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Dual Glory in Regenerative Endodontics

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Abstract: *Traditionally, apexification has been the mode of treatment for immature permanent teeth that have lost pulp vitality. Since tissue engineering cannot be attained with apexification, a novel technique called regenerative endodontic was developed. Regenerative endodontic has been proposed to replace damaged and underdeveloped tooth structure with normal pulp- dentine tissue by providing a natural ECM mimicking environment, stem cells signaling molecules and scaffolds. In addition, clinical success of regenerative endodontic treatment can be evidenced by absence of signs and symptoms, no bony pathology, a disinfected pulp and maturation of root dentine in length and thickness. The construction of biomimetic microenvironment of pulp dentine- tissueis a key component of tissue engineering based regenerative endodontic. The biomimetic microenvironment are composed of synthetic nano scaled polymeric fiber structure that mimics native pulp extracellular matrix and functions as a scaffold of pulp dentine tissue complex and recruit pluripotent stem cells from the vicinity of the apex. This review focuses on the combined benefits of electronspun nanofibers and development and application of biomimetic microenvironment of pulp – dentine tissue along with recent progress in endodontic particularly encouraging regenerative outcomes achieved by evoked bleeding therapy in treatment of necrotic immature permanent teeth.*

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I. Introduction

Regenerative endodontics is one among the most innovative developments in the field of dental science in this new era and endodontists are at the forefront of this leading edge research. Like iron and steel to the industrial revolution, like microchip to the tech revolution, regenerative endodontic have become the driving force to this next revolution in endodontics. The American association of endodontic glossary of endodontic term defines regeneration endodontic as biologically based procedure designed to physiologically replace damaged tooth structure including dentine and root structures as well as including dentin and cells of pulp dentin complex i.e it is the process of renewal , restoration and growth that makes genomes , cells or organism resilient to natural fluctuation or events that cause disturbance or damage by capturing the ability to use stem cells that naturally reside in and around the tooth (1). The periradicular tissues of immature teeth are rich in blood supply and contain stem cells that have the potential for tissue regeneration(2). Currently two conceptshave been devised in regenerative endodontic to treat non vital infected teeth - one is the active pursuit of pulp dentine regeneration to implant or regrow pulp tissues based on tissue engineering principles and the other in which new living pulp tissue is expected to form from the cells present in apical end of the teeth itself , by creating an environment conducive to revascularization of root canal system and allowing continued root development (3).

II. Development Of Regenerative Endodontic Procedures

The concept of regenerative therapy relies on the regenerative capacity of stem cells derived from apical papilla or other apical sources which are introduces into root canals through the intentional laceration of periapical tissues (4,5).During induction of periapical bleeding the bioactive peptides and immune cells which are contained in the blood has complement components such as c3bcan opsonize bacteria and immunoglobin can coat and localize bacteria to facilitate phagocytosis by activated polymorphonuclear leukocytes and macrophages through c3b and fc receptors on these phagocytes. In addition mesenchymal stem cells can secrete antimicrobial peptide LL – 37(6,7,8), up regulate genes involved in promoting phagocytosis and bacteria killing and augments the antibacterial activity of immune cells secrete large amounts of IL6, IL8 and MIF cytokines to recruit and activate PMN leukocytes and macrophages.It was also suggested that LL-37 might contribute to regeneration of dentine –pulp complex in regenerative endodontic(6,9). Therefore induction of periapical bleeding into the canal space during regenerative endodontic therapy may enhance antimicrobial clearance in canal space. (Figure 1). After which a thorough disinfection protocol performed to obtain bacteria free environment conducive to tissue regeneration Naocl is one the most popular irrigants in endodontic (4,10,11). EDTA is a chelating agent capable of removing inorganic components from the smear layer by binding divalent cations(4,10,11). In addition to its antiseptic effect Naocl can also dissolve organic tissue including necrotic pulp tissue. Recently , Nacl (1 – 6%) has shown to be extremely cytotoxic(12). Another study reported 1.5% Nacl is more favorable for stem cell survival when compared to 3% Naocl(4,13) . EDTA promotes stem cell survival , migration and attachment onto the dentine surface that is largely impaired if Naocl is used as last irrigant(4,14). Thus if only NaOCl was used stem cells delivered into root canal system would proliferate away from dentinal walls without the molecular cues present in dentin that cold maximize their dentinogenic differentiation and minimize the damaging effect of Naocl on the dentinal structures and composition necessary for desirable stem cell fate (4,13,5). The intracanal medicament mainly used is the triple antibiotic paste (TAP- ciprofloxacin, metronidazole, minocycline which is a highly concentrated antibiotic paste.Ruperel et al (4) have shown that the widelyused creamy paste(1g/ml) of the triple antibiotic mixture is toxic to stem cells from the apical papilla (SCAP)(4) and the deleterious effect of the antibiotics remained in the dentinal wall even after the mixture was removed from the root canal.Collectively the TAP

