Endodontic Pharmacotherapeutics

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Abstract

Managing dental pain of endodontic origin is complicated by the multiple biological mechanisms that contribute to several distinct painful clinical entities including dentinal hypersensitivity, pulpitis pain, periapical pain, postoperative pain, and persistent posttreatment pain. In general pain of endodontic origin is best managed by initiating endodontic treatment, during which time the source of inflammation is mostly removed. In order to successfully perform endodontic treatment, the affected pulpal tissues and adjacent periodontal tissues must be completely anesthetized using local anesthetics. This is complicated by the fact that inflammation reduces the efficacy of local anesthetics. Strategies for obtaining successful pulpal anesthesia so that endodontic treatment can be administered with minimal or no discomfort to the patient are discussed. Postoperative endodontic pain is common and can be severe, and clinicians need to utilize anti-inflammatory analgesics to manage their patient's symptoms. Occasionally antibiotics are required to manage a spreading infection. In summary, successful endodontic treatment requires the wise use of pharmacotherapeutics before, during, and after clinical treatment. This chapter provides a review of the evidence and practical guidance for the use of pharmacotherapeutics with the overall goal to improve the prognosis of eliminating endodontic pain for our patients.

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N. Chugal, L.M. Lin (eds.), *Endodontic Prognosis*,
DOI 10.1007/978-3-319-42412-5_6

6.1 Pain Is a Complex Sensory Experience

Orofacial pain is a widespread problem that accounts for around 40% of an estimated $80 billion in pain-related healthcare costs annually in the United States [1]. Odontalgia, or toothache, is a common source of orofacial pain and can be a distressing and intensely painful experience, often leading to disruption of daily activities [2–5]. Pain is an important motivator for symptomatic patients to seek dental care, while a fear of pain during or after dental procedures causes some patients to avoid seeking routine dental treatments [6–9]. Pain is a complex sensory experience with emotional, conceptual, and motivational components. As such the experience of pain is unique to each individual [9]. Given the multifaceted nature of pain, it is not surprising that there are numerous and diverse means to prevent or inhibit the pain in a clinical setting, which run the gamut from relaxation strategies to reduce patient anxiety, to blocking sensory nerves with local anesthetics. This chapter will focus on pharmacological approaches to managing pain and infection before, during, and after endodontic treatment.

6.1.1 Mechanisms of Pain of Endodontic Origin

One might think the term odontalgia or toothache should describe a fairly homogenous clinical phenomenon. However, we now know that there are multiple etiologies for pain originating from teeth that include inflammation of the dental pulp, inflammation of periapical tissues, transdentinal stimulation of pulpal neurons, and even persistent pain after surgical intervention.

6.1.1.1 Nociceptive Pain

Nociceptive pain describes the inherent ability of pain fibers, or nociceptors, to detect stimuli that are potentially tissue damaging, and can be of a thermal, mechanical, or chemical nature. Nociceptive pain is mediated by smaller-diameter sensory afferents that include the myelinated Aδ- and unmyelinated C-fiber classes. The dental pulp appears to have a unique sensory capacity, as almost any stimulus that activates pulpal nerve endings produces the sensation of pain. The neural component of the pulp tissue consists of sensory trigeminal afferents and sympathetic and parasympathetic efferent fibers [10, 11]. These fibers project into the pulpal tissues of the root canals through the apical foramen and are closely associated with blood vessels, forming a collagen-bound neurovascular bundle. Anatomical studies have demonstrated that the terminal portion of pulpal afferents can extend up to 150 μm into the predentin or the dentinal tubules and form a close association with the processes of odontoblasts [12, 13]. These sensitive fibers act like nociceptors, in that they produce pain when stimulated. However, according to their diameter, conduction velocity, and expression of specific markers that identify classes of neurons, most of these fibers are large-diameter myelinated Aβ-fibers, which typically transduce non-painful stimuli such as light touch [14–16]. This is an apparent paradox, as pain is thought to be exclusively mediated by the activation of Aδ- and C-fiber

nociceptive afferents. In an attempt to explain this paradox, Fried and colleagues have proposed the novel term "algoneuron" to explain the observation that the pulp is innervated primarily by larger-diameter fibers that appear to, paradoxically, transduce painful stimuli [17].

Also found in the pulp are Aδ-fibers, which have a smaller diameter and slower conduction speed relative to the Aβ-fibers. At this time it is not known whether these fibers have a distinct function from that of the Aβ-fibers. Collectively the Aβ- and Aδ-fibers respond to stimuli that would produce fluid movement in dentinal tubules such as drilling, sweet foods, cold air, and hypertonic solutions and produce a sharp, bright, pain when activated [18, 19]. The low threshold for activation and the peripheral localization of these fibers suggest that they can become activated and produce pain without the presence of irreversible damage to the pulp. These fibers contribute to the increased sensitivity observed after restorative work involving enamel and dentin removal or toothbrush abrasion (see Dentinal Pain Sect. 6.1.2.3) [20].

Finally, the C-fiber subtype of sensory neurons, although less abundant, is are also found in the pulp. These are unmyelinated fibers with a low conduction velocity, a smaller diameter, and a higher excitation threshold. They are located deeper within the pulp than the myelinated fibers. C-fibers are activated by heat, mechanical, and chemical stimulation and produce a dull, diffuse, and longer-lasting pain [13]. It is thought that when C-fiber involvement produces pulpal pain, the patient reports a diffuse, dull, and achy pain that can be difficult to localize. This type of pain may suggest that concomitant damage to the pulp proper has occurred, which is more likely to be irreversible. While an injury results in an interruption in the pulp microcirculation, the C-fibers continue to function for a longer time compared to A-fibers as their oxygen consumption is higher than A-fibers [20]. This characteristic also underlines the familiar clinical occurrence in which a tooth that responds negatively to testing with a cold CO_2 stick is painful to mechanical instrumentation during endodontic therapy [21].

