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OUTCOMES OF REGENERATIVE ENDODONTIC PROCEDURE IN IMMATURE PERMANENT TEETH WITH NECROTIC PULPS USING DIFFERENT ANTIMICROBIAL AGENTS AND/OR INTRACANAL MEDICAMENTS USING DIFFERENT PROTOCOLS: A SYSTEMATIC REVIEW

Endodontics

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ABSTRACT

Objective: To check the outcomes of Regenerative Endodontics procedure in immature permanent teeth with necrotic pulps using different antimicrobial agents And/Or Intracanal medicaments using different protocols.

Data sources: Internet sources of evidence were used were MEDLINE PubMed and the CENTRAL, Google Scholar, manual search using college library resources. All cross reference lists of the selected studies were screened for additional papers that could meet the eligibility criteria of the study. Articles published between 1st January 2000 and 31th August 2016

Results: Preliminary screening consisted total of 250 articles out of which 52 articles were selected. Only 29 papers with full- text were selected

Conclusion: Sodium hypochlorite was used in all the studies and hence thought to be the best irrigant. Triple/double antibiotic paste has shown maximum positive result. MTA was proved to be the best for coronal sealing over the blood clot.

KEYWORDS

Regenerative endodontics, immature tooth, intracanal medicament, CHX, TAP, Sodium hypochlorite, MTA

INTRODUCTION

Root canal therapy is a sequence of treatment for the infected pulp of a tooth which results in the elimination of infection and the protection of the decontaminated tooth from future microbial invasion.[1] Endodontic therapy involves the removal of the dental pulp, the subsequent shaping, cleaning, and decontamination of the hollows with small files and irrigating solutions, and the obturation (filling) of the decontaminated canals. Root canal treatment in pulpless or necrotic immature permanent teeth is considered to be the toughest task in endodontics.

The major challenges associated with endodontic treatment of teeth with open apices are achieving complete debridement, canal disinfection and optimal sealing of the root canal system.[3] In the absence of a natural apical constriction, the production of mineralized tissue in the apical region is important to create an apical barrier and allow 3-dimensional adaptation of obturating material within the root canal system.[3] Especially in young permanent teeth with immature roots, the pulp is integral to continue apexogenesis. Long term retention of a permanent tooth requires a root with a favorable crown/root ratio and dentinal walls that are thick enough to withstand normal function and apical barrier. Therefore, pulp preservation is a primary goal for treatment of the young permanent dentition. A tooth without a vital pulp, however, can remain clinically functional.[4]

Till date decontamination of root canal space by irrigation is considered key to success of endodontic treatment. Irrigation has a central role in during and after instrumentation, the irrigants facilitate removal of microorganisms, tissue remnants, and dentin chips from the root canal through a flushing mechanism. Irrigants can also help prevent packing of the hard and soft tissue in the apical root canal and extrusion of infected material into the periapical area. Some irrigating solutions dissolve either organic or inorganic tissue in the root canal.[5] Irrigators play a role of primary disinfection. They should have a maximal bactericidal and bacteriostatic effect while having a minimal cytotoxic effect on stem cells and fibroblasts to allow their survival and ability to proliferate. Commonly used irrigants are Saline, EDTA, Sodium hypochlorite, Chlorhexidine. Conventionally immature necrotic teeth where treated with calcium hydroxide apexification or apical barrier formation with MTA. Both the above mention procedure have various limitations.

Revascularization is a new treatment method for immature necrotic permanent teeth. Indeed, it would provide, after treatment, a vital tooth that would be able to complete its root maturation. The American Association of Endodontists' Glossary of Endodontic Terms (2012) defines regenerative endodontics as "biologically based procedures designed to physiologically replace damaged tooth structures, including dentin and root structures, as well as cells of the pulp-dentin complex." Up to now, apexification procedures were applied for these teeth: (i) using calcium dihydroxide to induce the formation of an apical calcified barrier; (ii) using mineral trioxide aggregate (MTA) or Biodentin to produce an artificial apical barrier.

