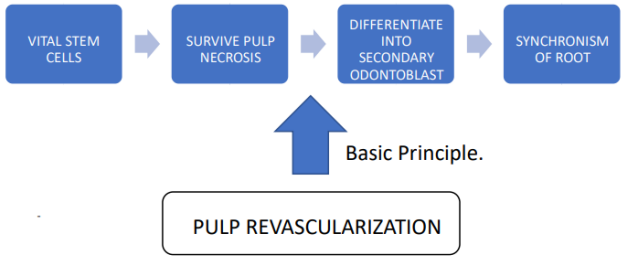

Fig. 1: Flowchart of Basic Principle of Pulp Revascularization.[6]

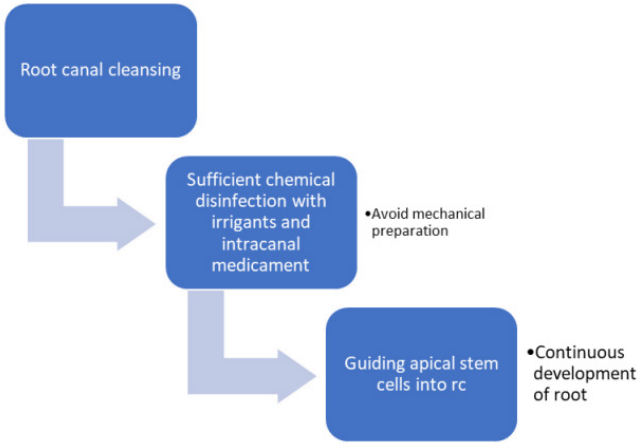

Fig. 2: Flowchart showing steps in pulp revascularization[3]

Table 1: Important stem cells and their properties

STEM CELL	ABOUT IT.
DPSCs (Dental pulp stem cell)	1.Have ability to regenerate dentin-pulp like complex. 2.Were first isolated from human tooth number 8 in 2000 by Gronthos et al.Contribute significantly to maintain a healthy balance between inflammation and repair/dentinogenesis shortly after infectious carious lesions or exposure to pulp. 3.Have demonstrated to express TLR4(Toll like receptors-4) and TLR2 Toll-like receptors in response to lipopolysaccharide(13).
SHED(Stem cells of human exfoliated deciduous/primary teeth)	1. Exfoliated deciduous teeth were used to harvest highly proliferative stem cells. 2.Capable of dividing to form a wide range of cell types like (Osteoblasts, neural cells, odontoblast) also induces bone formation(14).
PDLSCs(Periodontal ligament stem cells)	1. Isolated by Seo et al in 2004. 2.PDLSCs may have regenerative potential after seeding on a three-dimensional scaffold for application in regeneration, according to Trubiau et al. 3. It was reported by Li et al. that tissues similar to cementum and PDL are formed when PDLSCs are enrooted on biologically engineered dentin(15).

ramics. Their brittleness, difficulty in shape, and, in the case of HAP, an extraordinarily slow degradation rate has, however, limited their therapeutic applicability[3,8].

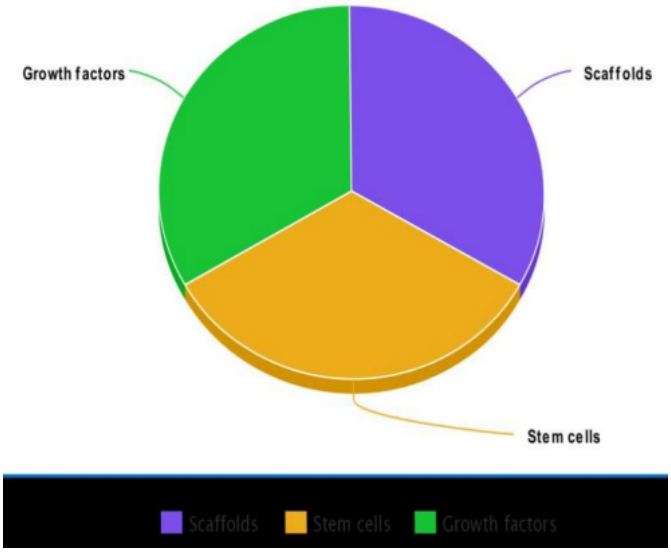

Fig. 3: Pie-chart of three important components of Pulp Revascularization.[7]

Conditions to be provided

Instead of tissue replacement using artificial swaps, utilising revascularisation/revitalisation methods to stimulate apexogenesis and tissue regeneration in developing teeth with non-vital pulps represents a new treatment modality. Repair of tissues can occur as in slough, unaffected, avulsed, immature adult teeth in aseptic conditions, in the residence of favourable 3D scaffold, progenitor cells and development of a bacteria-tight seal, is the theory on which revascularization/revitalization treatment is based on. Odontoblast like dentin producing cells can be formed/produced from SCAP due to their proximity to the blood circulation to the gums which might permit them to endure apical infection particularly in terms of building up dentinal walls and restoring root growth to improve the possibility of long-term tooth survival such approaches to treatment that are biologically based may be especially beneficial for necrotic, developing permanent teeth[10].