The ability of a sensory neuron to detect specific types of stimuli is dictated by the receptors that are expressed in the peripheral terminal. Of particular relevance to the detection of painful thermal, mechanical, and chemical stimuli is the presence of transient receptor potential channels (TRPs) [22, 23]. The most-studied TRP channels are TRPV1, TRPV2, TRPA1, and TRPM8, all of which are expressed in pulpal afferents and thus have the potential to mediate thermal and mechanical sensation in the dental pulp (Fig. 6.1). For example, applying heat directly in the tooth produces pain, which is most likely mediated by activation of the TRPV1 channel [24, 25]. In addition to heat, Aδ- and C-fiber neurons also are responsive to noxious and non-noxious cold temperatures. Calcium imaging studies revealed that neurons responding to cold temperatures <18°C are more common in the trigeminal ganglion (14%) than in the dorsal root ganglion (7%) [26]. Both the TRPM8 and TRPA1 channels are stimulated by cold temperatures with thresholds of 25°C and 17°C, respectively, and both receptors have been localized in nerve fibers innervating the dental pulp [27, 28]. Further work is needed to determine whether TRPM8 and TRPA1 contribute to the transmission of painful cold in the dental pulp.

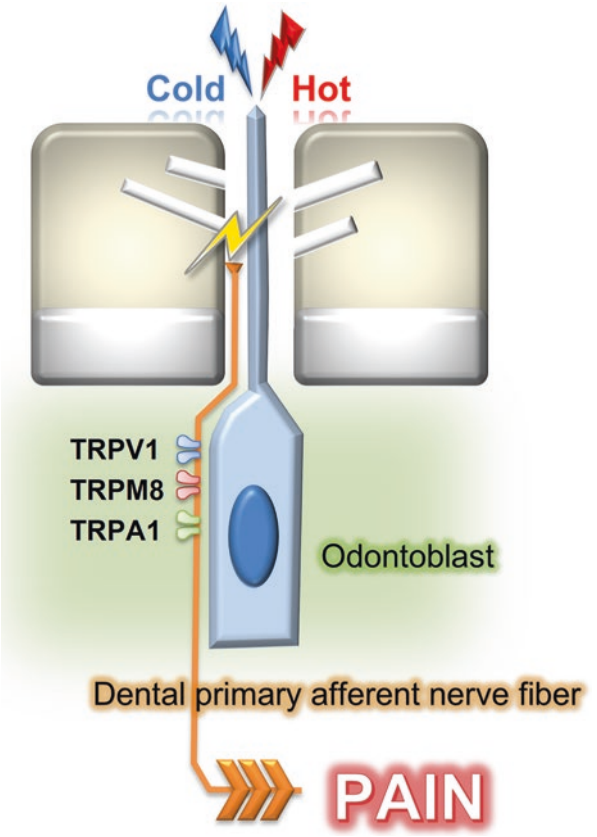

Fig. 6.1 Molecular mechanisms of neural theory. Thermo-TRP channels are functionally expressed by dental primary afferents (Figure adapted from Chung et al. (2013) [22])

The role of odontoblasts in transducing nociceptive pain in the dental pulp is an active topic of debate [29]. Importantly, odontoblasts also appear to express several of the TRP receptors, which support their role in detection of sensory stimuli [30, 31]. The mechanism transduction of sensory stimuli from odontoblast to peripheral nerve is not clear, and studies attempting to better understand these mechanisms are ongoing.

6.1.1.2 Inflammatory Dental Pain

Inflammation is a normal protective immune response of the host to tissue infection. Circulating immunocompetent blood cells migrate through the endothelial barrier to gain access to the damaged tissues and eliminate injurious pathogens. However, uncontrolled inflammation may result in a full range of acute, chronic, and systemic inflammatory disorders [32]. Dental pulp tissues are rich in blood vessels and nerve fibers and have a relatively low interstitial compliance because of its enclosure in a rigid dentin chamber. Inflammation of the dental pulp, or pulpitis, can be intensely painful [33].

When infected dental caries approximates the dental pulp, lipopolysaccharide (LPS) from bacterial cell walls, and other virulent factors, stimulate an

inflammatory response from a variety of cells residing in the dental pulp tissues [34, 35]. The affected cells release inflammatory mediators such as prostaglandins and bradykinin, which then activate or sensitize pulpal sensory neurons, leading to thermal and mechanical hyperalgesia and allodynia [24, 36]. In advanced stages of pulpal inflammation, large parts of the pulp become inflamed and the pulpal tissue may ultimately degrade. During the degradation process, pulpal nerve fibers might remain partially intact and continue evoke spontaneous pain sensations. The diagnostic terms reversible and irreversible pulpits are based on the clinical prognosis of the pulp, but evidence-based clinical measurements to determine whether a pulp is truly reversibly or irreversibly inflamed are lacking [37–39]. Nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, acetaminophen, and steroids are all effective analgesics for treating inflammatory pulpal pain.

6.1.1.3 Dentinal Pain

The loss or compromise of enamel or cementum can cause exposure of the dentin to the oral cavity and produce the clinical condition of dentinal hypersensitivity. Dentinal pain is usually a brief, sharp pain that occurs in response to thermal, evaporative, tactile, osmotic, or chemical stimuli. The hydrodynamic theory explains that stimuli producing fluid movement within the dentinal tubules can activate the very sensitive nerve fibers that innervate the dentinal tubules [40]. Dentin sensitivity has a direct correlation with the dentinal tubule size and patency [41]. The loss of the enamel or cementum is commonly a consequence of attrition, erosion, abrasion, or abfraction. It is estimated that 30% of adults have dentin hypersensitivity at some point in their lives [11, 42]. Ultimately the symptoms may resolve when the tubules become occluded by salts, smeared dentin, peritubular dentin, and secondary or reparative dentin. Most existing therapeutics for dentinal hypersensitivity occlude the tubules, thus preventing dentinal fluid movement and, eventually, pain. Therapies include toothpastes containing strontium or oxalate salts, which deposit salts within the dentinal tubule. Professionally applied glass ionomers, resins, and resin adhesives are also effective [43]. Conservative treatments such as these are recommended as an initial strategy for providing pain relief, as there is usually little pulpal inflammation or pathology observed in teeth with dentinal hypersensitivity. Rather, this condition is just the expression of the profound sensitivity of normal pulpal sensory neurons to stimulation when the protective enamel or cementum is compromised.