Several procedures are designed to treat the incompletely formed root that occur following endodontic procedures. Apexification is defined as a method to induce a calcified barrier in a root with an open apex or the continued apical development of an incompletely formed root in teeth with necrotic pulp tissue.[6]This is distinct from revascularization, since apexification does not attempt to regain vital tissue in the canal space. A second term, apexogenesis, is defined as a vital pulp therapy procedure performed to encourage continued physiologic development and formation of the root end.[2] An important distinction is that apexogenesis is indicated for teeth in which there has been no loss of vascularity, thus no need to "revascularize" the canal space. Another term used to describe root development is maturogenesis.[7] In that the desired outcome of revascularization procedures is to set the stage for physiologic root development, the term that best describes revascularization outcomes. Mineral trioxide aggregate (MTA) proved to be an excellent candidate; however, apical plugs do not solve the problem of the thin and weak dentinal root canal walls and compromised crown root ratio[8,9]

Various regenerative endodontic treatment protocols have been associated with a successful clinical outcome and currently there is no single recommended protocol. Common features of cases with successful clinical outcomes after REPs[10,11] are: 1. Young patient 2.Necrotic pulp and immature apex 3.Minimal or no instrumentation of the dentinal walls 4.Placement of an intracanal medicament 5.Creation of a blood clot or protein scaffold in canal 6.Effective coronal seal. Regenerative endodontics often involves a two- or multi-step procedure.[10,12] The first appointment is centered on proper access and disinfection of the pulp space. Upon confirming the absence of clinical signs and symptoms, the second appointment focuses on removing the antimicrobial medicament, releasing growth factors from the dentin (e.g., by irrigating with ethylene diamine tetraacetic acid (EDTA), delivering stem cells into the root canal by stimulating bleeding[13] creating a scaffold (e.g., blood clot or platelet-rich plasma)[14,15], sealing the tooth by placing a pulp space barrier (e.g., MTA or resin-modified glass-ionomer) and permanent coronal restoration to prevent bacterial reinfection.[16] At the second appointment, the use of local anesthetic without a vasoconstrictor may better facilitate stimulation of apical bleeding.[17] Periapical tissues in immature teeth are rich in blood supply and contain stem cells that have the potentiality for tissue regeneration.[13]

The regenerative endodontic protocol depends on the regenerative capacity of periradicular tissues, which act as an endogenous source of the key elements of regeneration. However, a disinfected empty canal space cannot support the ingrowth of new regenerated tissues on its

own so a scaffold is needed for support. Advances in research focused on 3 key elements for tissue regeneration:[18,19] (1) stem cells that have the ability for proliferation and differentiation; (2) scaffold, which is a 3-dimensional structure that supports the regenerated tissue integrity; and (3) growth factors, which are secreted signals governing morphogenesis and differentiation[20] with periradicular abscess after luxation.[21-24] Research with topical antibiotics showed that a combination of metronidazole, minocycline, and ciprofloxacin could be effective against common endodontic pathogens in vitro and in vivo.[25,26]

Several case reports and series were published concerning revascularization procedures; using scaffolds, MTA plugs, biodentine, growth factors which act as the confounding factors however, the deficiency of prospective studies and clinical randomized trials prevents the widespread application of this promising treatment protocol. As given by American Association of endodontics The Guidelines for follow up should be Tooth is asymptomatic and functional Radiographic evaluation: 6-12 months 1. Resolution of periapical radiolucency.[2] May see increased dentinal wall thickness 12-24 months 1.Increased dentinal wall thickness 2.Increased root length.

The aim and focused question of this systematic review is to check the outcomes of Regenerative Endodontic procedure in immature permanent teeth with necrotic pulps using different antimicrobial agents And/Or Intracanal medicaments using different protocols.

MATERIALS AND METHODS:

Internet sources of evidence were used in the search of appropriate papers satisfying the study purpose: the National Library of Medicine (MEDLINE PubMed) and the Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, Google, Clinical trials registry and manual search using DPU college library resources. All cross reference lists of the selected studies were screened for additional papers that could meet the eligibility criteria of the study. The databases were searched up to and including August2016 using the search strategy. Keywords used for search strategy were as follows Immature tooth, regenerative endodontics, pulp revascularization, Intracanal medicaments, antibiotic paste, antimicrobial agents, calcium hydroxide, chlorohexidine, chlorhexidine with calcium hydroxide, mineral trioxide aggregate, growth factor, platelet rich fibrin.

INCLUSION CRITERIA:

1. Articles in English or those having detailed summary in English
2. Studies published between 1st Jan 2000 to 31st Aug 2016
3. Studies that provided information on pulp revascularization in immature permanent teeth with necrotic pulps using different antimicrobial agents
4. Studies evaluated pulp vitality
5. Studies evaluated any discolouration of teeth
6. Studies evaluated radiographical outcomes like apex closure, root canal wall thickening
7. Studies which evaluated the finding till minimum of 12 months.

