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Review Article

Local Drug Delivery Systems for Pain Management During and After Endodontic Therapy

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Abstract

Endodontic therapy can land up in failures leading to intra-operative and post-operative pain due to multiple factors. Managing such pain becomes a crucial factor for success of endodontic treatment and patient satisfaction in dental practice. Various treatment modalities are utilized to manage such conditions such as de-occluding from antagonist, re-instrumentation, cortical trephination, incision followed by drainage, administrating systemic antibiotics and analgesics. Transformations in the regimen of therapy to has evolved from radical to conservative mode which nowadays utilize prolonged contact of the analgesic, antibiotic or anesthetic agents to alleviate intra and/or post-operative endodontic pain through controlled drug release system minimizing the risk of systemic as well as local tissue toxicity, and at the same time providing maximum benefits to the patients. Thus, aim of this paper is to review and highlight various controlled drug delivery techniques to manage intra and post-operative endodontic pain.

Keywords: Endodontic Therapy; Local Drug Delivery; Pain Management

Introduction

The high incidence of dental diseases, particularly caries and endodontic involvement of teeth is major health ailment in all parts of the world, common to all ages, races and genders [1]. It hinders lifespan of dental tissues, due to pulp-dentin complex exposure secondary to physical, chemical or biological insults landing up into pulpal and periradicular tissues diseases [2]. Colonization of pathogenic microbial species into endodontic system and tissues progresses to endodontic infections, rendering healthy pulp land up diseased condition [3]. The primary aim of endodontic therapy is complete removal of pathogenic microorganisms, infected tissue debris and inflammatory products from infected pulp spaces [4]. However endodontic treatment can land up in failures pertaining to myriad of factors implicated during treatment [5,6]. The most common factors attributed for it include, a) persistence of bacteria b) inadequate biomechanical preparation and obturation of canals c) overextensions of dentinal shaving, canal debris and obturating materials [5]. The pain condition perceived by patients undergoing endodontic treatment can be of two types on broader categories viz. intra-appointment and post-operative endodontic pain [7]. Reports from the literature have shown, patients to experience intra-operative and post-operative pain in up to 80% cases who suffered per-operative endodontic pain ranging from mild to severe [8,9]. Managing such pain is one of the crucial factors for success of endodontic therapy and patient satisfaction in dental practice. This paper discusses the various traditional, contemporary and novel possible techniques for managing the intra-appointment and post-operative endodontic pain.

Inflammatory pathways initiating endodontic pain

The inflammatory pathway initiated by caries that causes pulp necrosis is demonstrated briefly in fig 1. Progression of caries in pulp initiates inflammatory process that is encased in hard-tissue chamber [10] preventing tissue expansion and preventing edema, also known as "low-compliance system" [11]. The limited drainage capacity of pulp vasculature affects the repair and thin walled vessels collapse as intra-pulpal pressure increases, leading to inflammatory edema. As blood and lymphatic circulation decreases pulp ischemia followed by degeneration and necrosis sets up. Carious teeth are already infested with microbial penetration, which keep on releasing endotoxin and exotoxins adding to enhanced inflammation of pulp. These products when released in adjacent tissue environments; initiates pain. Further, metabolic byproducts from microbes, enzymes and biological mediators liberated in local tissues affect the diffusion kinetics of pulp tissues through these metabolic and degradation products [12]. Pulp being unable to swell, all the inflammatory fluid and products accumulate in confined nonyielding root canal space, resulting in increased intra-pulpal pressure and pain. Depending on specific protein content, either transudate or exudate is formed in connective tissues damaging the arterio-venous shunting of pulp vasculature [13] causing pulp death ultimately.