6.1.1.4 Neuropathic Pain

Neuropathic pain is a type of chronic pain condition, which is caused by a primary lesion or dysfunction in the peripheral or central nervous system. Neuropathic pain has a complicated pathophysiology and can affect the orofacial region as well as other parts of the body. Of relevance to dentistry and endodontics is that it is now understood that neuropathic pain might be initiated by dental procedures including third-molar or implant surgery, surgical and nonsurgical endodontic treatment, and even dental injections [44, 45]. Neuropathic pain can also occur as a consequence of other disorders including diabetes (diabetic neuropathy), HIV (HIV neuropathy), and herpes zoster (postherpetic neuralgia). These peripheral neuropathies can occur

in orofacial regions including inside the mouth, in which case diagnosis can be very challenging. Unfortunately, many patients undergo unneeded dental procedures in an attempt to alleviate their pain. As neuropathic pain can be severely debilitating and intractable, measures to prevent or minimize nerve damage should always be implemented during treatment planning [46]. Lower molars and premolar teeth with apical roots approximating the mental nerve foramen of inferior alveolar canal should be approached with care to minimize damage to major nerve branches [47]. Typical analgesics and NSAIDs have minimal efficacy for treating neuropathic pain, although opioids are somewhat effective. In general, drugs that depress the nervous system have been found to have efficacy in treating neuropathic pain, including anticonvulsants such as gabapentin and antidepressant drugs such as nortriptyline [48, 49].

6.2 Endodontic Pain Management

When an odontogenic source of pain has been identified, and the clinical intervention decided on by the practitioner and patient is root canal treatment, the most predictable route to alleviating pain is to remove the source of the infection, usually by caries removal, pulp extirpation (in vital cases), and some form of chemomechanical canal debridement. Pain management is essential, both during and after endodontic treatment, and knowledge of the judicious usage of pharmacotherapeutics is critical to a practitioner's success.

6.2.1 Intraoperative Pain Management: Local Anesthetics

The foundation of intraoperative pain management in the practice of endodontics is the effective administration of local anesthetics to block the transmission of sensory input from the nerve endings found in the dental pulp and periodontal tissues surrounding the treated tooth. Although this class of drugs is generally safe, practitioners should be familiar with dose limitations, side effects, and potential allergic reactions [50, 51]. Local anesthetics bind to sodium channels located on the cell membrane of sensory neurons, preventing the influx of sodium ions into the nerve fiber (Fig. 6.2). This prevents depolarization and action potential propagation along the neuron, effectively blocking the transmission of pain and other sensory signaling. As pain is the dominant sensation produced when stimulating sensory fibers of the dental pulp, complete pulpal anesthesia is required to be able to perform endodontic treatments, as well as many restorative treatments on teeth containing vital pulpal tissue.

6.2.1.1 Inflammation Reduces the Efficacy of Local Anesthetics

The ability to reliably obtain effective anesthesia is challenged in the setting of inflammation. A vital but inflamed dental pulp can be especially difficult to anesthetize, especially when attempting to utilize an inferior alveolar nerve (IAN) block to

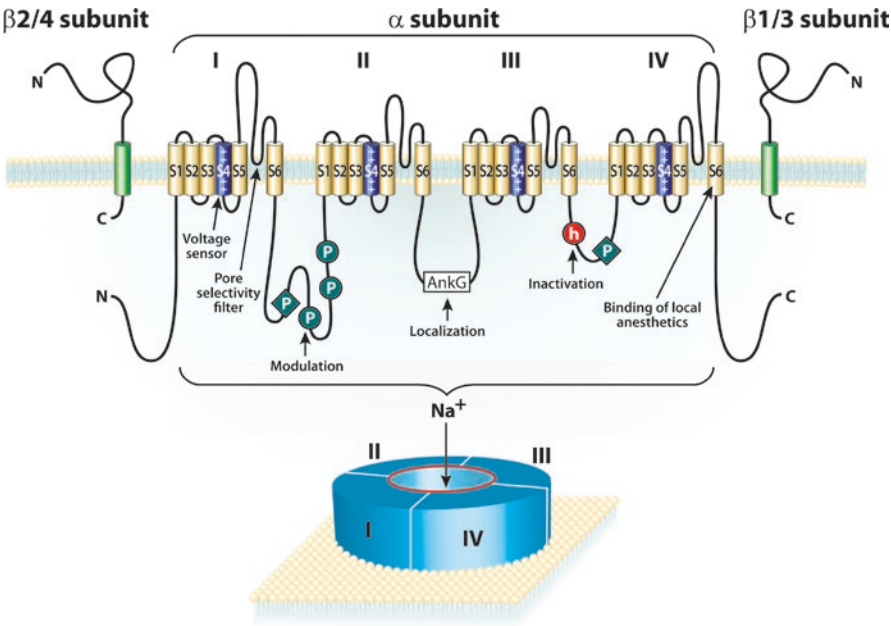

Fig. 6.2 Primary structures of the α- and β-subunits of the voltage-gated sodium channel. The α-subunit is composed of four homologous domains (DI–DIV), each with six α-helical transmembrane segments (S1–S6). The S4 segment of each domain contains positive charged amino acid residues and forms part of the voltage sensor. The linker that connects S5 and S6 forms the external mouth of the channel pore and the selectivity filter. The cytoplasmic linker between DIII and DIV contains a critical hydrophobic motif that acts as a "hinged lid" (h) and is responsible for fast inactivation. Slow inactivation depends in part on residues located in the external pore lining of the channel. The α-subunit contains several receptor sites for neurotoxins (not shown). Amino acid residues in the S6 segment of DI, DIII, and DIV in the inner cavity of the channel pore form the binding site for local anesthetics and related antiepileptic and antiarrhythmic drugs such as lidocaine, mexiletine, carbamazepine, and phenytoin. Sodium channel blockade by these drugs is relatively weak at resting potential but strong if the membrane is depolarized ("use-dependent" blockade). A conserved amino acid sequence at the intercellular loop linking the DII–DIII binds ankyrin G (Ank) and is critical for targeting the channels to specific domains of the cell. The large intracellular loop between DI and DIII contains several modulatory phosphorylation sites (P) by protein kinases A and C. The carboxy-terminus domain associates with the β-subunit and other adaptor and cytoskeletal proteins. The auxiliary β-subunits are proteins with a single transmembrane domain, a long, heavily glycosylated extracellular amino-terminal domain that has an immunoglobulin-like structure with homology to cell adhesion molecules, and a short intracellular C-terminal tail. These subunits regulate targeting and kinetics of the channel (With permission from [208])

treat a painful mandibular molar. In this scenario, the attempt to successfully anesthetize the inflamed pulp with IAN block alone is more likely to fail than to succeed, with success rates reported in the range of 25–40 % [52–55]. Multiple hypotheses exist to explain the reduced efficacy of local anesthetics in inflamed dental pulp (summarized here [56, 57]). Currently, the most accepted theory hinges on the concept of neuronal plasticity.