EXCLUSION CRITERIA:

1. Review, abstracts, letters to editors, editorial and in vitro studies are excluded
2. Studies that did not meet the inclusion criteria

Table 1- PICOS Format

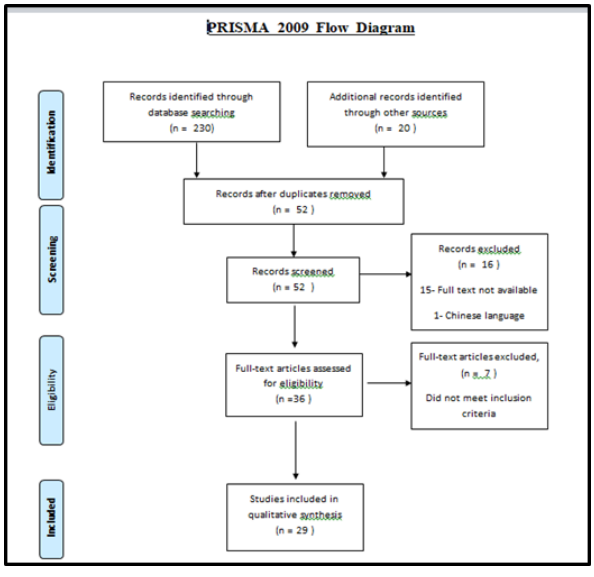
P	Participants- Immature permanent teeth with necrotic pulps
I	Intervention- Intracanal medicaments
C	Comparison- Calcium hydroxide Vs Antibiotic Paste Vs Chlorohexidine
O	Outcome- Pulp revascularization

STUDY SELECTION

Preliminary screening consisted total of 250 articles out of which 52 articles were selected. The papers were screened independently by two reviewers (SV and VP). At first the papers were screened by title and abstract. As a second step, full text papers were obtained when they fulfilled the criteria of the study aim. Any disagreement between the two reviewers was resolved after additional discussion. For full-text screening, the following criteria were taken into consideration: randomized clinical trials, case series, case reports were included. Only 29 papers with full- text were selected. Of the papers were selected, the data extracted were: Evaluation of increase in the thickness of the root walls and apex closure, evaluation of pulp vitality, evaluation of resolution of radiolucency, evaluation of discoloration of teeth.

DATA COLLECTION PROCESS

A standard pilot form in excel sheet was initially used and then all those headings not applicable for review were removed. Data extraction was done for one article and this form was reviewed by an expert and finalized. This was followed by data extraction for all the articles. The data items included were Author, Location, Year of publication, Sample size, Tooth number, Regenerative endodontic procedure, Outcomes, Time, Apical closure, Root lengthening, Dentin thickness, Apical lesion, Clinical findings, Response to pulp (table 2)



Study ID	Author,Year of publication & Location	Sample size	Tooth Number	Regenerative endodontic procedure	Outcome	Time	apical closure	Root lenghtning	dentin thickness	apical lesion	clinical findings	response to pulp testing
1	Johns et al (2016), India	2	11,21	Irrigation,with CHX, 5.25% NaOCl, Photoinitiater,Saline, PRF and MTA	Revas	10 months	yes	yes	yes	ne	No TOP +ve	negative
2	Faizuddin et al (2015), India	1	11	Irigtn with 5.25% NaOCl, Saline, 0.2% CHX, TAP, and 21 days PRF and after 3dy MTA	Revas	14 months	yes	yes	yes	ne	No TOP +ve	negative
3	Jadhav et al (2015), India	1	21	Irigtn with 5.25% NaOCl, Saline, 0.2% CHX, TAP, and 21 days PRF and after 3dy MTA	Revas	18 months	yes	yes	yes	ne	No TOP +ve	negativ e
4	Nagata et al (2014), Brazil	23	12G-1 TAP	Irrigation with 6% NaoCl, saline,2% CHX, TAP, after 21 days induce bleeding	Revas	19 months	yes	yes	yes	ne	No TOP +ve	negative