concentration ranging from 0.01 to 0.1mg /ml were not cytotoxic and concentration of 1mg/ml was only moderately harmful when applied directly onto SCAP(4,15).However antibiotics mixed with water or saline cannot be used as an intracanal medicament as the watery mixture cannot be retained inside the root canals(4,16).Therefore it would be beneficial and advantageous to use biocompatible nanofibers – based intracanal drug delivery construct to releaseantibiotics at lower yet antimicrobially effect concentration (4,16). However with current root canaltreatment modalities the challenge also lies in designing and fabricating biomimetic materials like enamel, dentin, cementum, pulp, bone and periodontal ligament and focus should be toward regenerating the diseased and necrotic tissues rather than replacing them(17).

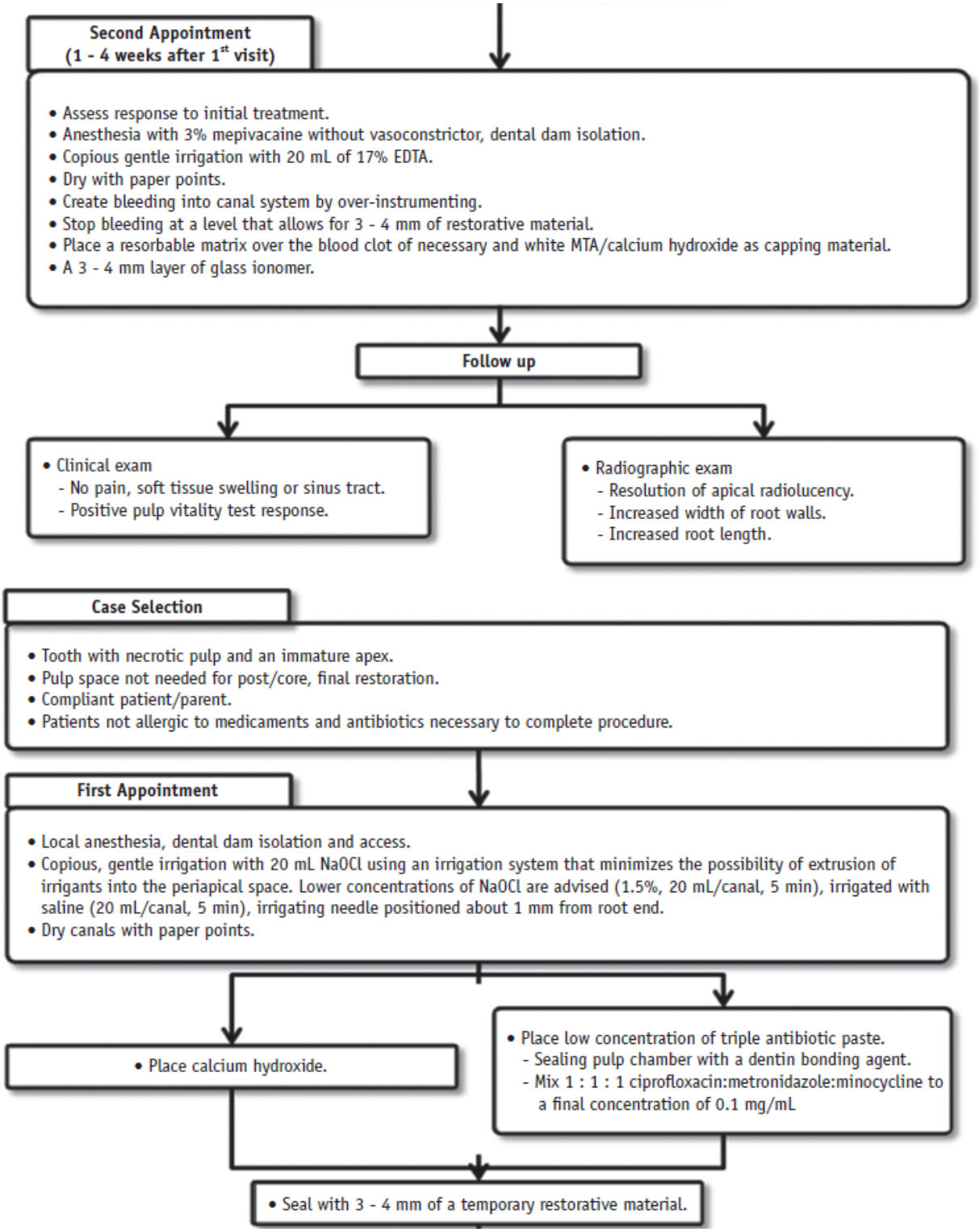

Figure 1: The current considerations for regenerative endodontic treatment procedures (courtesy of the American Association of Endodontics). NaOCl, sodium hypochlorite; EDTA, ethylenediaminetetraacetic acid; MTA, mineral trioxide aggregate. Ref (Bin Na Lee et all).

III. Electron Spun Nanofibers

