Pharmacotherapy in Endodontics

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Master's thesis / Diplomski rad

2023

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Zagreb, School of Dental Medicine / Sveučilište u Zagrebu, Stomatološki fakultet**

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:127:169919

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PHARMACOTHERAPY IN ENDODONTICS

GRADUATE THESIS

Zagreb, 2023.

The work was carried out at the Department of Endodontics and Restorative Dentistry, School of Dental Medicine, University of Zagreb.

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Paper contains: 42 pages

3 tables

0 figures

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Proclamation

To my mentor, izv. prof. dr. sc. Eva Klarić, thank You for your kind heart and for sharing your knowledge with me.

To my mom, dad, brother and sister, I love you more than you will ever know.

To Luka and Marta, without you I would feel like something is missing.

PHARMACOTHERAPY IN ENDODONTICS

Abstract

During endodontic therapy, effective management of infection and pain is essential. Research suggests that 20% of patients experience pain after endodontic procedures. Based on recent meta-analyses, a combination of ibuprofen and paracetamol is the most effective approach for relieving postoperative endodontic pain. It is recommended to administer the first dose of analgesics before the loss of local anesthesia and to follow a scheduled dosing regimen rather than taking medication as needed. In cases of severe postoperative pain, alternative drug classes are considered. In endodontic infections, the objectives of treatment are to eliminate pathogenic microorganisms, bacterial toxins, and necrotic tissue from the contaminated root canal system, which creates an environment that supports healing. This is achieved through mechanical debridement and chemical disinfection of the root canals, as well as establishing proper drainage from both soft and hard tissues. Antibiotics are indicated as adjuvant therapy in endodontics in specific cases, such as presence of systemic symptoms and diffuse spread of infection. According to current studies, prescription durations of 2 to 3 days, until symptom resolution, are as effective as longer courses. Prolonged exposure to antibiotics can lead to the development of antibiotic resistance and side effects because of the reduction of normal gastrointestinal microbiota. Amoxicillin, possibly combined with metronidazole, is the preferred antibiotic against odontogenic microorganisms. When treating patients, it is important to prioritize individualized management of pain and infections. This involves carefully assessing the effectiveness and safety of analgesics and antibiotics.

Keywords: pain, odontogenic infection, analgesics, antibiotics

FARMAKOTERAPIJA U ENDODONCIJI

Sažetak

Tijekom endodontske terapije, esencijalno je učinkovito liječenje infekcije i boli. Istraživanja pokazuju da 20% pacijenata osjeća bol nakon endodontskih zahvata. Na temelju nedavnih meta-analiza, kombinacija ibuprofena i paracetamola je najučinkovitiji pristup za ublažavanje postoperativne endodontske boli. Preporuča se primijeniti prvu dozu analgetika prije gubitka efekta lokalne anestezije i slijediti planirani režim doziranja umjesto uzimanja lijekova po potrebi. Kod jake postoperativne boli, u razmatranje dolaze druge skupine analgetika. Kod endodontskih infekcija, ciljevi liječenja su eliminirati patogene mikroorganizme, bakterijske toksine i nekrotično tkivo iz kontaminiranog sustava korijenskih kanala, čime se stvaraju uvijeti koji promoviraju cijeljenje. To se postiže mehaničkom instrumentacijom i kemijskom dezinfekcijom korijenskih kanala, kao i uspostavom pravilne drenaže iz mekih i tvrdih tkiva. Antibiotici su indicirani kao pomoćna terapija u endodonciji u specifičnim slučajevima kao što su prisutnost sistemskih simptoma i difuznoga širenja infekcije. Prema trenutnim istraživanjima, propisivanja antibiotske terapije u trajanju od 2 do 3 dana, odnosno do povlačenja simptoma, jednako je učinkovito kao i duža terapija (7-10 dana). Produljena konzumacija antibiotika može dovesti do razvoja rezistencije na antibiotike i nuspojava zbog smanjenja fiziološke gastrointestinalne mikroflore. Amoksicilin, po potrebi u kombinaciji s metronidazolom, je preferirani antibiotik protiv odontogenih mikroorganizama. Pri liječenju bolesnika važno je dati prioritet individualiziranom liječenju boli i infekcija. To uključuje pažljivo procjenjivanje učinkovitosti i sigurnosti analgetika i antibiotika.

Ključne riječi: bol, odontogena infekcija, analgetici, antibiotici

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List of abbreviations

PNS – peripheral nervous system

CNS – central nervous system

CGRP – calcitonin gene-related peptide

PDL- periodontal ligament

SAP – symptomatic apical periodontitis

AAP – asymptomatic apical periodontitis

AAA – acute apical abscess

CAA – chronic apical abscess

NSAIDs – non-steroidal anti-inflammatory drugs

tNSAIDS – traditional non-steroidal anti-inflammatory drugs

COX – cyclooxygenase

GPCRs – G protein coupled receptors

GABA – gamma-aminobutyric acid

i.v./IV – intravenous

IM – intramuscular

mg – milligram

g – gram

h – hour

PGE – prostaglandin E

ASA – acetylsalicylic acid

mg/kg – milligram per kilogram

IE – infective endocarditis

TJR – total joint replacement

CDH – congenital heart disease

1. INTRODUCTION

The majority of patients seek dental care due to pain, primarily caused by endodontic and periodontal pathosis. Dentists must place the highest priority on preservation of the natural dentition and the alleviation of dental pain. Hence, it is vital for dentists to distinguish odontogenic from non-odontogenic pain. In order to attain this, precise diagnosis of the pain origin is crucial, accomplished by clinical examination, vitality and sensitivity tests, percussion and palpation, as well as 2D and 3D radiographic examination. This precise identification is essential for providing comprehensive care of endodontic infection and related symptoms, including post-operative pain. Endodontic treatment is widely recognized as the golden standard for effectively relieving pain, restoring function and aesthetics, and preventing complications arising from endodontic infections (4, 6).

Endodontic pain, with its multi-factorial etiology and connection to acute periapical infection, resulting from microbial invasion, serves as the focal point of this graduate thesis. The primary objective is to summarize the relevant and safe pharmaceutical methods suggested for prevention of infection dissemination and managing of post-operative endodontic pain.

2. MECHANISM OF PAIN TRANSMISSION

Pain defined by The International Association for the Study of Pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage”. It acts as a vital protective mechanism that pursues to keep us safe from further harm. Pain is the leading cause patients seek medical help (1). Because of the subjective character of pain generated by emotional stress, a quantification of the sensation is difficult to obtain. The pain pathway is activated by stimulation of nociceptors of primary afferent neurons. Nociceptors are free nerve endings that serve as pain receptors. Noxious stimuli can be living (microbial) or nonliving (mechanical, chemical or thermal). The pain pathway is an intricate pathway involving transduction, transmission, and modulation of the pain signal. Primary afferent nerve fibers conduct sensory information from the peripheral nervous system (PNS) to the central nervous system (CNS) and are classified based on the velocity of signal transduction. A-β (beta) fibers are myelinated fibers of high conducting velocity (>20 m/s) and large diameter (6-12 μm) which conduct information of light touch, pressure and hair movement. A-δ (delta) fibers are myelinated fibers of moderate conducting velocity (2-20 m/s) and a diameter of 6-12 μm found in the skin. C fibers are unmyelinated slow fibers with a conducting velocity of <2 m/s and a diameter of 0.02-1.5 μm found in deep structures such as muscles and joints. Polymodal A-δ and C fibers conduct information on exponential temperature changes and pain. Polymodal fibers can perceive mechanical, thermal and chemical stimuli. Because of the presence of both slow and fast nerve fibers our organism has a dual-pain pathway. The main difference is that activation of A-δ fibers evokes a short, sharp pain which precedes activation of C fibers which evokes a prolonged, blunt pain (2). The origin of sharp pain is easier to locate, especially if tactile receptors are stimulated together with nociceptors. Sensory primary afferent neurons synapse with the second-order neurons in the dorsal horn’s gray matter in the spinal cord. From there on neurons cross over to the contralateral side of the spinal cord and ascend towards the thalamus via the spinothalamic and spinoreticular tract. Thalamus processes and perceives somatosensory data and passes it via third-order neurons to the cortex where the pain is interpreted (3). Pain can be classified as nociceptive or neuropathic pain and acute or chronic pain. Nociceptive pain is due to tissue damage whereas neuropathic pain is due to nerve damage. Nociceptive pain responds better to analgesics than neuropathic pain. Acute pain, mediated by A-δ fibers, acts as a protective mechanism against further injury. It is provoked by substantial tissue damage (1). Chronic pain, mediated by C fibers, is of no protective use and impedes patient’s well-being.