			11G-2 CHP	irrigation with 6% NaoCl, saline,2% CHX, CHP, after 21 days induce bleeding	Revas	19 months	yes	yes	yes	ne	No TOP +ve	negative
5	Nagy et al(2014), Egypt	36	12G-MTA	Irrigation with 2.6% NaOCl, TAP 2nd visit Irrigation 2.6% NaOcl, apical MTAplug, GP obturation	Revas	18 months	yes	yes	yes	ne	No TOP +ve	negative
			12G-REG(Blood Clot)	Irrigation with 2.6% NaOCl, TAP 2nd visit Irrigation 2.6% NaOcl, induce bleeding and coronal MTAplug			yes	yes	yes	ne	No TOP +ve	negative
			12G-FGF(blood clot +Scaffold)	Irrigation with 2.6% NaOCl, TAP 2nd visit irrigation 2.6% NaOCl, induce bleeding, hydrogel plcaed then MTA plug			yes	yes	yes	ne	No TOP +ve	negative
6	Shetty et al (2014), India	1		Irrigation with 5.25% NaOCl, TAP, 2nd Visit bleeding induced, and MTA	Revas	18 months	yes	yes	yes	no	no	negative
7	Becerra et al (2014), New york	1	35	Irrigation with 5.25% NaoCl+2 % CHX, TAP,2nd visit Irrigation Saline,5.25% NaOCl,Induce bleeding, MTA plug	Revas	24 months	yes	yes	yes	no	No TOP +ve	negative
8	Khimiya Paryani and Sahng Kim (2013), New York	2	11	Irrigation with 5.25% NaoCl, Calcium hydroxide,2nd visit Irrigation 5.25% NaOCl, 17%EDTA,Induce bleeding, Collacote with ciprfloxacin, MTA plug	Revas	22 months	yes	yes	yes	ne	No TOP +ve	negative
			21	Irrigation with 5.25% NaOCl,17%EDTA, ciprfloxacin poweder 22 days later same irrigation, Induce bleeding, Collacote, MTA plug	Revas	18 months	yes	yes	yes	ne	No TOP +ve	negative
9	Bezgin et al, (2013), Turkey	2	25	Irrigation with 2.5% NaOCl,012 CHX,TAP, 2nd visit iriigation then cPRP, MTA	Revas	12 months	yes	yes	yes	ne	No TOP +ve	negative
			35	Irrigation with 2.5% NaOCl,012 CHX,TAP, 2nd visit iriigation then cPRP, MTA			yes	yes	yes	ne	No TOP +ve	negative
10	Chen et al (2013), China	1	45	Irrigation with 3% NaOCl, Saline, CHX, TAP, 2nd Visit followup, 3rd visit bleeding induced, MTA	Revas	12 months	yes	yes	yes	ne	No TOP +ve	negative
11	D. Keswani and R. K. Pandey (2013), India	1	11	Irrigation with 5.25% NaOCl, TAP, 2nd visit irrigation 5.25% NaOCl, PRF, MTA plug	Revas	15 months	yes	yes	yes	no	No TOP +ve	negative
12	Yang et al (2013), China	1	22	Irrigation with 5.25% NaOCl, Saline, TAP, 2nd appointment 2.5% NaOCl, saline, bleeding induced	Revas	24 months	yes	yes	yes	no	No TOP +ve	negative
13	Martin (2013), New york	1	41	Irrigation with 5.25% NaOCl, TAP, 2nd visit irrigation 5.25% NaOCl, PRF, MTA plug	Revas	25 months	yes	yes	yes	no	No TOP +ve	negative
14	Jadhav et al (2012), India	20	10G-Conventional revascularisation	Irrigation with 2.5%NaOCL, TAP, 2nd visit bleeding induced	Revas	12 months	yes	yes	yes	no	No TOP +ve	negative
			10G-revascularisation+PRP	Irrigation with 2.5% NaOCl,TAP, 2nd visit iriigation then cPRP			yes	yes	yes	no	No TOP +ve	negative

