Journal of Drug Delivery Science and Technology 39 (2017) 334–340

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Local drug delivery in endodontics: A literature review

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ARTICLE INFO

Article history:
Received 21 August 2016
Received in revised form
12 April 2017
Accepted 12 April 2017
Available online 13 April 2017

Keywords:
Drug delivery
Endodontics
Regeneration
Dentistry

ABSTRACT

The oral cavity contains a wide variety of microorganisms responsible for numerous infectious diseases, such as dental caries and periodontitis. The presence of biofilm in the complicated dental anatomy makes it difficult to disinfect infected structures. In endodontic treatments, a variety of drugs and delivery systems are routinely used to overcome those difficulties, although they lead to limited success. This review discusses dental medicaments such as formocresol and formaldehyde, frequently used in the past, and their risks. Materials widely used in current practice will also be reviewed, including pulp capping materials, calcium hydroxide, endodontic sealers, calcium silicate–based cements, and endodontic irrigants. Recently introduced regenerative endodontic treatments require suitable vehicles for controlled release of disinfecting drugs and bioactive molecules for pulp regeneration. This review details the various applications of local drug delivery in the field of endodontics and highlights potential innovations for the future.

Contents

1. Introduction

The oral cavity contains a wide variety of microorganisms that can form biofilms and cause infectious diseases, such as caries and periodontitis. Dental caries, if not properly controlled, can progress from the surface enamel to the deep dentin and finally attack the underlying pulpal tissues, leading to pulpitis and apical pathosis [1]. Endodontic therapy or root canal treatment is a sequence of procedures to treat irreversibly or reversibly affected dental pulp, which results in the elimination of infection and protection of the decontaminated tooth from future microbial invasion [2].

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http://dx.doi.org/10.1016/j.jddst.2017.04.018
1773-2247/

Basically, pulpal and periapical inflammation are immunological responses to sustained bacterial stimuli [3]. The overall strategies for endodontic treatment can be summarized as complete removal of bacteria, their by-products, and pulpal remnants from infected root canals and hermetic sealing of the disinfected canals [4].

Endodontic treatment is considered fairly predictable, with reported success rates of 86–98% [5] despite a lack of a consensus on the criteria for success [6]. More often than not, endodontic biofilms are presumed to be one of the essential causes of refractory infections and subsequent endodontic failures [7] because they are highly resistant to contemporary antimicrobial measures. Specifically, resistant species include *Enterococcus faecalis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Streptococcus species*, *Actinomyces* species, and *Candida* species [8,9].

To enhance the efficacy of disinfection of the intracanal space, antibacterial medicaments and root canal irrigants are generally used as an integral part of treatment, but shaping and cleaning, i.e., mechanical debridement, is currently regarded as the key step in decontamination [4,10]. The intricate anatomy of root canal systems has always been a major obstacle to chemicomechanical preparations by hampering the intimate contact of antimicrobial agents. Therefore, various attempts to increase the efficacy of the antimicrobial approach under these harsh conditions, including irrigation, intracanal medicaments, and root canal sealings [11–15], have been the focus of extensive research. In this regard, it could be said that local drug delivery to the intended site of action has traditionally been sought in the field of endodontics. Local drug delivery is also required in other endodontic-related procedures, such as direct/indirect pulp capping, pulpotomy, and the recently introduced regenerative endodontic therapy. This review details the various approaches currently used for local drug delivery in the field of endodontics and examines potential future innovations.

2. Traditional chemical pulp devitalization and cessation of pulp inflammation: formocresol and formaldehyde release

The use of intracanal medicaments dates back to the 1840s, when their primary purpose was devitalization of pulp tissue [16]. A number of phenolics, such as parachlorophenol, camphorated parachlorophenol, creosote, cresol, cresatin, and thymol, are drugs with a long history that began in the 1800s. In the category of aldehydes, formocresol was popularly used as a root canal medicament and played a major role in the pulpotomy of deciduous teeth since Buckley introduced it in 1904 [17]. Halides (including sodium hypochlorite), antibiotics, steroids, and non-steroidal anti-inflammatory drugs have also been reported as intracanal medicaments, although none of them is dominant in current practice [18].