Pain to be considered chronic needs to persist for more than 12 weeks and is under cognitive and emotional influence. Because of the emotional influences, the severity of chronic pain is often amplified (2). Hyperalgesia is frequently present with chronic pain. Hyperalgesia is a state of increased sensitivity to pain due to prolonged stimulation of nociceptors (3). Prevention or proper and early treatment of acute pain is one of the best ways of preventing chronic pain. It is important to note that pain fades away before the completion of healing (2).

Sensory fibers make most of the nerve fibers in the pulp. The periphery of the pulp is innervated by A-δ fibers, which extend into dentinal tubules. The central pulp is innervated by C fibers. A-β fibers and sympathetic fibers are in the walls of arterioles. Tooth maturation and formation of the apical foramen restricts blood supply to the pulp thereby decreasing its ability to withstand noxious stimuli (e.g., caries). Arteriovenous anastomoses are coping mechanisms of the pulp against increased blood flow due to hyperemia. The pulp reacts to irritants with an inflammatory response. The severity of inflammation matches the scope of irritation to the pulp (4). The "inflammatory soup" alters the nociceptor function involved in the pain pathway (1). Allodynia is a phenomenon in which inflammation decreases the pain perception threshold and causes non-painful stimuli to cause pain. Allodynia in endodontics often impedes the effectiveness of local anesthesia (4). The "inflammatory soup" consists mainly of neutrophils but also of macrophages, lymphocytes, plasma cells, dendritic cells and mast cells. Molecular inflammatory mediator titter of neuropeptides, prostaglandins, cytokines, bradykinin, matrix metalloproteinases, chemokines correspond with the degree of pulpal pain. Bradykinin provokes the highest degree of pain in comparison to other inflammatory mediators (3). During inflammation, the number of nociceptors increases together with the titter of calcitonin gene-related peptide (CGRP) and substance P. CGRP and substance P reduce the pain threshold in the spinal cord and cause vasodilation of blood vessels. Augmented vascular permeability due to vasodilation allows the accumulation of additional inflammatory cells and causes edema and an increase in intrapulpal pressure.

Pain is a common symptom in endodontics. Depending on the severity of the pathological process in the pulp, pain can have different manifestations. This helps us with the diagnosis and thereby the treatment plan. We need to recognize that different parts of the pulp experience

different degrees of hyperemia at a given time, except total necrosis, thus the correct diagnosis is sometimes difficult to reach. Medical history, clinical and radiological examination need to be done in order to establish the final diagnosis (4).

A healthy pulp is clinically without any symptoms. During sensitivity testing with refrigerant sprays, a healthy pulp responds by mild to moderate pain, and the response is not delayed. In reversible pulpitis patients occasionally experience mild hyperalgesia of the pulp, but during cold testing, a sharp and short-lasting pain is provoked. Irreversible pulpitis differs from reversible pulpitis in the degree of hyperemia. Hyperemia is an excess of blood flow as a result of metabolic changes during acute inflammation. We accompany irreversible pulpitis with spontaneous and longstanding pain attacks, but the clinical findings are often inconsistent. Patients have trouble locating the origin of their pain contrary to periapical conditions. Cold testing provokes a prolonged pain response. Irreversible pulpitis, if not treated, always leads to liquefaction necrosis. Due to the destruction of sensory fibers, necrosis remains painless. Pulp necrosis is coupled with periapical lesions. Periapical lesions arise because of the progression of inflammation from the pulp through the apical foramen into the periapical tissue. Because the average thickness of the periodontal ligament (PDL) is 2mm, it is not capable of provoking a strong enough immune response against the microbial agents regardless of the abundance of inflammatory and immune cells, blood vessels, and lymph vessels. Consequently, bone resorption takes place to assure enough soft tissue for an immunologic reaction. Additionally, it acts as a barrier between the pathogen and healthy bone preventing osteomyelitis. If inflammatory processes are confined within the endodontic space, periapical tissue remains clinically and radiographically normal. This implies that no pain is provoked during percussion and palpation and PDL and lamina dura have a physiological appearance. The initial advancement of pulpal pathosis into periapical tissue is called symptomatic apical periodontitis (SAP). Apart from pulpitis or pulp necrosis, SAP may stem from inadequate endodontic treatment or hyperocclusion after restorative treatment. Patients complain of pain during mastication. Clinically, pain is provoked by percussion and palpation of the affected tooth. X-ray findings vary from physiological to enlargement of the PDL and lack of continuity of lamina dura. Asymptomatic Apical Periodontitis (AAP) presents as a radiolucent periapical lesion and is often an accidental finding. AAP is linked to pulp necrosis and may remain asymptomatic for

years. Sensitivity testing and percussion do not lead to pain. Acute Apical Abscess (AAA) is the most serious endodontic condition, therefore it seeks emergency care. It presents with spontaneous pain and swelling due to bacterial invasion, hence provoking a strong inflammatory response. Consequently, liquefaction necrosis forms and spreads through the bone towards soft tissues. AAA has a fast onset. Individuals may present with symptoms such as pyrexia, asthenia, and leukocytosis. If not treated, AAA can result in mortality due to its spread to extraoral regions. Condensing osteitis is a subtype of AAA. The bone around the apex of the affected tooth is more sclerotic. In this instance, low-grade irritation causes sclerosis instead of bone resorption. Chronic Apical Abscess (CAA) is characterized by sinus tract formation, usually on the attached gingiva of the involved tooth. Sinus tract forms by the law of least resistance. Sometimes it may go past muscles and drain on the skin or through a periodontal pocket. The cause of CAA is pulp necrosis. Because of the drainage patients have no symptoms. The sinus tract spontaneously heals after the proper treatment of the pathological process. All previously mentioned conditions, except reversible pulpitis, are treated with endodontic therapy or extraction. Teeth with reversible pulpitis experience low-grade inflammation and their pulp still has a healing capability. The therapy, therefore, is the removal of irritants and protection of the pulp and open dental tubules (4).

Post-operative endodontic pain is a frequent occurrence following root canal treatment. Possible causes are microbial, mechanical, or chemical irritation, which provokes an inflammatory response in the periapical tissue. This inflammation can lead to pain and discomfort after the procedure. Inadequate working length determination, overinstrumentation, overfilling or perforation of the root canal, irrigation solutions, remnants of infected or necrotic pulp, and bacteria all cause irritation to the periapical tissue (4).