15	Shivashankar et al (2012), India	1	11	Irrigation with 5.25% NaOCl, Saline,0.2% CHX, TAP, 2nd appointment bleeding induced then PRF,MTA	Revas	12 months	Yes	yes	yes	no	No TOP +ve	negative
16	Nosrat et al (2012), Iran	2	11,21	Irrigation with 5.25% NaOCl, TAP, 2nd visit irrigation 5.25% NaOCl, bleeding induced, MTA plug	Revas	6 yrs	Yes	yes	yes	no	No TOP +ve	negative
17	Soares et al (2012), Brazil	1	21	Irrigation with 2%CHX, 1:1 CH and 2% CHX, 2nd visit 17% EDTA induce bleeding, MTA	Revas	24 months	yes	yes	yes	no	No TOP +ve	negative
18	Cehreli et al (2012)	2	11,21	Irrigation with 2.5% NaOCl, Saline, TAP, 2nd Visit bleeding induced, and MTA	Revas	12 months	yes	yes	yes	no	No TOP +ve	negative
19	Jeeruphan et al (2012), Texas	20		Irrigation with 2.5% NaOCl,TAP, 2nd visit irrigation then bleeding induced, MTA	Revas	12 months	Yes	yes	yes	no	No TOP +ve	negative
20	Iwaya et al (2011), Japan	1	41	Irrigation with 5% NaOCl, 3% H2O2, 3rd visit CH and barium sulphate, 6th visit CH, 30% Iodoform 40.4% Silicon oil, Inert 6.9%	Revas	30 m then 13 yrs	yes	yes	yes	no	No TOP +ve	negative
21	Kim et al (2011), Korea	3	35	Irrigation with 3% NaOCl, TAP, 2nd Visit bleeding iduced, MTA	Revas	24 months	yes	yes	yes	no	No TOP +ve	negative
			35	Irrigation with 3% NaOCl, TAP, 2nd Visit bleeding induced, MTA		24 months	yes	yes	yes	no	No TOP +ve	negative
			35	Irrigation with 3% NaOCl,TAP, 2nd Visit bleeding induced, MTA		42 months	yes	yes	yes	no	No TOP +ve	negative
22	A Thomas, B Kahler (2010), Brisbane	1	35	Irrigation with 1% NaOCl,TAP, 2nd visit, bleeding induced and MTA	Revas	18 months	yes	yes	yes	no	No TOP +ve	negative
23	Petrino et al (2010), USA	3	11,21	Irrigation with 5.25% NaOCl, saline, 0.12% CHX, TAP, 2nd Visit bleeding induced, and MTA	Revas	12 months	yes	yes	yes	no	No TOP +ve	negative
			35,45	Irrigation with 5.25% NaOCl, TAP, 2nd Visit bleeding induced, and MTA		12 months	yes	yes	yes	no	No TOP +ve	negative
24	Ding et al (2009), China	12	only 3 revascul arization	Irrigation with 5.25% NaOCl, TAP, 2nd Visit bleeding induced, and MTA	Revas	18 months	yes	yes	yes	no	No TOP +ve	negative
25	Reynolds et al (2009), Washington	1	35,45	Irrigation with 6% NaOCl, Saline, 2% CHX, canal walls were etched with 35% phosphoric acid, TAP, 2nd Visit bleeding induced, and MTA	Revas	18 months	yes	yes	yes	no	no top +ve	negative
26	Cotti et al (2008), Italy	1	11	Irrigation with 5.25% NaOCl, CH, 2nd Visit bleeding induced, and MTA	Revas	30 months	yes	yes	yes	no	no top +ve	negative
27	Jung et al (2008), Texas	9	44,45	Irrigation with 5.25%NaOCl, TAP, 2nd visit bleeding induced	Revas	5 yrs	yes	yes	yes	no	No TOP +ve	negative
			45	Irrigation with 5.25% NaOCl, TAP, 2nd visit bleeding induced, amad		2yrs	yes	yes	yes	no	No TOP +ve	negative
			35,35,35,35	Irrigation with 5.25% NaOCl, TAP, 2nd Visit bleeding induced, and MTA		2yrs	yes	yes	yes	no	No TOP +ve	negative

			45	Irrigation with 5.25% NaOCl, TAP, 2nd Visit bleeding induced, and MTA		1yrs	yes	yes	yes	no	No TOP +ve	negative
			45	Irrigation with 5.25% NaOCl, TAP, 2nd Visit bleeding induced, and MTA		17 months	yes	yes	yes	no	No TOP +ve	negative
28	Francisco Banchs and Martin Trope (2004), USA	1	45	Irrigation with 5.25% NaOCl, TAP, 2nd Visit bleeding induced, and MTA	Revas	2yrs	yes	yes	yes	no	no top +ve	negative
29	Jojo Kottoor and Natanasabapathy velmurugan (2000), India	1	12	Irrigation with 5.25% NaOCl, TAP, 2nd visit irrigation 5.25% NaOCl, bleeding induced PRF, MTA plug	Revas	5 months	yes	yes	yes	no	No TOP +ve	negative

DISCUSSION

The management of immature necrotic teeth has been considered a great challenge in endodontics. Historically, the treatment of such cases was performed using calcium hydroxide apexification. However, the long-term use of calcium hydroxide has several drawbacks,[27] including multiple patient visits, low patient compliance, probability of canal contamination between visits, and increased dentin brittleness, which increase the risk of fracture. Recently, regenerative endodontics has gained much attention as a biologically based alternative. Regenerative approaches gained the advantage over apexification because they can allow for further root maturation in length and thickness by regenerated vital tissue.[1,28] Revascularization is considered a simple protocol by which pulp regeneration can be enhanced.[19,29]

Among the 30 included papers, the case reports and case series, randomized clinical trials have described the outcomes of treatment in patients who presented with immature permanent teeth with apical pathosis with or without associated sinus tract. Some of these cases were associated with apical periodontitis, or a dens evaginatus, where the thin occlusal tubercle often fractures, predisposing the tooth to bacterial infection and pulpal necrosis as often seen in mandibular premolars. After analyzing these case reports and series, it is understood that the following endodontic protocols had been followed for the treatment of necrotic immature permanent teeth. The procedure had been done in two to three visits.