Neuroplasticity describes the inherent property of individual neurons and complex nervous tissues (e.g., the brain or spinal cord), to adapt to injury or disease, as well as changes in behavior or environment. More specifically, sensory neurons are fundamentally altered when the nerve terminals themselves are damaged or the surrounding tissues are inflamed. The amount and type of receptors and neurotransmitters that are expressed in a given class of sensory neurons are dynamic and change in response to growth factors and inflammatory mediators. Ultimately these changes can cause the neuron to exist in a sensitized state, where it is more easily activated by both painful and non-painful stimuli. These molecular changes underlie the clinical observations of hypersensitivity and allodynia after injury. Clinical examples of the manifestation of allodynia in the inflamed periodontal ligament include pain on biting or to mild percussion of the tooth. A typical example of hypersensitivity in the inflamed dental pulp is an exaggerated painful response to a cold stimulus. Of interest to the discussion of local anesthetics, inflammatory mediators directly influence the expression and activity of several important sodium channels, thus influencing the excitability of sensory neurons, and the efficacy of local anesthetics (Fig. 6.2).

6.2.1.2 Sodium Channel Subtypes

Sodium channels are divided into two distinct classes based on the presence or absence of sensitivity to tetrodotoxin (TTX). The Nav1.8 and Nav1.9 channels mediate the TTX-resistant (TTX-R) current [58, 59]. The $Na_v1.8$ channel is expressed at higher levels under inflammatory conditions, and an increased expression has been demonstrated in human dental pulp in persons experiencing painful pulpitis [60–63]. Importantly, increasing the expression of the $Na_v1.8$ channel reduces the efficacy of lidocaine in blocking neural transduction. Thus, the upregulation of $Na_v1.8$, within nerves innervating the inflamed dental pulp, could contribute to the clinical challenge of achieving adequate local anesthesia during dental procedures. Other sodium channels are likely also involved in mediating inflammatory pain. The channel $Na_v1.7$ is upregulated in many animal models of inflammatory pain and also in humans with painful pulpitis [64, 65]. In summary, multiple sodium channels are involved in the sensitization of sensory neurons. A change in expression of sodium channels, especially $Na_v1.8$, is likely responsible for the clinical observation of reduced local anesthetic efficacy in the setting of inflammation.

6.2.1.3 Pulpal Anesthesia Versus Soft Tissue Anesthesia

When attempting to anesthetize asymptomatic, i.e., noninflamed pulpal tissues, it is important to remember that soft tissue anesthesia of adjacent tissues does not guarantee that pulpal anesthesia was achieved. This is especially true in the mandible, where successful pulpal anesthesia after an inferior alveolar nerve block is 35–60 %, depending on the tooth [66–68]. So before initiating endodontic treatment, especially in the setting of inflammation, it is important to determine whether pulpal anesthesia was obtained. This can be accomplished by repeating pulpal sensibility tests with either a cold or electrical stimulus. However, in the setting of irreversible

pulpitis, even cases where pulpal anesthesia was confirmed using sensibility tests, some patients will still experience pain during treatment [69]. For this reason, supplementary injections and/or other adjunctive therapies are always recommended to minimize the chance of patient discomfort.

6.2.1.4 Supplementary Injections/Adjunctive Therapies

As mentioned previously, given the high rate of local anesthetic failure when performing endodontic treatment on painful teeth, especially in the mandible after IAN block, it is essential to administer additional anesthesia via supplementary routes before attempting to initiate treatment [70, 71]. Although a comprehensive review of the methods and evidence for the various supplementary anesthetic approaches are beyond the scope of this chapter, we wanted to mention that there is a strong support for the use of buccal infiltration (especially with 4% articaine), periodontal ligament injections, as well as intraosseous injections to supplement the IAN block and improve the likelihood of obtaining pulpal anesthesia [69, 72–78].

6.2.1.5 On Choosing a Local Anesthetic

Although there are several types of local anesthetic agents to choose from in the United States, the vast majority of dental practitioners utilize 2% lidocaine, and it remains the standard against which other anesthetics are compared. Articaine (4%) is another commonly used local anesthetic, and numerous studies have compared the ability of lidocaine to articaine in achieving soft tissue and pulpal anesthesia in teeth with normal pulps as well as those with symptomatic irreversible pulpitis. In general the two agents demonstrate comparable efficacy in achieving pulpal anesthesia [79, 80]. The exception is that articaine is more effective at accomplishing anesthesia when administered via infiltration [81]. This appears to be especially true for pulpal anesthesia in both symptomatic and asymptomatic cases when administering supplementary anesthetic via buccal infiltration in the mandible [53, 72, 73, 82]. Therefore, there is strong support for the choice of articaine over lidocaine as a supplementary anesthetic for buccal infiltration, in order to accomplish pain-free endodontic procedures in posterior mandibular teeth [81].

Lidocaine is the anesthetic of choice for nerve blocks including IAN, lingual, and mental nerve blocks. All local anesthetics are neurotoxic and have the potential to cause a neuropathy when administered in sufficient concentration adjacent to a nerve bundle or branch [83, 84]. Clinically this can produce prolonged numbness (anesthesia), prickling or "pins and needles" sensations (paresthesia), or more severe neuropathic pain symptoms in the region innervated by the damaged nerve. Higher concentration formulations such as articaine (4%) and prilocaine (4%) are associated with a higher risk of nerve damage, usually when administered for an IAN block [85–87]. Given the comparable efficacy of articaine and lidocaine in accomplishing pulpal and soft tissue anesthesia, combined with the increased risk of nerve damage with articaine, lidocaine is the anesthetic of choice for IAN block.

Bupivacaine (0.5%) is notable as a local anesthetic agent because it produces long-lasting anesthesia of up to 8 h [88]. Administration of bupivacaine at the end of a clinical procedure is a useful strategy to help reduce postoperative pain

[89–91]. This is ideal when significant levels of postoperative pain are anticipated, including surgical endodontic cases, and for patients who present with a high level of preoperative pain.

6.2.1.6 Preemptive Analgesics for Improving the Efficacy of Local Anesthetics

Given the inherent challenge in obtaining adequate pulpal anesthesia in the setting of inflammation, multiple strategies are needed to optimize the chances for clinicians to perform pain-free endodontic procedures. Studies evaluating the effects of inflammatory mediators on sodium channels have demonstrated that prostaglandin E2 increases the activity of TTX-R sodium channels [92]. Given that TTX-R channels are more resistant to local anesthetics, the important, clinically relevant question is whether pretreatment with an anti-inflammatory agent, for example, the nonsteroidal anti-inflammatory drug (NSAID) ibuprofen, improves the chances of obtaining pulpal anesthesia in patients with symptomatic pulpitis.