3. ANALGESICS IN ENDODONTICS

Endodontic treatment besides root canal instrumentation and obturation consists of effective pre-operative, intra-operative, and post-operative pain control. Pain control is essential to patients since it improves their quality of life (5). Proper pain control relies on precise diagnosis, obtained by taking medical history and clinical and radiological examination. Post-operative pain is a common occurrence with a 40% incidence within 24 h following the endodontic intervention and can persist for days (6). Endodontic pain treatment can be local or systemic. Analgesics are frequently prescribed by dentists for pain management. The efficiency and safety of each type of systemic therapy must be kept in mind when administering it to patients (5).

Analgesics are pharmacological substances used to relieve pain. Two main groups of analgesics are opioid or narcotic analgesics and non-opioid or analgesics-antipyretics (9). Non-opioid analgesic drugs cover acetaminophen (paracetamol) and non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are divided into selective cyclooxygenase-2 (COX) inhibitors and nonselective traditional non-steroidal anti-inflammatory drugs (tNSAIDs) (7).

3.1 Opioid analgesics

Opioid analgesics are natural and semi-synthetic alkaloid derivatives of opium, as well as synthetic proxies which are fabricated analogs. The main wanted feature of opioid drugs is strong analgesia. The effect of opioids on pain happens within the spinal column. Unfortunately, the supraspinal effect of opioids causes certain side effects, such as respiratory depression, sedation, constipation, emesis, and substance dependence. In nature, opium is sourced from Papaver somniferum, known as the poppy. The white exudate from the poppy seed pod contains raw opium. Phenanthrene derivatives and isoquinoline derivatives are the main two groups of alkaloids derived from opium. Morphine is the fundamental alkaloid of the phenanthrene group of derivatives followed by codeine. Isoquinoline derivatives are papaverine, narcotine, narceine (8).

The endogenous opioid system contains G protein-coupled opioid receptors (GPCRs) found in the CNS, PNS, and digestive tract. The system controls pain, reward, and addictive behavior. Endogenous opioid peptides are enkephalins, endorphins, and dynorphins. Naturally derived opioids can only exhibit a certain degree of potency. Synthetic opioids undergo a refinement process that renders them much more powerful. The majority of opioid analgesics are well

absorbed after subcutaneous and intramuscular administration. If given orally the dosage needs to be higher because of the first-pass effect. The primary categories of opioid receptors are mu, delta and kappa receptors. Large numbers of all three receptor types are in the dorsal horns of the gray matter. When it comes to the mechanism of action, opioid alkaloids can be absolute agonists, partial agonists, and antagonists on receptors. Most analgesics currently in use exert their effects mainly by targeting the mu receptors, imitating the action of natural opioid peptides. Agonists of opioid receptors inhibit the function of pre-synaptic voltage-gated calcium channels which disables the release of neurotransmitters such as glutamate, substance P, CGRP into the synaptic cleft and reduce post-synaptic excitability. Additionally, the activation of opioid receptors inhibits adenylyl-cyclase and enhances potassium channel opening which causes the outflow of potassium and cellular hyperpolarization, resulting in reduced sensitivity of neurons to stimuli. The result of the action is inhibition of the transmission of pain impulses within the spinal cord (8). Nausea, as a side effect of opioid use, occurs due to the stimulation of the chemoreceptors in the medulla. Decreased responsiveness of the respiratory center in medulla, coupled with depression of the respiratory center in the pons and medulla that govern respiratory rhythm, is responsible for dose-dependent respiratory depression under the opioid influence. The antitussive effect happens because of the depression of the cough center in the medulla. Opioids increase vagal stimulation which in turn causes bradycardia. Opioid intake can lead to pruritus because of its effect on the pruritoceptive neural circuits. They cause constipation by slowing down digestive motility and prolonging the gastric emptying time. The antidiuretic effect of opioids is a result of depressed renal function and increased sphincter tonus. The biggest problem is that opioids cause psychological and physical substance dependence. In the nucleus accumbens, which is the brain's reward and pleasure system, gamma-aminobutyric acid (GABA) reduces the release of dopamine. When opioids bind to mu receptors, the action of GABA is inhibited, and dopamine activity is enhanced. Consistent usage of opioids results in the desensitization of receptor signaling and the downregulation of receptors, leading to reduced sensitivity to the effects of opioids. Once the intake of opioids stops, the absence of receptor activity is evident through withdrawal symptoms, which typically exhibit opposite effects to the therapeutic effect of opioid drugs (8).

Activation of mu receptors causes supraspinal analgesia, euphoria, respiratory depression and the development of addiction. Stimulation of kappa receptors presents as spinal analgesia, sedation and myosis. Delta receptors are probably responsible for changes in affective behavior (9).

Morphine is a phenanthrene alkaloid of opium with a half-life up to 4 hours. It is a strong analgesic used for management of intense acute pain (e.g., posttraumatic pain, burns, in cancer patients as palliative therapy) or severe chronic pain (e.g., terminal patient care). It can also be used as an adjunct in anesthesia causing sedation and relaxation. Acute morphine overdose is characterized by the onset of myosis, respiratory depression, and coma (9).

Codeine is a less potent opioid analgesic used as an antitussive. Usually, it is used in combined pharmaceutical formulations (e.g., Caffetin tablets) which contain a mixture of analgesics and antipyretics. Codeine can be taken in pregnancy, but long-term use is not recommended (9).

Representatives of synthetic opioids are fentanyl and methadone. Fentanyl is used an adjunct in anesthesia and for postoperative pain. Its effect lasts for 1 to 2 hours. Methadone is used for relieving nociceptive and neuropathic pain. Its half-life is up to two days. Methadone, being a mu receptor agonist, can relieve symptoms of withdrawal syndrome (7, 9).

Naloxone, a nonselective antagonist of mu, kappa, and delta receptors, is used in emergencies for the treatment of opioid drug-induced respiratory depression. Naloxone has a stronger affinity towards opioid receptors thus blocking the attachment of opioids to the receptors. Dose of 0.1 to 0.4 milligrams (mg) intravenous (IV) is used for the treatment of respiratory depression (8).

In dentistry, the administration of opioid analgesics for the therapy of dental pain is considered appropriate only in cases where maximum doses of NSAIDs have been unable to effectively alleviate the pain. In cases where non-opioid analgesics prove ineffective in reducing pain, a combination of opioids and non-opioid analgesics may be used to achieve a synergistic effect. This is why, in dentistry, opioids are often not prescribed as a standalone treatment but are instead administered in conjunction with acetaminophen (paracetamol) or NSAIDs to enhance their analgesic properties (7). Opioid analgesics use is contraindicated in individuals with severe chronic respiratory conditions, severe inflammatory bowel diseases, and alcoholism. Upon establishing the correct diagnosis and indications, the initial pharmacological intervention for pain management involves administering 30-60 mg of codeine every 4-6 hours. If codeine fails

to provide adequate analgesia, oxycodone may be introduced. Oxycodone is available in combination with acetaminophen, given a dosage of 5-10 mg four times a day. Other opioids can only be used exceptionally for the therapy of postoperative dental pain. Meperidine, a synthetic opioid analgesic, is reserved for patients allergic to codeine and morphine derivatives. The best route of administration is parenteral. Peroral administration is not advised due to the significant risk of acute intoxication with the drug and its metabolites. Croatian literature gives preference to tramadol. Tramadol is a weak mu-receptor agonist. For adults and children over 14 years old, the recommended oral dose is 50-100 mg, to be taken every 4-6 hours, 400 mg being the maximum daily dose (e.g. ″Lumidol″, Belupo, caps. 20 x 50 mg). Ultracet is a combination medication comprising of 325 mg of acetaminophen and 37.5 mg of tramadol (10). It is considered to be a viable treatment choice in case of severe postoperative pain (8). Some studies suggest that a combination of paracetamol and caffeine may improve pain management and minimize the occurrence of adverse effects, and have a quicker onset of action compared to monotherapy with paracetamol. However, clinical trials have not proven a synergistic effect, and the risk of developing side effects is greater (9). One such combined preparation is "Caffetin" by Alkaloid, which contains 210 mg of paracetamol, 250 mg of propyphenazone, 50 mg of caffeine, and 10 mg of codeine. For adults, the recommended dose is 1-2 tablets daily, while children over 12 years old should take ¼ to ½ of a tablet daily. The maximum daily dose for adults is 6 tablets (10).