The success of pulp revascularization treatment depends on three elements: root canal disinfection, the presence of a scaffold (blood clot), and hermetic coronary filling. In the first visit, disinfection of the root canal system had been carried out. This is considered the vital step for the success of the regeneration procedure. Bacterial invasion of root canal system causes the formation of bacterial biofilms. Hang on root canal walls, entrance of dentinal tubules, and in the apical area containing more complex anatomical crevices, bacterial biofilms are more resistant to disinfection procedures. Bacteria existing in depth and within the biofilm are in lag phase and therefore refractory to action of antibiotics and irrigators. To ensure optimal root canal disinfection for tissue regeneration, it is necessary to disrupt or eliminate biofilms. Most of authors agree to advocate no instrumentation procedure. Using root canal instrument could not only increase fragility of dentin walls but also injure stem cells present in the apical area of these dentin walls. Growth factor and other cells essential for the regeneration process could also be eliminated by instrumentation.

Various irrigant such as Hydrogen peroxide, sodium hypochlorite, EDTA, Chlorhexidine, Saline, Iodine are used in different concentrations and are thought to be excellent in achieving positive regenerative results Elimination of microorganisms and necrotic tissues from the root canal system is the key factor in successful revascularization8. Consequently, revascularization generally starts with chemical disinfection of the root canals using passive NaOCl4, chlorhexidine (CHX)[14,] NaOCl-CHX[30] or NaOCl–hydrogen peroxide (3%).[31] irrigation. Different concentrations of NaOCl including 6%, 5.25%, 2.5% and 1.25% and different concentrations of CHX including 2% and 0.12% have successful been used for this purpose; however, recent studies have shown that irrigation with CHX may be detrimental to stem cells.[32]

Studies have also revealed that CHX irrigation might have cytotoxic effects on human stem cells and interfere with the attachment of Dental Pulp Stem Cells to the root canal walls.[33,34] Additionally, it has been reported that interactions between NaOCl and CHX forms para-chloroaniline, which is known to be a carcinogen.[35]

So far, sodium hypochlorite remains irrigator reference in endodontic. It has a solvent action on necrotic tissue and an antiseptic effect widely demonstrated. However, it must be supplemented by a desalting. Recommended concentrations vary between 0.5 and 5.25%. Cytotoxicity of sodium hypochlorite is proportional to its concentration. The concentration of 2.5% seems to be the best compromise between efficiency and lack of toxicity.[36] Furthermore, Cunningham showed that elevation of the temperature at 37 C of the 2.5% sodium hypochlorite solution potentiates its solvent power and its efficiency becomes comparable to that of the solution to 5.25%.[37] Chlorhexidine 2% gel was proposed as a temporary medication. It has good action on candida and gram+ bacteria by the carryover effect. Indeed, its positively charged molecules confer the property of being adsorbed by the dentin walls and thus allow release of chlorhexidine for at least two to twelve weeks, preventing reinfection of the root canal during this period.[38] Despite this advantage, chlorhexidine does not have an effective dissolving action.

Johns et al (2016)[39] used photosensitizer to increase the potential of disinfectant or irrigant. Solution (tolonium chloride 0.01% w/v in aqueous solution) of the photosensitizer was placed inside the root canal (0.5 ml) with an endodontic needle and left inside the root canal for 2 minutes as pre-irradiation time. This report of pulp revascularization showed that disinfection with PDT combined with PRF leads to satisfactory root development in necrotic immature teeth.