Currently electron spinning or electric spinning a textile technology is employed to fabricate antibiotic containing polymer based nano fibers for drug delivery applications in dentistry, to eradicate periodontal and endodontic infection (4,18,19,16)(Figure 2).The reason behind the use of antibiotic containing nanofibers as 3D tubular drug delivery system is based on the fact of addition of low antibiotic concentration and slow drug release provided by these nanofibers constructs will be able to eradicate infection, biofilm colonization inside dentinal tubules and thus create a bacteria free environment favorable to tissue regeneration (4,18,16,20-26).In electrospinning, a polymer solution/melt containing the desired concentration of antibiotics is prepared in order to produce nanofibers [4,16,19]. A high-voltage source is used to generate an electrical potential difference between the metallic needle tip and the grounded collector fixed at a predetermined distance, which overcomes the surface tension of the fluid droplet, creating a jet. The fluid jet experiences whipping instabilities and tends to dry and produce nano- to micron-sized polymeric fibers(4,16,19). As previously indicated, the chosen polymer solution can be incorporated with one or a combination of antibiotics, making it possible to fabricate fibers with a narrow or wide spectrum of action (e.g., ciprofloxacin [CIP], metronidazole [MET], and minocycline [MINO], among others) that have been shown to inhibit the growth of endodontic pathogens.(4)(Table 1).