3.2 Non-opioid analgesics

Non-opioid analgesics relive pain by peripheral inhibition of prostaglandin synthesis. Generally, they are successful in alleviating dental pain. Furthermore, they share a common therapeutic profile, exhibiting anti-inflammatory, analgesic, and antipyretic properties. Unlike opioid analgesics, non-opioid analgesics are associated with fewer side effects, exhibit lower levels of toxicity and do not cause addiction (9).

Prostaglandins, derivatives of prostanoic acid, are synthesized in response to a variety of physiological, biochemical, mechanical, pharmacological, and pathological stimuli that activate the phospholipase A2 enzyme. This activation leads to an increase in intracellular arachidonic acid, which acts as a precursor for prostaglandin synthesis. Arachidonic acid is converted into

prostaglandins and thromboxane by the COX enzyme complex, while the lipoxygenase enzyme converts it into 5-hydroperoxy-arachidonic acid and subsequently leukotrienes (9).

Prostaglandins are effective mediators of inflammatory reactions which sensitize pain receptors and regulate body temperature in the hypothalamus. Moreover, prostaglandins stimulate mucus and bicarbonate secretion and inhibit acid secretion in the stomach, they cause vasodilation, increase vascular permeability and inhibit platelet aggregation. On the other hand, thromboxane causes vasoconstriction and promotes platelet aggregation. NSAIDs act as inhibitors of COX, impeding the synthesis of prostaglandins and thromboxanes, thus reducing inflammation, relieving pain and acting as an antipyretic. COX-1 and COX-2 are types of cyclooxygenase enzymes. Most NSAIDs inhibit the action of both isoenzymes. The anti-inflammatory action is attributed to the suppression of COX-2. Conversely, the blocking of COX-1 results in NSAID-induced nephropathy, gastropathy and prolonged bleeding (7, 9).

NSAIDs act anti-inflammatory by diminishing the level of vasodilatory prostaglandins. This, in turn, results in a reduction of edema; however, it does not lead to a decrease in the count of inflammatory cells. The analgesic effect is concomitant with the suppression of prostaglandin production and a decrease in the sensitivity of nociceptors to inflammatory mediators: bradykinin and serotonin. The antipyretic effect is due to the reduced synthesis of prostaglandin E (PGE) in the hypothalamus. By suppression of PGE synthesis, the thermoregulation center returns to maintaining normal body temperature (9).

Analgesics-antipyretics include: salicylic acid derivatives (acetylsalicylic acid), para-aminophenol derivatives (paracetamol), propionic acid derivatives (naproxen, ibuprofen), pyrazolone derivatives (propyphenazone, metamizole), indole derivatives (indomethacin), aminophenylacetic acid derivatives (diclofenac) and oxicams (piroxicam) (9).

Most common side effects from NSAID intake are dyspepsia, diarrhea, nausea and vomiting. With prolonged consumption, gastric ulcers with the risk of bleeding are frequent. Hence, gastric mucosal protective agents or stomach acid secretion inhibitors (e.g., proton pump inhibitors) can be prescribed together with NSAIDs. The risk of such effects is highest when taking piroxicam and acetylsalicylic acid, lower with diclofenac and naproxen, and lowest with ibuprofen and paracetamol. Another option is prescribing paracetamol or selective COX-2 inhibitors. To avoid

the negative effects brought on by COX-1 inhibition, selective COX-2 inhibitors emerged. Unfortunately, the intake of COX-2 inhibitors is associated with a risk of thrombosis, heart failure, coronary heart disease, high blood pressure, and stroke. In some patients, reversible renal insufficiency occurs. In addition, long-term use of large doses of paracetamol leads to analgesic nephropathy (chronic nephritis and renal papillary necrosis). In children, acetylsalicylic acid intake is associated with the development of Reye syndrome (7, 9).

According to recent systematic reviews and meta-analyses, the best approach for relieving postoperative endodontic pain involves administration of 600 mg ibuprofen, either alone or in combination with 1000 mg of paracetamol. The maximum daily dose of paracetamol recommended by the Food and Drug Administration is 4 grams (g) per day. In order to prevent the accumulation of arachidonic acid metabolites and possible consequent inflammatory pain following endodontic treatment, patients should take the first dose of NSAIDs prior to the loss of local anesthesia. Subsequently, they are advised to adhere to a "by the clock" dosing regimen instead of taking medication "as needed". In cases of severe postoperative pain, alternative drug classes like opioids may be taken into account. Nevertheless, it is crucial for the clinician to be well-informed about the current opioid crisis, which has resulted in a five-fold increase in deaths related to opioid overdose since 1999. Moreover, research indicates that endodontists, after oral surgeons, prescribe the largest sum of opioid analgesics in case of severe pain. Tramadol should be taken into account in case of persistent and severe pain after endodontic therapy. Tramadol has demonstrated fewer opioid-like central effects as compared to morphine; however, it can lead to addiction development. A phenomenon known as central sensitization is primarily responsible for postoperative pain. Constant stimulation of primary afferent nerve fibers increases the activity of second-order neurons, resulting in hypersensitivity to stimuli and increased pain response. Preoperative delivery of 0.5% bupivacaine with 1: 200,000 epinephrine results in a significant reduction in postoperative pain in comparison to 2% lidocaine with 1: 80,000 epinephrine. Additionally, corticosteroids with their inhibition of phospholipase A2 can reduce postendodontic pain (e.g., prednisolone, dexamethasone) (4).

3.2.1 Acetylsalicylic acid

Acetylsalicylic acid (ASA) irreversibly inhibits both cyclooxygenase enzymes by acetylation of the COX active site, causing analgesia, antipyretic and anti-inflammatory effect. It is used as an

analgesic for mild to moderate pain, and for febrile conditions. ASA irreversibly inhibits thromboxane A2 synthesis by platelets during hemostasis. Thromboxane A2 stimulates the production of new thrombocytes and enhances thrombocyte aggregation. The antithrombotic effect of ASA can lasts up to 10 days, which is the life span of thrombocytes. The annual risk of major vascular events is decreased by long-term aspirin intake. Other tNSAIDs reversibly inhibit COX, thus their antiplatelet effect lasts significantly shorter (7).

In dental medicine, it is a common dilemma whether to recommend stopping antiplatelet treatment before dental procedures in which bleeding is expected. However, research has proven that it is only necessary to take care of local hemostasis measures. Although, statistically, it is a greater risk for the patient to discontinue antiplatelet therapy due to a higher incidence of ischemic attacks, some authors suggest that in more extensive procedures, where major bleeding is expected (11, 12), patients should stop taking salicylate one week before the procedure (9).