Faizuddin et al (2015)[40] used Chlorhexidine with sodium hypochlorite and normal saline for irrigation and then gave triple antibiotic paste followed by platelet rich fibrin followed by MTA seal. PRF is potentially an ideal scaffold for regeneration of vital tissue in the necrotic immature teeth. Same results were observed by Bezgin et al (2013)[41]. Nagata et al (2014)[42] used two protocols in on 2% chlorhexidine with triple antibiotic paste followed by over-instrumentation and blood clot was formed and MTA was given to seal the canal and in other patient 2% chlorhexidine was used with calcium hydroxide paste in 1:1 ratio followed by over-instrumentation and blood clot formation and final seal with MTA. The tooth treated with TAP caused esthetic problem leading to tooth discoloration, which can be considered a disadvantage when compared with Calcium hydroxide paste. Whereas Reynold's et al[30] used chlorhexidine with sodium hypochlorite to disinfect the canal, He etched the walls with 35% phosphoric acid and used sodium perborate as bleaching agent. If crown discoloration occurs, treatment by intracoronal bleaching with sodium perborate should be attempted. In addition, the use of white MTA instead of grey MTA should also be considered. The modified protocol described in the present article is an attempt to avoid the undesired crown discoloration. Berecca et al (2014)[43] used 2% Chlorhexidine for irrigation then used Triple antibiotic paste and induced bleeding to forn a blood clot in the canal ant sealed the canal with MTA and found positive result radiographically and even

histologically. Similar results were found with Petrino et al(2014)[17] who used 0.12% CHX , Chen et al(2013)[44] 2% chlorhexidine and Shivashankar et al(2012)[45] who found who used 0.2% chlorhexidine.

Along with irrigation disinfection is also an important step in pulp revascularization. Disinfection in immature necrotic teeth is mainly dependent on chemical means including antimicrobial irrigation and intracanal medication without mechanical instrumentation. Calcium hydroxides, Calcium hydroxide in combination with chlorhexidine, triple antibiotic paste, double antibiotic paste and ciprofloxaxin alone.

Calcium dihydroxide, is a strong base (pH = 12.5–12.8); its ionic dissociation in Ca2+ and OH− induced genesis of hard tissue (apexification, tertiary dentin) and has an antibacterial effect by the release of ion OH-45. These ions OH− damage the cytoplasmic membrane, suppress the bacterial enzyme activity, denature proteins, damage DNA and thus inhibit any replication, and inactivate endotoxins.[46] Calcium dihydroxide has a low coefficient of dissociation (0.17), which is a good clinical feature since it allows a long term release of Ca2+ and OH−. Seven days seem sufficient to reduce the bacterial load in root canal at a level of negative culture.[47] Khimiya Paryani et al (2013)[48] resolution of clinical signs and symptoms with complete periapical healing and root lenghtning in mature permanent incisors with apical periodontitis after regenerative endodontic treatment after using calcium hydroxide as an intracanal medicament followed by only dusting ciprofloxacin powder in the canal in the next appointment and sealed the canal with MTA. In the 2nd case report only ciprofloxacin was used as intracanal medicaments after irrigation with 5.25% NaOCl, and bleeding was induced to form blood clot and sealing was done with MTA, this also showed positive radiographic as well as clinical results.

Iwaya et al (2011)[20] preformed regenerative endodontic procedure 3% calcium hydroxide and barium sulphate, after irrigation with 5% NaOCl, 3% Hydrogen peroxide. In the 6th visit the canal was disinfection using Calcium hydroxide, 30% Iodoform 40.4% Silicon oil, Inert 6.9%. As in this case no anti biotic was used still the results were satisfactory and no clinical signs and symptoms were seen. Especially no discoloration was noticed which is generally seen after use of triple antibiotic paste.

Triple antibiotic pastes are used commonly as intra canal medicaments. It contains Ciprofloxacin, minocycline and metronidazole in 1:1:1 ratio respectively. The triple antibiotic paste seems to be biocompatible but its current problem is the possible bacterial resistance. Minocycline is a semisynthetic tetracycline derivative with a similar action spectrum. It may be replaced by cefaclor in order to avoid any risk of unaesthetic coronary coloring[48] because minocycline binds to ions Ca++ by chelation and form insoluble complexes. However, cefaclor appears to be less effective against enterococci. An alternative could be to previously seal the dentinal tubules of the pulp chamber (etching and bonding) which was done Reynold's et at. Tetracycline would have ability to inhibit collagenase and metalloproteinases; it is not cytotoxic and is capable of increasing the level of interleukin-10 (anti-inflammatory cytokine). Acid pH of minocycline is not favorable to cultivation of stem cells; it would probably facilitate cell permeability of the antibiotic, which would keep long-term cytotoxicity. Ciprofloxacin has also an acid ph. Metronidazole is the only antibiotic of the mixture to have a neutral pH and thus it has no cytotoxicity for needed stem cells[49]