Cascade of events in case of intra-operative and post-operative pain

The pain experienced by the patients at interappointment periods follows the similar cascades of events as shown in figure 1, and is caused due to development of acute inflammatory responses in the periarticular areas. Countless immunological responses are initiated after injury to the periarticular tissues, which release or activate chemical substances mediating events of inflammation, such as vasodilatation, increased vascular permeability and chemotaxis of inflammatory cells [7,12]. Various chemical mediators of inflammation include vasoactive amines, prostaglandins (PG), leukotrienes (Lt), histamines (Ht), cytokines, neuropeptides (SP, CGRP), nitric oxide, lysosomal enzymes, free oxygen radicals, and plasma-derived factors, kinins, and clotting systems [14]. Though these mediators are responsible for pain experience through direct sensory nerve stimulation, increased vascular permeability, followed by exudation and accumulation of edema fluids seems to be the major inflammatory response for initiating periradicular pain [15].

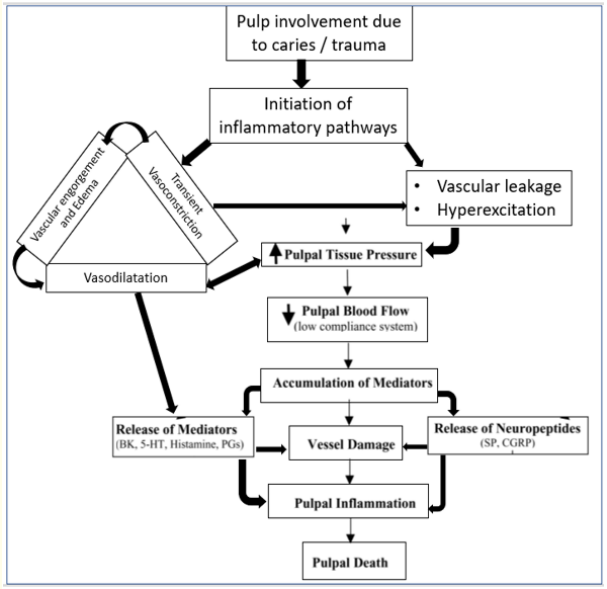

Figure 1: Inflammatory pathways of pulp degeneration and necrosis.

Intra-operative pain

When pulp is vital, intra-operative pain is associated with incomplete cleaning and shaping pertaining to inaccurate measurement od root canal dimensions [16]. When pulp is non-vital, intra-operative pain is usually caused due to forceful pushing of microbial and pupal debris [17] as well as shavings from root dentin [18], intracanal medicaments [19] used during the procedure into the periapical areas. This alters the host–parasite balance initiating the immune response and acute inflammation [20].

Post-operative pain

Studies have shown that the incidence of post-operative pain varies patient to patient; and most frequently seen within first 24 h of endodontic treatment. Co-relation have been proved between the level of obturation and pain incidence, with overextension associated with the highest incidence of discomfort [21,22]. It is also related to pre-obturation pain. And its levels are correlated with levels of pain before the appointment [21,23].

Management of intra-operative and post-operative pain

Various treatment modalities are utilized to manage the intra-appointment and post-operative pain in the field of endodontics.

These include occlusal reduction [24], re-instrumentation [7], cortical trephination [25], incision and drainage [26,27], antibiotics [28,29] and analgesics [30,31] through systemic as well as local rout of administration.

As the horizons of science has evolved, the concept of radical and empirical therapy has also evolved with it to more of the conservative mode of therapy. These transformations of the therapeutic modalities have changed the modes of drug delivery from tablet, syrups and injectables to the more sophisticated forms. Since then, a number of products have been developed to treat such conditions; targeting the specific affected regions and demonstrating controlled drug release with tissue specific actions. Most dental ailments require a prolonged contact of the active therapeutic agent at the site of action that can be achieved through a system providing controlled drug or local drug delivery (CDD/LDD) approach.

Local drug delivery systems for pain management in endodontic treatment

The controlled drug delivery method can have a significant effect on its efficacy. This system can be further classified as.

Classification for controlled drug delivery [32,33]

1. Localized Drug Delivery.
2. Targeted Drug Delivery.
3. Sustained Drug Delivery (Zero Order Release Profile).
4. Modulated Drug Delivery (Nonzero-Order Release Profile).
5. Feedback Controlled Drug Delivery.
6. Implantable Controlled Drug Delivery Devices.