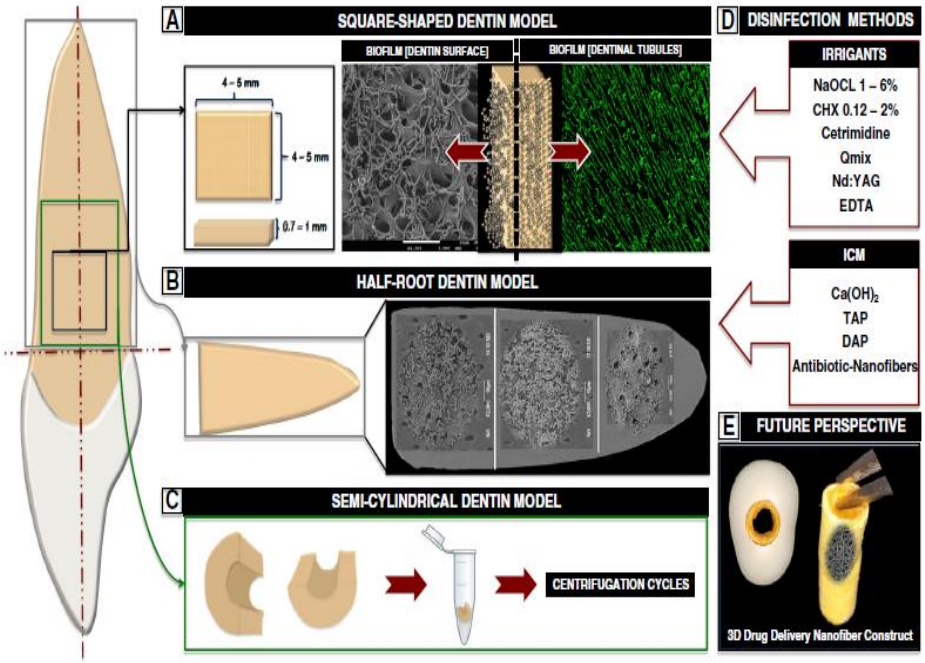

Fig 2: In vitro human teeth models for biofilm formation. A Square – shaped dentin model for biofilm formation both on the surface and inside the dentinal tubules. B. Half- root dentin model for biofilm growth induction on the cervical, medium and apical thirds. C. Semi –cylindrical root dentin model to mimic long term biofilm infection throughout the dentinal tubules using centrifugation. D. Disinfection methods including chemical irrigants and intracanal medications. (ICM).E. Future perspective of a novel 3D tubular drug delivery construct designed to perfectly adapt to the root canal shaped and diameter(4).

EVIDENCE TO SUBSTANTIATE

MICRO ORGANISM	FINDINGS
E. faecalis	Susceptible to 25wt % of CIP Nano fibers(1,21)
A.naesludii	Significant bacterial death on exposure to triple antibiotic containing Nano fibers (1,20)
P. gingivalis	Susceptible to triple antibiotic containing Nano fibers(1,19).

Ref: Maria T. P. Albuquerque1,2&Julianay. Nagata3 &Anibal R.Diogenes4 &Asma A. Azabi1 & Richard L. Gregory1 & Marco C. Bottino1 ; Clinical Perspective Of Electron Spun Nanofibers.; 17 June 2016 ; Curr Oral Health Rep (2016) 3:209–220 ;

IV. Biomimetic Microenvironments

The key factors to regenerate the function and form of pulp dentine complex is the construction of biomimetic microenvironment(27).Generally cells respond differently to physiochemical and mechanical properties of microenvironment The interaction between the cells and the Extracellular Matrix(ECM) control differentiation, migration , and proliferation as well as tissue remodeling (27).Therefore to overcome this scenario an ECM mimicking biomimetic microenvironment has been designed by incorporating various moieties and features derived from ECM.This biomimetic microenvironment is mainly developed through peptide amphiphiles, cell homing , stem cells , growth factors(27,28-32).

Stem cells

Stem cells from apical papilla (SCAP) will have higher proliferation rate as compared to dental pulp stem cells (DPSC). Therefore a stem cell based engineering approach can produce realistic pulp dentine regeneration .

Growth factors

Growth factors are proteins that bind to receptors on the cell and act as signals to induce cellular proliferation and / or differentiation. Examples of key growth factors present in pulp and dentine formation include bone morphogenic protein (BMP), transforming growth factor beta (TGF-β) and fibroblastic growth factor(FGF)(2). Current regenerative endodontic procedure aims to utilize growth factors found in platelets and dentine (2). Recent studies have shown that dentine contains a number of bioactive molecules that when released play an important role in regenerative endodontic. EDTA is believed to stimulate stem cell proliferation by facilitating the release of growth factorsgrowth factor like (TGF-β1), (FGF-2), and (VEGF) from the dentine matrix (4,5,14,12).