As an analgesic and antipyretic, the adult dose of ASA is 325 - 1000 mg four times a day, and the daily maximum is 4 g. Contraindications for the use of ASA are active peptic ulcers, bleeding disorders, children under 12 years because of suspicion of a causal relationship between ASA intake and viral infections and Reye's syndrome, asthmatics, the last trimester of pregnancy and breastfeeding. In the event of an acute overdose, the treatment involves gastric lavage and the administration of vitamin K to combat bleeding (9).

3.2.2 Ibuprofen

Ibuprofen, a propionic acid derivative, is highly effective in relieving mild or moderate dental pain. Ibuprofen is frequently prescribed, because if taken properly, the risk of a side effect is relatively low. Ibuprofen is a nonselective COX inhibitor. The recommended dose in dentistry is 200 mg to 400 mg, four times a day. However, the dosage can be raised to 600 mg in order to achieve enhanced pain relief (Table 1). Maximum daily dosage should not exceed 2,6 g. Higher dosage increases the risk of gastrointestinal bleeding in case of peptic ulcers and cardiovascular events. Ibuprofen intake is not recommended in the last trimester of pregnancy, because it causes prenatal closure of the ductus arteriosus through prostaglandin inhibition (7).

3.2.3 Paracetamol

Paracetamol (acetaminophen) exerts its mechanism of action through inhibition of COX-2, leading to the inhibition of prostaglandin synthesis. Paracetamol does not possess anti-inflammatory effects because it does not inhibit peripheral cyclooxygenase activity. On the other hand, cardiovascular gastrointestinal complications, and prolonged bleeding occur relatively rarely in comparison to other tNSAIDs (7).

Paracetamol is one of the choices of drugs for controlling postoperative and dental pain in children and adults. The recommended daily dose is 500 to 1000 mg every 4 to 6 hours. In children, it is used in a dose of 10 to 15 milligrams per kilogram (mg/kg), the maximum recommended therapeutic dose is 65 mg/kg a day (13).

Paracetamol is considered safe for children since there is no correlation between its intake and the increased risk of Reye syndrome. Paracetamol does not have significant restrictions or concerns regarding its use in pregnancy. However, it's important to use the appropriate dose derived from the child's weight and age and to follow recommended guidelines for use in pregnancy. However, excessive production of its toxic metabolite by the hepatic cytochrome P450 system may lead to severe liver damage. Thus, it is crucial not to exceed the recommended dose of 4 grams. Patients with liver damage and those who intake substantial amounts of alcohol daily should be particularly careful when taking this medication (7).

Table 1. Analgesic strategy of postoperative pain (4).

Pain level	Patient history	Drug
Mild to moderate pain	No history of opioid abuse	Acetaminophen or NSAIDs
	History of gastrointestinal problems, renal disease or anticoagulant therapy	Acetaminophen
	History of asthma, liver disease or bleeding disorders	NSAIDs
Severe pain	No history of opioid abuse	Combination of acetaminophen and an NSAID, or tramadol
	History of opioid abuse	Tramadol
	History of gastrointestinal problems, renal disease or anticoagulant therapy	Acetaminophen or tramadol
	History of asthma, liver disease or bleeding disorders	Tramadol

4. ENDODONTIC INFECTIONS

Periapical infection is the prevailing type of odontogenic infection, caused by microbial invasion of the endodontic system. Upon periapical tissue infiltration via the apical foramen, the microorganisms stimulate an inflammatory cascade, which leads to the development of periapical pathosis. In the majority of instances, the infection tends to be mild and confined to the oral cavity (buccal, labial, or lingual vestibule). However, if left untreated it may spread into deeper tissues of the head and neck region, precipitating a range of serious complications, such as airway obstruction, sinusitis, Ludwig's angina, mediastinitis, endocarditis, brain abscess, cavernous sinus thrombosis or death. Ludwig's angina is a fast progressing diffuse cellulitis of the submandibular, mental, and sublingual spaces. In most cases, the infection originates from pericoronitis or infected mandibular molars. Mediastinitis is the consequence of infection invasion of the danger space aided by respiration, gravity and negative intrathoracic pressure. Hematogenous dissemination of bacteria by the angular, facial or ophthalmic veins into the cavernous sinus can lead to cavernous sinus thrombosis. The lymphatic system in the head and neck region allows the transmission of an odontogenic infection from a nearby primary node to a secondary node located at a distant site via veins. Lymph nodes serve as antimicrobial filters, producing lymphocytes to combat infection. The spread of the infection typically occurs through the path of least resistance, which is determined by the root position within the alveolus, the orientation of the apices of the affected teeth relative to muscle attachments, the proximity of the apices to the lingual and buccal surfaces of the jaw bones, and the thickness of the adjacent bone. In the molar region of the mandible, the path of least resistance is towards the lingual aspect of the alveolar ridge, while the thin buccal plate is the most accessible route for infection spread in the maxilla. Additionally, the progression of the infection is determined by both the microorganism virulence and host immune system activity, in addition to the regional anatomy. Acute periapical infections are typically characterized by pain and tenderness upon percussion or mastication, along with redness and swelling. Pain arises due to the local accumulation of inflammatory mediators such as kinins and histamines and exudation which increases the pressure within the boundaries of the underlying alveolar bone. Symptoms such as pyrexia and lymphadenopathy can be present. If unaddressed, the lesion may persist as a low-grade virulence chronic inflammatory response, which can result in sinus formation. Rarely, symptoms worsen because of quick dissemination of infection (severe complications), requiring patient

hospitalization for IV antibiotics and, potentially, tooth extraction under general anesthesia (14, 15).

The dentin-pulp complex is shielded from oral cavity microorganisms by cementum and enamel. However, once the integrity of these barriers is compromised, the complex becomes vulnerable to oral environment exposure. Subsequently, the pulp is susceptible to infection by oral microorganisms from caries, dental plaque and saliva. If commensal bacteria from the oral cavity's physiological flora have access to the sterile dental pulp and periapical tissue, the development of opportunistic infection occurs resulting in pathological changes in the form of pulpitis, pulp necrosis or periapical lesions. The endodontic space can have orthograde exposure to microorganisms from the direction of the tooth crown, which can occur through deep caries, crown fractures, or coronal leakage. Following necrosis of the pulp, microorganisms can freely penetrate the endodontic system without encountering the host immune system. Furthermore, bacteria and their by-products may also access the necrotic pulp through the process of anachoresis, as well as through the apex, lateral canals, accessory canals, and furcations (16).

Endodontic infections have a polymicrobial pathogenesis, with microorganisms in the endodontic system existing as a multispecies biofilm (17). The prevalent microorganisms are strictly anaerobic gram-negative rods and gram-positive cocci, alongside microaerophilic and facultative streptococci. The most abundant phyla are Actinobacteria, Firmicutes, Bacteroidetes, Fusobacteria and Proteobacteria. The genera most commonly identified include Fusobacterium, Prevotella, Porphyromonas, Streptococcus and Parvimonas.