Nagy et at (2014)[51] performed randomized clinical trials on 36 teeth to check different agents and protocol for the regenerative endodontic procedure. 36 teeth were divide into 3 groups: Group1 was only MTA group, Group 2- regenerative procedure with over instrumentation and inducing bleeding for forming blood clot and Group 3: Scaffold was used at the end to create regenerative outcomes. Irrigation with 5.25% NaOCl and the Triple antibiotic paste was used in all the groups for intracanal medicament. Under the circumstances of this study, it can be concluded that both treatment protocols (ie, MTA apical plug and the regenerative endodontic procedure) were successful treatment options with regard to the closure of open apices. Regenerative endodontic procedures induced increase in root length, thickness, and apical closure. The use of an artificial hydrogel scaffold and bFGF was not essential for repair increase in root length, thickness, and apical closure increase in root length, thickness, and apical closure. Triple antibiotic paste caused esthetic problem leading to tooth discoloration, which can be considered a disadvantage when compared with Calcium hydroxide paste.

Out of 30 selected articles 22 articles have used triple antibiotic paste leading to success of the regenerative endodontic procedure. Considering the high success rate it has shown there is major drawback of it, that the minocycline present in the paste causes discolorations of the tooth. To overcome with this double antibiotic paste was introduced. Minocycline is a semisynthetic tetracycline derivative with a similar action spectrum.[48] It may be replaced by cefaclor in order to avoid any risk of unaesthetic coronary coloring because minocycline binds to ions Ca++ by chelation and form insoluble complexes.[49] However, cefaclor appears to be less effective against enterococci. An alternative could be to previously seal the dentinal tubules of the pulp chamber.

Soares et al(2013)[52], used 2% chlorhexidine with 1:1 calcium hydroxide and 2% chlorhexidine as intra canal medicament, followed by 17% EDTA as irrigant for the next appointment and induced bleeding to form blood clot and sealed it with MTA. Satisfactory results were observed in pulp revascularization using calcium hydroxide and 2% chlorhexidine.

After disinfection step, a suitable scaffold to encourage generation of new tissue must be filled in the root canal. At the same time, coronary access must be sealed to prevent further reinfection.[14] Induction of the root canal bleeding is done to bring in situ fibrin, platelets, and growth factor. All these elements are indispensable to formation of tissue regeneration. It would also create a matrix from which the growth of new vital tissue is possible into root canal space.[32] This would contribute to bring more growth factors and to create a biological tissue scaffold, which promotes tissue growth. Petrino et al (2010)[17] suggested using a collagen matrix to achieve optimal placement of MTA. However, in the cases reported here, a matrix of sufficient hardness to allow for proper placement of MTA below the CEJ was secured without the use of collagen. This may be attributed to the use of bovine thrombin and calcium chloride as cPRP coagulates in these cases, which resulted in adequate coagulation within 10 min of application. Bezgin et al (2013)[41] said that Concentrated platelet-rich plasma (cPRP) was found to be useful in constructing a scaffold for revascularization in the successful treatment of a periapical lesion and open apices. Although the use of PRP has certain disadvantages, such as the need for special equipment and drugs, drawing blood from young patients and high treatment costs.

All of the revascularized teeth from the included articles have showed satisfactory clinical and radiographical performances at long-term follow-ups. Therefore, the revascularization technique can be regarded as a reliable treatment modality for clinical use in necrotic immature teeth. Scarcity of randomized controlled clinical trials related to this topic resulting in a major limitation for this review, a proper Regenerative Endodontic procedure protocol need to made to have uniformity in the study design.

CONCLUSION:

The results obtained from included Randomized clinical trials, case reports, and case series it can be concluded that revitalization of necrotic infected immature tooth is possible under conditions of total canal disinfection using different concentration of irrigants like sodium hypochlorite, chlorhexidine, hydrogen peroxide and PRF, PRP are an ideal biomaterial for pulp-dentin complex regeneration. Sodium hypochlorite was used in all cases n hence it can be thought to be the best irrigant with goon antimicrobial property which would help in revascularization Various formulations of intracanal medicaments can be used to disinfect the canals like Calcium hydroxide, calcium hydroxide with chlorhexidine, Triple/double antibiotic paste, ciprofloxacin alone out of which Triple/double antibiotic paste has shown maximum positive result, only the disadvantage being the discoloration due minocycline. MTA was proved to be the best for coronal sealing over the blood clot. The only disadvantage faced with it was its manipulation to place inside the canal.

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