Peptide amphiphiles

ECM proteins potentially carry problems for clinical applications including undesirable immune response, higher risk for infection, array in biological sources and increased clinical cost(2,28). To overcome such limitations small peptide sequences derived from ECM proteins have been utilized such as Gl-Arg-Gly-Asp-Ser(33,34). But these isolated ECM peptide still possess some limitation of encapsulating biomaterials. To overcome such limitations Nano – scale Peptide Amphiphiles (PA)Nano matrix gel(35) have been proposed as a promising solution by synthetically recapitulating the ECM structure. The PA is a hydrophilic head , consisting of a functional peptide sequences attaches to a hydrophobic alkyl tail .The internal peptide structure can be modified to mimic the characteristic properties of the natural ECM (27,36-39). PA Nano matrix gel possesses qualities such as rapid gel like 3D network formation by self assembly, versatility to incorporate various cell adhesive moieties and cell mediated degradable sites for progressive scaffold degradation and eventually replaced by host ECM. (40).The development of the gel which uses PA for encapsulation of the antibiotics to create a sustained local release drug delivery system is still in preliminary stages but shows very promising results . The developed gel which contains ciprofloxacin and metronidazole was tested against two prominent bacterial strain in endodontic infections E.faecalis and T. denticola. Their results portrayed that the developed gel had a greater synergistic antibacterial effect than antibiotic alone (27,41).

Cell homing

The cell homing is a process migration of mobilized hematopoietic stem cells via vascular structure towards certain tissue using active navigation(27,42-44) . This involves the use of chemotactic factors like stromal cells derived factor (SDF-1) that can induce migration of stem cells from the periapical area into the root canal .a variation of pulp dentine regeneration can be resulted from the combination of cell homing with cell transplantation and a variety of growth factors(2,45). Immune rejection is not an issue and the regulatory approval process to use this technique in human patients would be much easier and cost much lower. However the results may depend on the distance that cells need to migrate so the longer the root length , less favorable the prognosis would be.

V. Theory Behind The Science

Collagen and chitosan constitute the base materials of the biomimetic scaffold. These are both naturally occurring biopolymers are biocompatible and biodegradable without causing adverse immune reactions . .Moreover chitosan also possesses antimicrobial properties that can potentially prevent secondary infections during and after pulp tissue regeneration especially after the native pulp has been under bacterial attack. In combination with the immunomodulatory property of BMSCs, a potent system to actively fight infection can also be developed. The ECM itself is secreted by the cells, consists of structural and functional proteins present in the pulp tissue and is incorporated three dimensionally within the collagen/chitosan framework. One of the features of the ECM is that it presents a completely engineered pulp environment containing physiologically relevant amounts of growth factors, cytokines, and metalloproteases. Structural proteins such as collagen and fibronectin can sequester the growth factors and present them to the cells in a manner that mimics the biological scenario in vivo.

VI. Future In Regenerative Endodontics

Recent studies in tissue engineering have adopted extracellular matrix (ECM) derived scaffolds as natural and cytocompatible microenvironments for tissue regeneration. The dentin matrix, specifically, has been shown to be associated with a host of soluble and insoluble signaling molecules that can promote odontogenesis. Recently developed novel bioink, which is a blending printable alginate (3% w/v) hydrogels with the soluble and insoluble fractions of the dentin matrix. With optimized printing parameters and the concentrations of the individual components of the bioink for print accuracy, cell viability and odontogenic potential. This novel bioinks have demonstrable cytocompatibility and natural odontogenic capacity, which can be a used to reproducibly fabricate scaffolds with complex three-dimensional microarchitectures for regenerative dentistry in the future.

VII. Conclusion

Regenerative endodontic strategies have the potential to save lots of teeth which have compromised structural integrity. Each of the regenerative techniques has merits and demerits, and a few of the techniques are hypothetical, or at an early stage of development. This review article is focused on the current prospects onbiomimetic microenvironments as a scaffold of pulpdentincomplex regeneration via current tissue engineeringconcepts and electronspun polymer nanofibres for

intracanal drug delivery. The future will show which of the multiple approaches in regenerative endodontics will withstand the test of clinical usage with more number of in vitro and in vivo tests. Therefore we can build up an imperative future stating that vitality is not just an ability to persist but is an ability to start over.

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