We have restricted our discussion of controlled drug delivery systems upto classification only, as detailed discussion of it, is out of the scope of the present topic.

Various modes of LDD for intracanal medication

Use of traditional intracanal medicaments for endodontic pain

Calcium hydroxide [$Ca(OH)_2$]

Apart from antibacterial property, calcium hydroxide also shows anti-endotoxic property [34]. When hydroxyl ions from $Ca(OH)_2$ come in contact with infected acidic tissues; its alkaline nature tends to restore the tissues as well as terminal nerve endings to normal physiologic resting state from hyperexcited state. Reports from Anjaneyulu and Nivedhitha [35] has revealed very little role of $Ca(OH)_2$ to manage severity of postoperative endodontic pain. However, when used as intracanal dressing during treatment, it demonstrates effects against pro-Inflammatory cytokines such as interleukin-1α (IL-1α), tumor necrosis factorα (TNFα) and calcitonin gene-related peptide (CGRP) by denaturing them and reduction in apical periodontitis [36].

$Ca(OH)_2$ mixed with other therapeutics agents

Looking at results of $Ca(OH)_2$ used alone, attempts were made to mix it with other agents like, chlorhexidine, or steroids like dexamethasone.

$Ca(OH)_2$ with steroid

In a study, effect of $Ca(OH)_2$ powder with normal saline, 2% chlorhexidine and dexamethasone was evaluated to reduce postoperative pain. It was observed that Ca $(OH)_2$ and dexamethasone group significantly reduced pain from a span of 4th hour to 4th day post treatment than $Ca(OH)_2$ with chlorhexidine and saline [37].

$Ca(OH)_2$ with eugenol

$Ca(OH)_2$ was mixed with eugenol (oil of cloves and other sources) as an intracanal dressing for intra-operative endodontic pain management in which properties of both agents are utilized to alleviate pain [38].

Ca $(OH)_2$ with CMCP

Ca $(OH)_2$ mixed with (camphorated mono-para-chlorophenol) is also used as an intra-canal medicament to counteract pain associated with intra-operative pain. It helps to reduce pain by forming calcium p-chlorophenol ate salt, which along with water, absorbs free H ion and helps to maintain physiologic pH of surrounding tissues and alleviate pain [39].

Ca $(OH)_2$ with anesthetic solutions

This combination also help to alleviate intra-operative pain. The main mode of action of this paste is through leaching of active anesthetic agents into surrounding medium to impart analgesia. Long acting anesthetic agents like bupivacaine, etidocaine, or ropivacaine with or without a vasoconstrictor, have been used effectively in many cases of apexification or pulp capping with considerable success rates as intracanal medicament and to relive intra-operative pain [40].

$Ca(OH)_2$ with antibiotics

$Ca(OH)_2$ mixed with antibiotics as pastes was documented as potential intracanal medicament to manage intra-operative end-

odontic pain. Metronidazole and chlorhexidine are these two agents which were tested for its antibacterial effect. These agents eliminate noxious stimuli associated with bacterial exotoxins, endotoxins and numerous tissue irritants [41], reducing the pain. Apart from these, ciprofloxacin has also been advised along with polyethylene glycol [42].

$Ca(OH)_2$ with corticosteroid-antibiotic solutions

This mixture of agents was advised to reduce pulp and periarticular tissue inflammation. The steroid and antibiotic used were prednisolone-sulfacetamide and neomycin [43]. Another combination advised successfully was hydrocortisone, polymyxin B sulphate, and neomycin as an interappointment dressing helps to reduce intra-operative endodontic pain significantly [42]. Third in the series, and very popular development was combination of $Ca(OH)_2$ with triamcinolone acetonide and demethylchloro-tetracycline calcium combination also known as Ledermix® and found effective in endodontic therapies, that help to reduce intra-operative pain [44].