This hypothesis has been well tested in clinical studies, many of which were high-quality randomized controlled clinical trials. Several studies demonstrate efficacy for NSAIDs versus placebo in achieving more frequent pulpal anesthesia and/or pain-free endodontic treatment [93–96]. However several trials failed to observe significant differences between drug and placebo, although it should be noted that in the majority of these studies, the trend was for the subjects receiving the NSAID to have more successful rates of anesthesia [97–100]. The variance in results between the studies could be due to differences in study design including varying definitions of irreversible pulpitis (i.e., different subject populations), differences in the definition of successful vs. failed anesthesia, and differences in how the study was powered (i.e., sample sizes). Importantly, the overall evidence supports the use of a single preoperative dose of NSAIDs for improving the chances for successful mandibular pulpal anesthesia via IAN block in patients with painful pulpitis, as demonstrated in a recent systematic review (ibuprofen 600–800 mg, lornoxicam 8 mg, and diclofenac potassium 50 mg were demonstrated to be better than placebo with ketorolac, ibuprofen/acetaminophen combination, and acetaminophen alone being no better than placebo) [101]. Although less studied, there is evidence that pretreatment with other anti-inflammatory agents, such as steroids, can increase the efficacy of pulpal anesthesia or the duration of anesthesia [102, 103]. In summary, pretreatment with an NSAID, such as 600 mg ibuprofen, 1 h prior to initiating endodontic therapy will increase the chances of obtaining pulpal anesthesia, helping to minimize the amount of pain experienced during endodontic treatment.

6.2.2 Postoperative Pain Management

6.2.2.1 Prognostic Factors Related to Endodontic Postoperative Pain

Studies regarding postoperative pain after endodontic treatment, both post-obturation or post-instrumentation for multi-visit treatments, suggest that the frequency and severity of pain are quite varied [104]. This is likely due to differences in when and

how pain was measured, in the patient population studied, and, importantly, in the preoperative pulpal and periradicular status of the subject populations. A recent systematic review reports that the prevalence of postoperative pain reported in individual studies ranges from 20–90 % and severity is usually in the mild-moderate range (10–60 mm on a 100 mm VAS). One week after endodontic treatment, pain prevalence is typically less than 10 %, and reported pain is, on average, reported to be at a low level of intensity [105]. Administering endodontic therapies is clearly an effective way to reduce pain of endodontic etiology, with postoperative pain levels dropping to 50 % of preoperative levels after 24 h [105, 106]. This supports the idea that endodontic interventions, including root canal treatment, and emergency procedures such as pulpectomies and pulpotomies, in the appropriate clinical situations (e.g., the tooth is restorable, the tooth is in function), are the best way to quickly and predictably reduce the frequency and intensity of odontogenic pain.

Several patient factors have been identified that appear to predict the occurrence of postoperative pain. Numerous studies have identified the presence and/or intensity of preoperative pain to be one of the strongest predictors of postoperative pain (Fig. 6.3) [107–109]. This strong association was found in studies on subjects receiving endodontic therapies as well as studies involving subjects receiving other non-dental surgical interventions [110]. The clinical implication of this finding is that patients presenting with pain are more likely to experience significant postoperative pain, and care should be taken to ensure that appropriate postoperative analgesics are prescribed. Biologically, this observation is likely associated with plasticity in the central nervous system associated with the increased input from nociceptors in the peripheral nervous system, with central sensitization likely being an important contributory mechanism.

Other factors associated with postoperative pain include gender (with females experiencing more pain), tooth type (with posterior multi-rooted teeth more painful), and experiencing inter-appointment pain [107–109, 111, 112]. Most importantly, postoperative pain after completion of root canal treatment, or after a first of two or more visits, is a common enough occurrence that analgesics should be

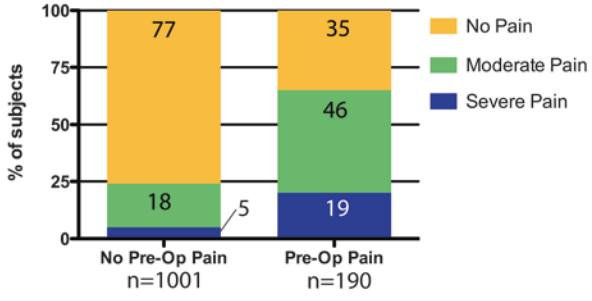

Fig. 6.3 Preoperative pain level is an important predictor of postoperative pain level. This figure shows an example of a study demonstrating how the severity and incidence of postoperative pain after the first day of root canal treatment are predicted by the presence or absence of preoperative pain (Modified from Genet et al. 1986 [209])

regularly prescribed, regardless of the presence or absence of predictive factors. However, the presence of some of these predictive factors might make a clinician more likely to consider a multimodal analgesic approach and/or higher doses, as discussed further below.

6.2.2.2 Nonsteroidal Anti-inflammatory Drugs

The first choice of analgesic class for odontogenic pain, including postoperative endodontic pain, is the nonsteroidal anti-inflammatory drugs (NSAIDs) and includes common analgesics available over the counter such as ibuprofen, aspirin, and naproxen. As inflammation is an important contributory mechanism to odontogenic pain, it follows that anti-inflammatory drugs are quite effective analgesics. Ibuprofen is more effective than aspirin, acetaminophen, or combination drugs such as Vicodin that contain acetaminophen and an opiate type drug such as hydrocodone, in relieving postoperative pain in an oral surgery model [113–115]. There is also good evidence that ibuprofen is an effective analgesic for relieving postoperative endodontic pain [116, 117]. It is important to note that many of these studies are testing a single dose of drug given perioperatively and measuring effects out to 24 h or longer. Continued dosing of the analgesic, at the recommended time intervals, will have a greater impact on reducing postoperative pain. In conclusion, a single dose of ibuprofen (400–600 mg) administered perioperatively will predictably reduce postoperative pain, but dosing should be continued for 24–48 h every 6–8 h, in patients in which this class of drugs can be safely administered (for more detail regarding the safety, see [118] and Fig. 6.4).