Generally, the presence of gram-negative anaerobic bacilli and anaerobic gram-positive cocci is associated with incidence of acute signs and symptoms, such as pain, sensitivity to percussion and palpation, and cellulitis. Aerobic bacteria, primarily invasive Streptococcus species, are present in initial phases of infection, causing a cellulitic reaction. They act as infection initiators and create local conditions that facilitate the anaerobic bacteria invasion as the tissue becomes more hypoxic, favoring anaerobic bacterial growth. Apical abscess microbiota are predominated anaerobic bacteria. Anaerobes (75%) include Bacteroides, Prevotella organisms, Peptostreptococci and Fusobacterium nucleatum and aerobes (25%) include α-hemolytic Streptococci. Culture-independent molecular biology has enabled the identification of numerous novel species of pathogens involved in endodontic infections (14).

Endodontic infections can be primary/initial intraradicular infections or secondary and persistent intraradicular infection. Primary intraradicular infections are brought on by bacteria that initially infiltrate the necrotic pulp, whereas secondary infections are brought on by microorganisms that reestablish themselves within the endodontic system after or during initial endodontic treatment. In contrast, primary infection pathogens that resisted antimicrobial treatments and persisted inside the root canal system are the cause of persistent infections. Secondary and persistent infections have a more complex etiology and cause a variety of problems, including chronic exudation, inter-treatment flare-ups, and endodontic treatment failure. Gram-positive facultative anaerobic bacteria are the main cause of secondary intraradicular infections. The prevalent bacterial genera include Streptococcus, Lactobacillus, and Enterococcus. Extraradicular endodontic infections are characterized by the destruction of periapical tissue due to microbial invasion and interaction with the host defense mechanism resulting in apical periodontitis. Clinical approaches, such as endodontic therapy, extraction, incision and drainage, mechanical instrumentation and irrigation are all methods of reducing the endodontic bacterial load and thus decreasing the infectious biological burden (4, 14).

5. ANTIBIOTICS IN ENDODONTICS

Antibiotics are antimicrobial substances active against bacteria. The objective of administering antibiotic therapy is to augment the individual's natural defense mechanisms and facilitate the control and elimination of microorganisms that have surpassed the host's immune system and caused infection (18). Antibiotics selectively target specific types of microorganisms without causing harm to the host, known as selective toxicity. Antibiotics can be classified into two groups according to their impact on microbial cells, employing two primary mechanisms: bacteriostatic or bactericidal. Bactericidal antibiotics induce bacterial death, whereas bacteriostatic antibiotics inhibit bacterial growth by suppressing protein synthesis pathways, thereby maintaining them in the stationary phase of growth. Bactericidal antibiotics are penicillins, cephalosporins, aminoglycosides, polymyxins, vancomycin, and metronidazole. Bacteriostatic antibiotics are erythromycin, lincomycin/clindamycin, tetracyclines, chloramphenicol, and sulfonamides. Certain antibiotics can exhibit both bactericidal and bacteriostatic effects depending on the dosage concentration. An intact immune system is crucial for the efficacy of bacteriostatic agents. Therefore, immunocompromised patients (diabetes, leukemia, AIDS, Addison’s disease, alcoholism, corticosteroid and immunosuppressive therapy) should receive bactericidal antibiotics. In combination therapy, it is important to avoid the concurrent use of bacteriostatic and bactericidal agents. This is due to the fact that bactericidal antibiotics target bacterial cells during their division phase, whereas bacteriostatic antibiotics inhibit bacterial replication, leading to a diminished therapeutic effect (9, 19).

The objectives for treatment of endodontic infections are the elimination of pathogenic microorganisms, their metabolic toxins, and necrotic tissue from the infected endodontic system that led to periapical pathosis, and the creation of an environment that facilitates lesion resolution. Successful management of endodontic infections centers on mechanical debridement and chemical disinfection of the infected root canals and establishment of proper drainage from both soft and hard tissues. Drainage establishment can be achieved through: trepanation of the affected tooth, intraoral or extraoral incision, or extraction of the tooth with drainage through the extraction alveolus (20).

Antibiotics as adjuvant therapy to local endodontic treatment are indicated in case of: diffuse swelling and spread of infection beyond the extraoral musculofascial tissues and cortical bone; the presence of systemic symptoms such as elevated body temperature; malaise; trismus and,

regional lymphadenopathy (21). Prescribing narrow spectrum antibiotics that target the involved microorganisms is desirable. Narrow spectrum antibiotics are more effective against specific pathogens and have less impact on the commensal oral flora, reducing the risk of superinfection (9). To minimize unfavorable reactions to the antibiotic and an increase in antibiotic-resistant bacteria strains, it is advisable to prescribe antibiotics at the minimum effective dosage for the shortest effective duration. According to new research, a shorter course of treatment, 2 to 3 days, until symptoms resolution, is just as effective as a longer course of treatment, 7 to 10 days. Additionally, prolonged exposure of commensal microorganisms to antibiotics can cause development of antibiotic resistance and side effects due to the reduction of normal gut flora (22).

In irreversible pulpitis the hyperemic pulp is vital and immunocompetent, with the ability to withstand infection. Therefore, antibiotics are not recommended. In pulp necrosis with symptomatic apical periodontitis or abscess with localized intraoral swelling, the primary therapy is canal debridement and drainage. Antibiotics are contraindicated due to the lack of systemic involvement and circulation in the pulp, which hinders antibiotics to reach the affected area. Drainage provides pain relief by removing bacterial toxins and by decreasing high pressure associated with edema which promotes better antibiotic penetration into the infected space. In the case of pulp necrosis with diffuse swelling, referral of patients for extraoral incision, IV antibiotics, and pain control is necessary to prevent potential lethal complications. Patients with cellulitis need to be monitored daily until the symptoms subside. Patients with systemic disorders and weakened immunity are more likely to experience odontogenic infections complications, hence antibiotics should be considered. The choice of an antibiotic, in dental medicine, is based on empirical criteria and the bacterial strains that are regularly identified from periapical lesions, which are frequently anaerobic and facultative in character. Therefore, it is recommended to use antimicrobial agents that cover the spectrum of action against frequently encountered bacteria.

Penicillin VK, alone or with metronidazole, is very successful against dental infections, but amoxicillin, coupled with clavulanic acid, is preferred due to lower risk of adverse effects and better absorption. Clindamycin is the medication of choice with verified penicillin allergy. (4, 22).

In 2017 the International Endodontic Journal published guidelines that outline the appropriate uses of antibiotics in endodontic treatment.

Indications for adjunct antibiotics in endodontic therapy:

1. Acute apical abscess in medically compromised patients (localized fluctuant swellings, patient with systemic disease causing impaired immunologic function);
2. Acute apical abscess with systemic involvement (localized fluctuant swellings, fever (>38 °C), malaise, trismus, lymphadenopathy);
3. Progressive infections (fast onset of severe infection (within 24 h), cellulitis or a diffuse infection, osteomyeliti) which could necessitate oral surgical intervention;
4. Persistent infections (chronic exudation, unresponsive to endodontic therapy);
5. Replantation of avulsed permanent teeth;
6. Soft tissue laceration requiring debridement or suturing (22).

Given that local endodontic treatment and the establishment of drainage can effectively resolve the majority of endodontic infections, the use of adjunct antibiotic therapy is not recommended in the following cases:

1. Symptomatic irreversible pulpitis which presents only with pain (no other signs of infection);
2. Pulp necrosis (nonvital teeth, widening of PDL);
3. Acute apical periodontitis (pain, pain to percussion, pain during mastication, widening of PDL);
4. Chronic apical abscess (dental sinus tract, periapical radiolucency);
5. Acute apical abscess with no systemic involvement (localized fluctuant swellings) (22).