Use of herbal agents as intracanal medicaments for endodontic pain

Anodyne agents like eugenol / clove oil

Eugenol is an essential oil, and demonstrates various biological properties, such as antimicrobial, analgesic, anti-inflammatory, antioxidant, antimutagenic, and anticarcinogenic effects [45,46]. It inhibits expressions of cyclooxygenase II enzyme, cytokines in macrophages, as well as inflammatory cell proliferation via suppression of NF-Kappa B (NF-kB). Eugenol has been also found to lower levels of various inflammation markers like TNF-α, interferon gamma and TNF-β [47]. It also exerts dose dependent reversible vasodilator response on small vessels endothelium. It can also be used effectively to reduce intra-operative endodontic pain. However, it's dose should be tittered to avoid cytotoxicity of the adjacent mammalian tissues [48].

Steroids to manage endodontic pain

Usage of corticosteroid in endodontics has been a topic of controversy for a long time with variable suggestions from different researchers all over the world. Various ways to manage intra-operative and post-operative endodontic pain have been tried by administrating corticosteroids. Those include injectable [49], intraperiodontal ligament [50], supraperiosteal [51], intraosseous [52], parental [53], systemic rout [54], or as an intra-canal medicament [55]. When corticosteroid is placed into the root canal as ana intracanal medicament in form of paste or gel, comes in contact with inflamed periapical tissues directly through dentinal tubular diffusion. It exerts anodyne effect and act as local drug delivery system to reduce intra-operative and post-operative endodontic pain [56,57,58].

Antibiotics and mixture of antibiotics having analgesic effects

Antibiotics and anti-bacterial are frequently used to eliminate pathogenic micro-organisms from root canals. However, it has been observed by few researches that, apart from antibacterial effect, few antibiotics also possess allodynic properties and help to alleviate postoperative pain. Such antibiotics can be utilized through systemic and local drug delivery methods to reduce endodontic pain. Borsook and Edwards reported attenuation of neuropathic pain associated with monoclonal gammopathy, Raynaud's disease, through trial of chemotherapeutic agent KRN5500; derived from antibiotic spicamycin. Looking into these findings, they conducted animal studies that supported their notion of using KRN5500 to treat neuropathic pain [59]. Macaluso., *et al*. studied the effect of single dose administration of ceftriaxone in patients undergoing surgical procedures. They found that ceftriaxone elevated pain threshold of patients to achieve analgesia in all patients. They reconfirmed the human study findings through animal studies and found that it induced analgesia reduced inflammatory postsurgical pain in mice by upregulating GLT-1 in the spinal cord. They observed that ceftriaxone-induced analgesia achieved due to blockade of mGlu5 receptors, activated by extra-synaptic glutamate. If ceftriaxone is used as an intracanal agent, it can help reducing intra-operative endodontic pain along with antimicrobial prophylaxis [60]. Various application devices comprising antimicrobial agents are developed [61] to offer local drug delivery that include tetracycline fibers, doxycycline polymer, chlorhexidine chips, as well as metronidazole and minocycline gels [62]. These agents act by eliminating microbial population in the root canal and periapical space, and reduce the intra-operative as well as post-operative pain.

Intracanal placement of analgesic agents

Negm advised use of two nonsteroidal anti-inflammatory drugs (NSAIDS), diclofenac and ketoprofen, as intracanal delivery modality to control of post-operative endodontic pain. Several clinical trials have been conducted with NSAIDs like flurbiprofen, ketoprofen and naproxen [64].

Combined with the ability of compact controlled-release therapeutic systems to deliver intracanal medicaments at a predictable rate for extended periods, the intra-operative and post-operative endodontic pain can be minimized along with the systemic toxicity.

Conclusion

Though technologies described here represent little more than the tip of the iceberg, controlled drug delivery systems can offer a potential treatment for such conditions increasing predictability of the procedures.

Conflict of Interest

Declared none.

Finding Source and Sponsorship

Nil.

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