Phenolics, aldehydes, and their combinations show strong, nonspecific, bactericidal effects. Because it is difficult to apply them to the root canal exclusively, they were often applied to the pulp chamber or at the orifice of the root canal. However, delivery control was impossible, and their marked cytotoxicity [19] prevented their continued use. In addition, formaldehyde from formocresol demonstrates teratogenicity and tumorigenicity [20,21]. The American Association of Endodontists issued a position paper on the use of formaldehyde- and paraformaldehyde-containing materials, recommending against the use of these compounds during endodontic treatment due to their toxicity and carcinogenicity [22]. However, the use of formocresol in the pulpotomy of deciduous teeth is still advocated as the standard procedure with reliable prognosis, although the identification of alternatives is a topic of ongoing research [23,24].

The use of formaldehyde might be less concerning than was originally believed [25]. Newer studies with more rigorous methodologies have revealed that the amount of formaldehyde released during formocresol pulpotomies is only 1/40 of the normal endogenous level in humans [26,27]. In fact, formaldehyde is a natural by-product of amino acid metabolism in almost all cells, with the endogenous level known to be 3–12 ng/g in tissue [28] and 2.5 ppm in plasma [29]. Interestingly, popularly used endodontic epoxy resin sealers, like AH26, AH Plus, N2, and EZ-Fill contain hexamethylenetetramine, which owes its antibacterial action to the release of formaldehyde in acidic environments [30,31]. Thus, formaldehyde is released after the application of these endodontic sealers, but in quantities considered negligible. In addition, dissolved formaldehyde is eliminated rapidly in the urine. Though unintended, the antimicrobial effect of formaldehyde is beneficial for removing bacteria that remain around a root canal, and it has an advantage over other materials used as root canal sealers. The antibiofilm properties of endodontic sealers are briefly discussed later in this review.

3. Vital pulp therapy (or pulp preservation)

3.1. Pulp capping

Pulp capping is a treatment for exposed or nearly exposed vital pulp using various dental materials, such as calcium hydroxide [32], bonded composite resins [33], or mineral trioxide aggregate (MTA) [34]. This treatment attempts to facilitate reparative dentin formation [35] and vital pulp maintenance [36]. However, reported 5-year success rates for direct pulp capping in permanent teeth with a mature apex are fairly low (33–50%) [37]. A primary reason for this low rate of success is the lack of an established strategy for improving pulp inflammation [38]. Steroids [39], osteogenic protein-1 [40], and transforming growth factor-beta [41] have been studied as potential anti-inflammatory agents for treating inflamed pulp.

In an attempt to ensure suitable application of these drugs to exposed dentin, various drug delivery vehicles have been evaluated [42]. A clinically relevant vehicle should possess acceptable maneuverability and required drug delivery properties followed by complete degradation. Komabayashi et al. [43] reported the use of light-cured hydrogels of polyethylene glycol-maleate-citrate (PEGMC) in an in vitro study. This biocompatible and biodegradable hydrogel showed controlled $Ca2+$ release with low cell toxicity when calcium hydroxide was incorporated. On the other hand, the release profiles of two interesting drugs for dental pulp protection (propolis and sildenafil citrate) were evaluated after incorporation into a thermoresponsive vehicle that was liquid at room temperature and a gel at mouth temperature. The vehicles were made of various combinations of P407 poloxamer and Carbopol 934P [44]. Propolis is a strong resinous adhesive used in endodontics for its antimicrobial, anti-inflammatory, and antioxidant properties. Sildenafil citrate, a phosphodiesterase type-5 inhibitor that is commonly used in the management of erectile dysfunction, has been reported to increase the concentration of NO, an important factor in pulp protection, resulting in reduced inflammation. However, there have been no preclinical or clinical evaluations of those drugs in a promising thermoresponsive delivery vehicle.

4. Drug delivery through the pulp chamber in a pulpless tooth

4.1. Root canal disinfection

For root canal disinfection, multitude of irrigants have been applied, including sodium hypochlorite [45], ethylene-diamine-tetra acetic acid (EDTA) [46], and chlorhexidine [47]. Without any exceptions, this procedure carries an innate danger of apical