The results of antibiotic sensitivity testing affirm that most isolates from endodontic infections display susceptibility to penicillin VK. As a result, it can be considered a viable first choice for adjunctive antibiotic treatment for endodontic lesions. Penicillin VK is a narrow-spectrum antibiotic that is effective against infections brought on by anaerobic microorganisms, aerobic gram-negative cocci and facultative microorganisms. It acts on Streptococcus, penicillinase-

negative Staphylococcus, Treponema, Actinomyces, Fusobacterium species, and oral anaerobes. It exerts selective toxicity by inhibiting cell wall formation of bacteria. Unfortunately, penicillin is poorly absorbed from the gastrointestinal tract, resulting in wastage of at least 70% of the oral dose and depletion of gut commensal flora, leading to diarrhea. Additionally, penicillin is a short-acting medication, with a half-life of 30 minutes. A loading dose of 1000 mg of penicillin VK should be administered orally followed by 500 mg every 6 h to achieve a steady serum level. Clinical improvement becomes evident within 48–72 h. However, because metronidazole is efficient against anaerobes, it should be added to the regimen if penicillin VK treatment fails to provide results in 2 days. Penicillin VK is associated with the risk of allergic reactions. They can manifest immediately – acute (anaphylactic reaction, urticaria and angioedema) or after a few days – delayed (serum sickness and exfoliative dermatitis). Around 8% of the population has a documented history of penicillin allergy, yet less than 5% of individuals have been clinically confirmed to have an immunoglobulin E mediated penicillin allergy. Clindamycin, clarithromycin, azithromycin or metronidazole must be substituted for penicillin in patients with penicillin allergy confirmation (21, 22).

Amoxicillin, possibly with clavulanic acid, is the recommended antibiotic prescribed in endodontic infections. Antibiotic susceptibility testing of a bacteria isolated from endodontic infections revealed that amoxicillin had a susceptibility percentage of 91%, amoxicillin with clavulanic acid 100%, penicillin VK 85%, metronidazole 45% and clindamycin 96%. Amoxicillin, a synthetic modification of the original penicillin molecule, is a moderate-spectrum β-lactam antibiotic. Compared to penicillin VK, its spectrum is broader as it also targets gram-negative aerobes like Escherichia coli and Haemophilus influenzae. Moreover, it is better absorbed, and thus can be administered at lower doses, which may help in reduction of gastrointestinal side effects. To achieve steady serum levels, a loading dose of 1 g of amoxicillin, followed by 500 mg every 8 h for the duration of 2 to 3 days, is recommended. However, because β -lactamase-producing bacteria can degrade amoxicillin, it is frequently combined with clavulanic acid, which makes it effective against Staphylococcus aureus. One dose of the combination contains 125 mg of clavulanic acid and 875 mg of amoxicillin, and it should be taken every 12 h (Table 2). Patients taking oral contraceptives and receiving amoxicillin should also be advised to use alternative contraceptive methods throughout the duration of antibiotic

therapy and for an additional week thereafter. Penicillin, amoxicillin, and clindamycin are considered safe options for prescribing during pregnancy (21, 22).

Clindamycin is the alternative for patients with penicillin allergy. Clindamycin belongs to the lincosamide class and exerts its antimicrobial action by inhibiting bacterial ribosomes. At lower doses, it has a bacteriostatic effect, while at higher doses it has a bactericidal effect. Clindamycin is known for its excellent distribution in bone and is effective against a broad spectrum of microorganisms, including most anaerobes, gram-negative and gram-positive facultative bacteria and gram-positive aerobes. It is advised to start with a loading dosage of 600 mg before continuing to take 150 to 300 mg every 6 hours for the duration 2 to 3 days. However, it is important to recall that oral antibiotics can lead to a reduction in physiological gut flora and occasionally cause complications such as pseudomembranous colitis due to Clostridium difficile overgrowth. Clindamycin has a higher risk of causing pseudomembranous colitis compared to penicillin VK, with an eight-fold increase. Therefore, patients should be warned to watch for symptoms such as watery diarrhea, fever and functional dyspepsia (21, 22).

Metronidazole is a nitroimidazole agent that exhibits both antiprotozoal and antibiotic activity against anaerobic bacteria. It is often used as an adjunct medication to amoxicillin due to its exceptional activity against anaerobic endodontic bacteria (22). Metronidazole independently is used for the treatment of acute necrotizing ulcerative gingivitis, while in the therapy of endodontic infections it is always combined with other antibiotics. Its mode of action involves inhibition of nucleic acid synthesis within the cell. Concomitant use of metronidazole with alcoholic beverages or alcoholic mouthwashes can induce an antabuse reaction by inhibition of aldehyde dehydrogenases. Common side effects of metronidazole include dry mouth and unpleasant or metallic taste sensation. Administration of metronidazole during breastfeeding may result in diarrhea in the nursing infant. The recommended dosage for metronidazole is 400 mg three times per day (19, 23).

Table 2. Effective antibiotics prescribed in endodontics (22).

Antibiotic of choice	Loading dose	Maintenance dose
Penicillin VK	1000 mg	500 mg, every 4-6 h
Amoxicillin (with clavulanic acid)	1000 mg	500 mg, every 8 h (1000 mg, every 12 h)
Clindamycin	600 mg	300 mg, every 6 h
Azithromycin	500 mg	250 mg, every 24 h
Metronidazole	1000 mg	500mg, every 6 h

5.1 Antibiotic prophylaxis in Endodontics

The objective of administering antibiotic prophylaxis is to deter local postoperative infections and impede the potential metastatic spread of infection in compromised patients. Although blood is normally sterile, bacteria residing in the site of infection or commensal bacteria may gain entry into the bloodstream, leading to bacteremia. While the immune response to bacteria could potentially trigger sepsis and septic shock, bacteremia is generally benign and transient, due to the response of the immune system. On rare occasions, however, bacteria may endure and colonize specific areas of the body (locus minoris resistentiae), causing infections in distant sites. Even daily activities, like tooth brushing, can give rise to bacteremia. In addition, invasive dental procedures which require manipulation of periapical tissue, gingiva and oral mucosa and endodontic treatment also induce bacteremia. The risks of adverse antibiotic reactions and the growing emergence of drug-resistant microorganisms outweigh the benefits of prophylaxis for majority of patients. Although endodontic instrumentation or surgery extending beyond the apex are still factors that indicate the need for prophylaxis, the administration of antibiotic prophylaxis should be constrained to individuals with the highest risk of postoperative complications (22).

According to the new guidelines, the indications for prophylaxis are reduced, and include patients with a high risk of developing complications of infective endocarditis (IE): patients with artificial cardiac valves; history of IE; congenital heart diseases; cardiac transplantation recipients (22).

Infective endocarditis is characterized by inflammation of the endocardium, caused by microorganisms. The structures most frequently implicated are the heart valves. Although bacteremia typically resolves swiftly without negative outcomes in healthy individuals, a destroyed heart valve with an altered endothelial consistency can be susceptible to bacterial adhesion. Thus, if heart valves have been damaged or replaced with an artificial biomaterial, the likelihood of bacterial colonization is increased. The bacterial vegetations may impede the proper functioning of affected valves and enable infection to disseminate to other areas of the heart tissue. Several causative organisms are associated with infective endocarditis, with staphylococci, Streptococcus viridans, and enterococci being the most prevalent pathogens involved. Consequently, surgical procedures that could give rise to bacteremia, particularly invasive oral surgical procedures, are thought to be linked to the development of infective endocarditis in patients with predisposing factors (15).