Radiographic evaluation for revascularization.

Pulp regeneration and apexification by using MTA (Mineral trioxide aggregate) apical plug are efficient treatments for developing teeth that are not vital. The results of teeth's radiographs that received MTA apexification when they were juvenile and those that underwent revascularization are equivalent. The results of the present investigation state that regenerative endodontic therapy leads to larger rise in root and dimen-

Table 2 : Different GFs (growth factors) with their source, functions, benefits(12) .

GF	PRIME SOURCE	FUNCTION	EFFECTIVENESS
BMP(Bone morphogenetic protein)	Osteoid	Osteoblast proliferation Calcification of bones are induced by BMP	BMP is utilized to induce mineral matrix secretion and synthesis by stem cells, and matrix CSF could be employed for boosting progenitor cell count
CSF(colony stimulating factor)	Multiple/large number of sources	Certain pluripotent bone stem cells are induced to proliferate by cytokines called CSFs	CSF could be administered for boosting progenitor cell production
FGF(Fibroblast growth factor)	Varied cell types.	Most cells are encouraged to grow by FGF	The number of stem cells can be increased by FGF
EGF(Epidermal growth factor)	Submandibular gland	EGF promotes the growth of glial, mesenchymal, and epithelial cells.	Stem cell count can be increased by EGF
IL (Interleukins IL-1 till IL-13)	white blood cells(WBCs)/ Leukocytes	The cellular and humoral immune responses are stimulated by Interleukins	The activity of inflammatory cell is promoted by interleukin
IGF(Insulin like growth factor can be I/II)	II-a number of cells, Liver	It assists many cell types to increase to increase in number	The number of stem cells can be increased using this growth factor
TGFAlpha(Transforming g factor	Keratinocytes, Cells of brain, macrophages	Importance in normal healing of the wound	The development of tissue and epithelial structure is caused
PDGF(Platelet derived growth factor)	Placenta, Endothelial cells, Platelets	The rapid increase in number of smooth muscle cells, glial cells, connective tissue cells is promoted	Number of stem cells can be promoted by this factor
NGF(Nerve growth factor)	It is a type protein that is secreted from tissue target of neuron.	It's very important for maintaining, making survive the sensory and sympathetic neurons	Encourages neuronal cell growth and survival

sions. Revascularization (mean=14.03±4.36% and 34.57±16.62%, respectively) was observed to result in a rise in root width when compared to MTA apexification (mean=-1.25±2.8% and - 3.36±4.13%, respectively) in postoperative x-rays after 3 and 6 months. This difference was statistically significant at the two time points (p 0.05). Additionally, significantly different among the two therapy groups was the elevation in root length (p 0.05). In particular, the revascularization group's percentage change in root length at three and six months, respectively was 3.44% and 12.76%, compared to 0.22% and 0.29% within the MTA group with its apexification[6].

To fully restore biological function, pulp regeneration includes restoring the missing or injured portions from the initial tooth pulp tissue. The revascularization of a developing adult tooth having an Infected pulp with necrosis and a periodontitis in the apex or ulceration is known as pulp revascularization. By depositing hard tissue, it can encourage the growth of roots and strengthen dentinal walls, offering a different therapeutic approach[3]. Revascularization is a current Treatment option technique for decaying teeth with an undeveloped apex; it is a much more conservative therapeutic option compared to conventional apexification treatments, in which a bleeding within the root canal is caused by inducing a stem cell response of the periapical dental papilla, which then forms a stable clot that permits the natural process of radicular maturation besides thickening the duct walls[11]. Immature secondary teeth with open apexes can go for Apexification however the teeth which are mature with closed apexes RCT is suitable, unfortunately due to Apexification and RCT there's loss of vitality of tooth. Pulp capping, pulpectomy and irreversible pulpitis procedures can be done/taken into account to treat the exposed pulp when there's no inflammation present and the pulp is partially vital. High success rate is shown by RCT but due to RCT these teeth loose vitality in addition to this there's loss of chief functions like root thickening, lengthening, maturation and dentin formation, this eventually gives rise to teeth which are non-vital, hard but break easily, vulnerable to reinfection and fracture. Anterior teeth show lower healing rates as compared to posterior teeth, also studies proved that rate of success is related or greatly depends on the correct canal filling length whether its anterior or posterior[12]. According to a study conducted by Tanida Srisuwan, Daniel J.Tilkorn, Sammy AL-Benna, Direct blood supply and stem cells have a role of success in revascularization and tissue regeneration[11]. For revascularization/revitaliza-

Fig. 4: Periapical index (PAI) scores of apical periodontitis 32 based on the reference radiographs[6]

Table 3: Comparison of Pulp Revascularization with other options[3].