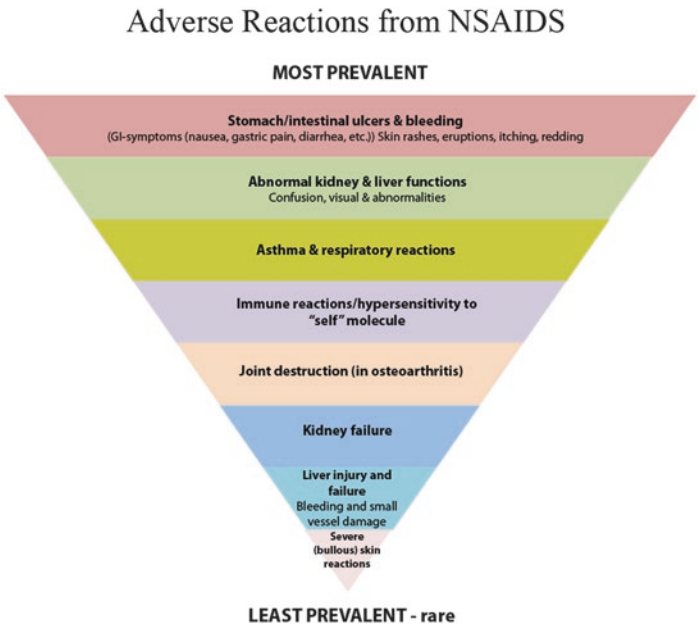

Fig. 6.4 Adverse reactions from the NSAID class of drugs. The occurrence and severity of these reactions differ with each drug (Reproduced with permission from Birkhäuser Verlag [118])

6.2.2.3 Combination Ibuprofen and Acetaminophen

Strong evidence exists that the combination of ibuprofen and acetaminophen produces greater analgesia than either analgesic alone in the relief of acute pain, as described in several controlled clinical trials and summarized in a recent Cochrane review [119, 120]. There is also evidence for the efficacy of this combination specifically in postoperative endodontic pain ([121] but also see [122]). The concept of using combination analgesics makes sense from a biological standpoint, as different analgesics target different pain pathways, and so combining analgesics will more broadly inhibit pain signaling pathways, producing greater analgesia. The combination of ibuprofen and acetaminophen should be prescribed when moderate to severe pain is anticipated.

6.2.2.4 Opioids and Combination Opioid Drugs

Combination opioid drugs such as those that combine acetaminophen and hydrocodone or codeine (e.g., Vicodin or Tylenol III) are commonly prescribed for the management of odontogenic pain and postsurgical pain. However, on their own they are less effective pain relievers than analgesics available over the counter with anti-inflammatory properties, such as ibuprofen [114, 123]. As the availability of prescription opioid pain killers has increased in recent years, so has the nonmedical use and abuse of these agents, as well as the most undesirable outcome of death by overdose [124]. In looking further into this alarming trend of prescription opioid misuse and abuse, dentists have been identified as a major source of opioid prescriptions (second only to family physicians). This has brought attention to the fact that greater care should be taken when prescribing these types of medications, as there is a chance that the drugs could end up being used for nonmedical purposes by someone other than the patient [125, 126]. With caution, combination opioids can be used in cases when severe pain is anticipated and NSAIDs are contraindicated, or pain is not relieved by NSAIDs or the combination of ibuprofen/acetaminophen. To prevent mishandling of any leftover medications, the dosing period can be limited to 24–48 h, during which time pain is anticipated to be most severe.

6.2.2.5 Steroids

Numerous studies have evaluated systemic and locally administered corticosteroids for the reduction of postoperative pain. Generally, there is ample support in the existing literature that steroids are effective at reducing postoperative pain after an endodontic intervention [127]. Systemic steroids, most commonly dexamethasone, administered intramuscularly or by oral tablets, decrease the incidence and intensity of postoperative endodontic pain [128–131]. These agents are also effective against postoperative pain when administered locally including intracanal, by intraligamentary injection and intraosseous administration [132–135]. Local administration has the benefit of limiting the systemic exposure to corticosteroids, thereby limiting potential side effects (although the short-term administration of steroids is quite safe for the vast majority of patients [136]). Further clarification is needed regarding which subclasses of endodontic pain are most responsive to corticosteroids (e.g., irreversible pulpitis pain versus periapical pain from a tooth with a necrotic pulp versus flare-up pain) [127].

6.2.2.6 Persistent Posttreatment Pain

Persistent pain after surgical procedures has gained attention recently as a public health problem and a potential opportunity for implementation of preventative methods to prevent the transition from acute to chronic pain [137]. Although occurring much less frequently than after major medical surgical procedures, the possibility for persistent pain after surgical dental interventions including surgical and nonsurgical root canal treatment, implant placement, and oral surgery procedures has been recognized for quite some time [138–143]. Although persistent symptoms after endodontic treatment could be due to ongoing odontogenic causes such as an undetected root fracture or recurrent infection, there are clearly cases when pain persists despite the absence of detectable pathology. Historically, such persistent pain was referred to as atypical odontalgia, or phantom tooth pain. The more current nomenclature is persistent dentoalveolar pain or peripheral painful traumatic trigeminal neuropathy [144, 145]. Although debates regarding the criteria for classification of this clinical entity are ongoing, and will surely continue, it likely represents a very specific type of persistent postsurgical pain. The etiology of non-odontogenic persistent post endodontic therapy pain is unknown, but there is some evidence that neuropathic mechanisms are involved [146–148]. More research is needed to better understand the biological mechanisms contributing to the development of persistent posttreatment endodontic pain.

6.3 Infection Management

6.3.1 The Role of Bacteria in Endodontic Pathology

Invasion of the root canal system by microorganisms precipitates the subsequent pathology of pulpal and periradicular tissues. The ultimate goal of endodontic treatment is biomechanical preparation of the root canal system, which includes cleaning, shaping, and disinfection, as well as hermetically sealing the canals, thereby creating the conditions for the healing of diseased periradicular tissues [149–151]. Primary endodontic infections are polymicrobial and caused predominantly by gram-negative anaerobic bacteria such as *Prevotella* ssp., *Porphyromonas* ssp., *Treponema* ssp., and *Fusobacterium* ssp. [152, 153]. Endodontic infections can spread beyond the root canal system producing localized inflammation and swelling in the soft tissue adjacent to the involved teeth or, more rarely, a nonlocalized spreading cellulitis.