In addition to the mentioned cardiac patients, patients with total joint replacement (TJR) are considered at risk within the first 3 months after operations due to incomplete endothelialization, as well as patients with a history of artificial joint infection and therefore antibiotic prophylaxis must be prescribed (15, 22).

Moreover, immunocompromised patients (leukemia, HIV or AIDS, dialysis, end-stage kidney disease, therapy with corticosteroids and immunosuppressants, chemotherapy and inherited gene defects) (22); patients with hemophilia; uncontrolled diabetes; patients exposed to high-dose irradiation for head and neck cancer treatment; patients on intravenous bisphosphonate therapy are considered high risk patients. Patients on intravenous bisphosphonates as cancer therapy compared to osteoporosis run a significantly higher risk (24).

The proposed prophylaxis regimen is outlined in Table 3 as approved by the American Heart Association (25). Administration of a single oral or intravenous dose of antibiotic is suggested. Oral administration of amoxicillin 1 hour prior to a dental procedure is recommended as a first-choice antibiotic. The standard dose is 2 g of amoxicillin per os for adults and 50 mg/kg for children. For adults with penicillin allergies, clindamycin 600 mg is recommended, while children receive 20 mg/kg. In case of inability of peroral intake, intramuscular or intravenous administration is recommended. If the patient is already under treatment with antibiotics from the penicillin group, and prophylaxis is indicated, clindamycin, clarithromycin, or azithromycin are

administered on the assumption that the microbiological flora has developed partial resistance to penicillins (22). Antibiotic prophylaxis is normally prescribed if at least 10 days have passed since taking antibiotics. In the case of an extensive dental procedure lasting more than 6 hours, it is advisable to supplement the antibiotic prophylaxis with another 2 g of amoxicillin (26).

Table 3. Antibiotic prophylaxis for medically compromised patients (22).

Patient Population	**Antibiotic Regimen (Adults)**	**Antibiotic Regimen (Children)**
Previous infective endocarditis, prosthetic cardiac valve, congenital heart disease (CHD) (repaired CHD with residual defects, unrepaired cyanotic CHD), heart transplant recipients with valvulopathy	Oral: Amoxicillin 2g, 1h prior to procedure Penicillin allergy: Clindamycin 600mg, 1h prior to procedure Inability of peroral intake: Ampicillin 2g IM/IV, or cefazolin/ceftriaxone 1g IM/IV, 30 min prior to procedure	Oral: Amoxicillin 50mg/kg (max 2g), 1h prior to procedure; Penicillin allergy: Clindamycin 20mg/kg (max 600mg), 1h prior to procedure Inability of peroral intake: Ampicillin 50mg/kg (max 2g) IM/IV, or cefazolin/ceftriaxone 50mg/kg (max 1g) IM/IV, 30 min prior to procedure
Other cardiac conditions (e.g. acquired valvular disease)	No prophylaxis recommended	No prophylaxis recommended
Joint replacement	Oral: Amoxicillin 2g, 1h prior to procedure Penicillin allergy: Clindamycin 600mg, 1h prior to procedure Inability of peroral intake: Ampicillin 2g IM/IV, or cefazolin/ceftriaxone 1g IM/IV, 30 min prior to	Oral: Amoxicillin 50mg/kg (max 2g), 1h prior to procedure; Penicillin allergy: Clindamycin 20mg/kg (max 600mg), 1h prior to procedure Inability of peroral intake: Ampicillin 50mg/kg (max 2g) IM/IV, or cefazolin/ceftriaxone 50mg/kg

	procedure	(max 1g) IM/IV, 30 min prior to procedure
Immunocompromised patients	Consult with a healthcare provider	Consult with a healthcare provider
No underlying cardiac conditions	No prophylaxis recommended	No prophylaxis recommended

6. DISCUSSION

Pharmacotherapy plays a pivotal role in the management of endodontic infections and associated pain. However, usage of systemic antibiotics and systemic analgesics in endodontics has been a subject of debate due to concerns regarding antimicrobial resistance and potential side effects.

Effective pain management is a vital component of endodontic treatment. Studies report that one in five patients experience post-operative endodontic pain and 10% of patients may continue to experience persistent pain up to six months after the completion of endodontic therapy (6).

Systemic analgesics, particularly NSAIDs, are used to alleviate endodontic pain. NSAIDs are the preferred first-line analgesics because of their anti-inflammatory and pain-relieving properties. Research has indicated that ibuprofen alone (600 mg) or in combination with paracetamol (1000 mg) effectively controls post-operative endodontic pain if administered six hours after endodontic treatment. NSAIDs are favored due to their efficacy and favorable safety profile, provided they are used at recommended dosages and durations. In contrast, opioids are reserved for treatment of severe pain that does not respond to NSAIDs or when NSAIDs are contraindicated. However, caution must be exercised when prescribing opioids due to their potential for addiction, respiratory depression, and other adverse effects (6).

Dentists should keep up to date with the latest guidelines and research in pain management to provide optimal care for endodontic patients while minimizing the potential risks associated with analgesic medications.

Systemic antibiotics are frequently prescribed in endodontic practice to control or prevent the spread of infection. However, their indiscriminate use raises concern about the emergence of antibiotic-resistant strains. Therefore, a cautious approach is necessary, reserving antibiotic therapy for cases with specific indications. These include severe infections with systemic manifestations, spreading cellulitis, and compromised host immune response. By selecting the appropriate antibiotic, considering the spectrum of activity, pharmacokinetics, and microbial susceptibility, clinicians can optimize the therapeutic outcomes while minimizing the risk of antibiotic resistance. The most effective antibiotic against microorganisms causing odontogenic infections is amoxicillin, either alone or in combination with clavulanic acid. Clindamycin is the preferred choice for patients with a penicillin allergy. In cases where inflammation persists

despite the use of penicillin, adding metronidazole to the therapy is necessary as it targets anaerobic bacteria (22, 27).

Furthermore, the adjunctive use of systemic antibiotics should always be accompanied by appropriate endodontic treatment, such as root canal instrumentation, disinfection and obturation, to ensure the elimination of the source of infection (20).

7. CONCLUSION

Pharmacotherapy, including the use of systemic antibiotics and systemic analgesics, serves a significant part in the treatment of endodontic infections and odontogenic pain. However, responsible prescribing practices based on benefit-risk analysis and the adherence to evidence-based guidelines are paramount to ensure optimal patient outcomes. Dentists must exercise professional judgment, adhere to evidence-based guidelines, evaluate potential benefits and risks and make informed decision with their patients in their prescription practices to ensure optimal therapeutic outcomes while minimizing risks and adverse effects. The key determinants of success in endodontic therapy rely on proper elimination of microorganisms within the endodontic space and the establishment of a local environment favoring healing. While pharmacotherapy undeniably contributes to successful endodontic outcomes, its usage should always be guided by appropriate indications and supplemented by accurate diagnosis, suitable treatment planning, and proper therapeutic techniques.

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Jelena Kiš was born in Zagreb on December 30, 1997. She attended Elementary School "Zdenko Turković" in Kutjevo and Gymnasium in Požega, from where she graduated in 2016. In 2017, she commenced her studies at the University of Zagreb, School of Dental Medicine. During her studies she was honored with three Dean's awards for best academic achievement in the 3rd, 4th and 5th year of studies. She participated in the periodical reaccreditation process of the University of Zagreb, School of Dental Medicine as a student representative.