TREATMENT OPTION	TREATMENT PROCEDURE	CONSTRAINTS AND SIDE-EFFECTS	RESULTS	RC (root canal) FILLINGS
RCT	Cultivating or preparing the root canal, sterilizing, filling	Pulp function loss Reinfection Restrictions due to age. Sensitivity due to technology	Teeth which don't contain living tissues(nonvital teeth).	Gutta percha(passive or inert material).
Pulp revascularization	Disinfection using sufficient amount of chemicals required, induction of bleeding followed by careful sealing.	Discoloration and calcification Outcomes which can't be predicted Individual differences Standardised clinical evaluation protocols do lack. Blood clots with effective molecules that aren't clear.	There's formation of novel dentin, development of root is continued.	Tissue similar to Periodontal.
Pulp regeneration	On the basis of strategies of tissue engineering eg.Endogenous cell homing, exogenous cell transplantation.	Unpredictable outcomes. Strict selection of case. Methods of storage, potential contamination immunorejection, transmission of pathogen, tumorigenesis	The homeostasis is restored and natural defence which promotes survival, the teeth are vital.	Dentin or pulplike tissue.

tion therapies, coronal sealing provision of a scaffold and disinfection of the RC system are to be taken into consideration[10].

1. Regenerated tissue can't be identified and clinical results with long term follow-up not yet available.

2. Discoloration of tooth due to the use of TAP(Triple antibiotic paste)[3].

3. There is no data demonstrating which type of scaffold is more effective in the treatment of adult permanent teeth.

4. In case of post and core, revascularization is not right treatment plan because vital tissue in apical two third of canal couldn't be violated for post placement.

Results

Revascularization can be considered as a successful vital therapy because the root canal gaps of the tooth contain vital tissue. The tissue which is formed is true pulp or pulp-like matter is unimportant as long as the walls of root canal and apex are still developing and protecting the tooth from fracture. Major Challenge is to be familiar with the various component steps which are optimised and combined to create a pulp-dentin complex that has been rejuvenated. One of the advantages of this therapy is that in a year follow-up, a tooth could possibly respond to an electric pulp test. Hence, revascularization is considered as a good alternative. Needful studies to be done in the future to research the vitality of pulp revascularization.

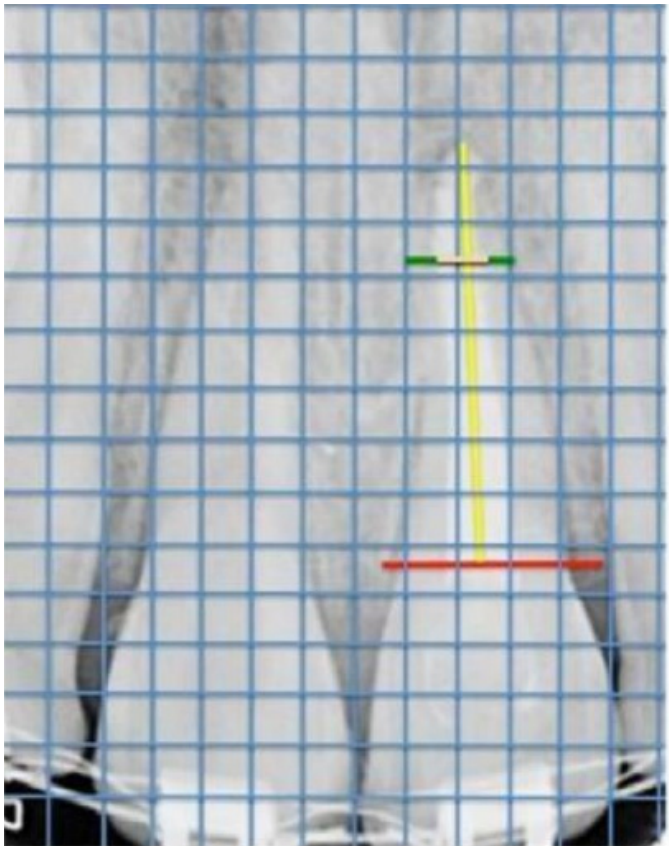

Fig. 5: Measurement of the differences in root length and dentin wall[6]

Adaptation from: Caleza-Jiménez C, Ribas-Pérez D, Biedma-Perea M, Solano-Mendoza B, Mendoza-Mendoza A. Radiographic differences observed following apexification vs revascularization in necrotic immature molars and incisors: a follow-up study of 18 teeth. European Archives of Paediatric Dentistry. 2022 Jun 1;23(3):381–9.

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