As such, root canal disinfection is the fundamental component of successful root canal treatment. Contemporary techniques to eliminate or significantly reduce microorganisms in the root canal system include mechanical debridement, intracanal irrigation with antimicrobial/tissue dissolving agents, and placement of intracanal dressings. Importantly, the process of obturating the root canal and subsequently sealing the coronal aspect of the tooth prevents the introduction of new microorganisms. However, even during ideal treatment, some microorganisms can survive within the root canal system, causing persistent periapical inflammation, persistent

symptoms, and sometimes flare-ups [154]. Some patients can experience flare-ups of endodontic infection within a few hours or a few days following the root canal treatment [149, 154–156]. The flare-up rate after endodontic treatment varies from as low as 1.5 % [157] to as high as 20 % [158–162].

The composition of the microbiota in secondary or recurrent infections in previously treated teeth differs from that found in untreated teeth. Gram-positive bacteria are more frequently present and gram-negative bacteria, which are the most common component of primary infections, are usually eliminated. Frequently found organisms include streptococci, *Parvimonas micra*, *Actinomyces* species, *Propionibacterium* species, *Pseudoramibacter alactolyticus*, *Lactobacillus*, and *Enterococcus faecalis* [163]. *Enterococcus faecalis* is the species most often found in the case of treatment failure (Fig. 6.5) [164–166]. Existing evidence suggests

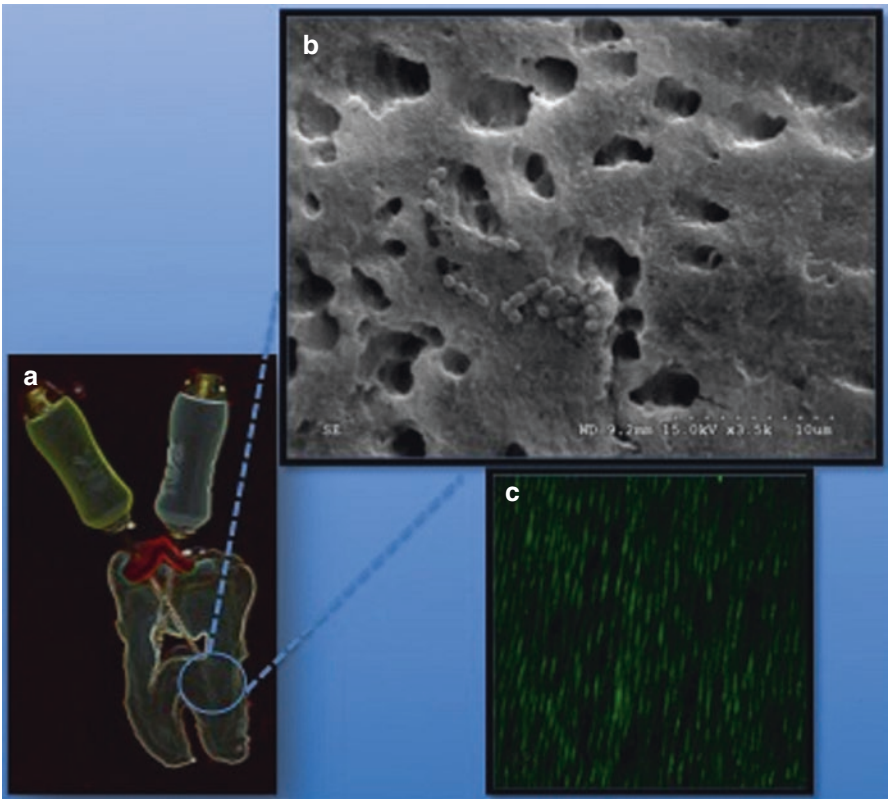

Fig. 6.5 (**a**) Longitudinal aspect of an extracted tooth with a necrotic pulp, showing hand files placed in a working length. (**b**) A colony consisting of cocci of *Enterococcus faecalis* in an ecological niche on the root canal wall. The aggregated bacteria also show some penetration into the dentinal tubules. Scanning electron microscopy, magnification ×3,500. (**c**) Images using a confocal laser scanning microscopy of dentin tubules with *Enterococcus faecalis*. These fragments were stained with Live/Dead dye, showing alive bacteria stained with *green* (Acknowledgment to Dr. Simone Duarte and Department of Basic Science of Craniofacial Biology. New York University)

that, after *Enterococcus faecalis* and *Actinomyces* species, *Candida albicans* are the most prevalent microorganisms associated with failed endodontic treatment [167, 168]. This species can colonize and invade the dentin and seems to be resistant to calcium hydroxide dressing (Fig. 6.6) [153, 169].

The presence of microorganisms in the root canal system evokes the pathogenesis of apical periodontitis. The microorganisms and their virulent factors can penetrate periradicular tissue, resulting in an inflammatory process, the intensity of which depends on the virulence and amount of the microorganisms present (Fig. 6.7) [170]. In the case of symptomatic apical periodontitis, the predominant strains of microorganisms found are *Parvimonas micra*, *Eubacterium*, *Porphyromonas endodontalis*, *Porphyromonas gingivalis*, *Prevotella*, and notably the "black-pigmented bacteria" which have gained much attention [171]. In the complex anatomy of the root canal system with its ramifications, isthmi, apical deltas, and accessory canals, the complete removal of microorganisms from the root canal system remains a challenge (Fig. 6.7) [165, 170, 172]. Positive correlations were found between the persistence of high levels of bacteria and endotoxins and pain on palpation, exudation, and levels of TNF-α and IL-1β [173].

6.3.2 Antibiotics in the Management of Endodontic Infections

The first-line treatment for teeth with either symptomatic apical periodontitis or an acute apical abscess is the removal of the source of inflammation or infection by local, operative measures including endodontic treatment or extraction of the tooth

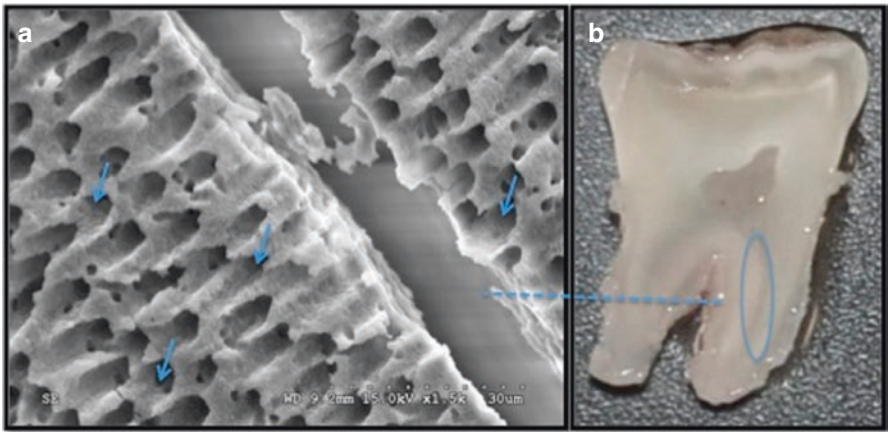

Fig. 6.6 (**a**) Scanning electron microscopy showing a hand file after passing the apical foramen while carrying smear layer from the root canal wall. Magnification ×120. (**b**) Image using a fluorescence microscopy of the smear layer with *Candida albicans*. These fragments were stained with Live/Dead dye, showing alive bacteria stained in *green* and dead in *red* (**c**) (Acknowledgment to Dr. Simone Duarte and Department of Basic Science of Craniofacial Biology. New York University College of Dentistry)

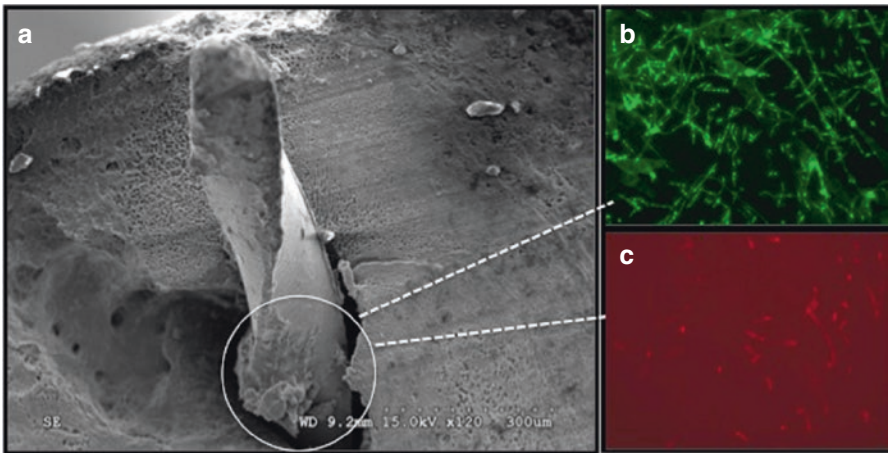

Fig. 6.7 (**a**) Dentinal tubules of root canal wall filled with a colony consisting of cocci along its path to the pulp, after the mechanical debridement with hand files. (**b**) Extracted human mandibular molar: longitudinal aspect of the endodontic space. Scanning electron microscopy, magnification ×1,500 (Acknowledgment to Dr. Simone Duarte and Department of Basic Science of Craniofacial Biology. New York University)

and incision and drainage for localized swellings [174, 175]. Systemic antibiotics are recommended in situations where there is evidence of a spreading infection (cellulitis, lymph node involvement, diffuse swelling) or systemic symptoms (fever and malaise) as well as in treating refractory infections [176]. The overuse of antibiotics increases the chances for bacteria to develop antibiotic resistance and of an alteration of the commensal flora, thus increasing the potential for adverse events such as allergies, anaphylactic reactions, nausea, vomiting, etc. [177–179]. Since dentists prescribe approximately 8–10 % of the antibiotics dispensed in developed countries, it is important not to underestimate the contribution of the dental profession to the increasingly serious problem of antibiotic-resistant bacteria [180, 181].

Systemically administered antibiotics should be considered an adjunct to endodontic therapy, and they should not be used to treat localized inflammatory conditions such as pulpitis and apical periodontitis. Several studies appear to indicate that antibiotics do not reduce the pain or swelling arising from teeth with symptomatic apical pathology in the absence of systemic involvement [45, 76]. Nevertheless, in a survey of members of the American Association of Endodontics, 54% of respondents reported that they would prescribe antibiotics as a first treatment for people with dental pain [182]. Except in patients with compromised immune system, antibiotics are not curative but instead function to assist in the reestablishment of the proper balance between the host's defenses and the invasive agent [183].

In order to maximize the effects of antibiotics and minimize the chances of resistant strains developing, patients must be instructed to initiate the course of antibiotics as soon as possible. Some controversy exists regarding the prescribing of long-term antibiotics. The typical regimen for treating an endodontic infection is 6–10 days on an around-the-clock schedule.

6.3.3 Endodontic Dressings

The anatomical complexity of the root canal systems, especially in the critical apical region, makes it impossible to completely remove all pulp tissue remnants and residual microorganisms, even when applying the highest technical standards of chemomechanical debridement (Fig. 6.7) [164, 165]. Because root canal infections are polymicrobial, consisting of both aerobic and anaerobic bacterial species, several intracanal dressings have been suggested to accomplish root canal disinfection [184, 185]. Local applications of antibiotics within the root canal have been proposed to overcome the potential risk of adverse systemic effects of antibiotics and as an active mode for drug delivery in teeth lacking blood supply due to necrotic pulps or pulpless status [185–187].

Several reports have been recently published describing revascularization or revitalization of immature permanent teeth with a necrotic dental pulp. In addition to traditional nonspecific endodontic disinfecting irrigants, these reports have documented the use of triple antibiotic paste (ciprofloxacin, metronidazole, and minocycline) [185–191], calcium hydroxide [192–195], or formocresol [196] as inter-appointment intracanal dressings. The triple antibiotic mix and calcium hydroxide appear to sometimes allow for continued increased root thickening and lengthening, but formocresol did not achieve the same effect [197]. The antimicrobial effectiveness of intracanal antibiotics versus calcium hydroxide requires further study, but the combination appears to be effective against endodontic pathogens [185, 198].

Calcium hydroxide has been widely accepted as an intracanal medicament because of its antimicrobial properties, especially on gram-negative bacteria [199, 200]. Studies *in vitro* and *in vivo* have shown an intracanal reduction of the microbial population or at least inhibition of bacterial proliferation [201–203]. Some authors have discussed whether calcium hydroxide is effective at eliminating *Enterococcus faecalis*. Other studies have evaluated the effect of intracanal calcium hydroxide on the incidence of posttreatment pain and found that calcium hydroxide is not very effective in reducing posttreatment pain when it is used alone [204, 205], but its effectiveness increased when used in combination with other medicaments like 2% chlorhexidine gluconate and camphorated monochlorophenol [206]. Additionally, several other studies have concluded that medicaments with the corticosteroid component in them are significantly better than calcium hydroxide in reducing the posttreatment pain, attributing to the anti-inflammatory action of corticosteroids (see Sect. 6.2.2.5) [206, 207].

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