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Effect of different Analgesics as a Premedication on Postendodontic Pain – A Literature Review

Research Article

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Abstract

Pain is seen to be a subjective experience and the intensity of pain is shown to be very different among different individuals. Different factors such as age, genes, Gender, Age, Type of teeth can influence the pain occurrence in individuals. The most commonly used analgesics being NSAIDs but the response of these analgesics can vary from different individuals based on genetics and plasma life. Recent evidence has shown the use of different analgesics such as corticosteroids for post reduction of endodontic pain by reduction of prostaglandin synthesis. Though different factors are there to influence post endodontic pain and how to manage them there is still a dilemma on how to adequately manage pain reduction post endodontic treatment by different analgesics. In regard to this the present review comprehensively discusses all the analgesics which has been used in endodontics and newer analgesics which can show potential to be used in endodontics for post endodontic pain reduction.

Keywords: Pain; NSAID; Corticosteroid; Endodontics.

Introduction

Pain is said to be defined as an unpleasant sensory or emotional experience associated with actual or potential tissue damage [1]. Pain can range widely in intensity, quality, and duration and has diverse pathophysiologic mechanisms. Although tissue injury is a common antecedent to pain, pain can be present even when tissue damage is not present [2, 3]. Pain perception is identified as a mental process, a psychical adjunct, added to a nociceptive mechanism [4]. Pain perception is also can be considered as part of our protective response to prevent further tissue damage [5-7].

The experience of pain is a personal and subjective experience which can vary from different individuals. Accurate diagnosis and relevant treatment procedures are successful in affecting a cure. In endodontics, the occurrence of pain is seen to be multifactorial and is primarily associated with the activation of the receptors in the primary afferent fibres, which is inclusive of the unmyelinated C-fibre and myelinated Aσ-fibre[8]. The need to perform endodontic treatment is likely due to the inflamed and or infected pulpal tissue which is shown to affect these fibres to a certain extent.

This pretreatment histologic pulp status can have a direct correlation to a patient's odontogenic pain symptoms. Patients' pain perception is shown to be complex and is seen to be varied among different individuals. Some of the factors are the following [9].

Previously our team had a rich experience in working on various research projects across multiple disciplines [10-24]. Now the growing trend in this area motivated us to pursue this project

Factors having an overall influence in Pain

Genes: The variation of pain perception is seen to be varied among different individuals due to the presence of pain gene which is described as a gene with one or more polymorphisms that affect the perception of pain response and is considered to be large families of lineage series. This gene is seen to be varied among different individuals and is one of the factors responsible for different pain perception in humans [25].

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Gender: It is now seen that pain perception is seen to be varied based on gender and was seen that females had more pain perception compared to male. This is due to lifestyle habits which can have a contributing effect in pain perception with males shown to sustain painful experiences more frequently than females [26].

Age: Increase of pain threshold is seen to be directly proportional with the age of the individual with A-delta and C-fibres seen to comparatively less with increase in age and hence lesser pain stimulation through the electrical conduction is seen to be same [27].

Psychological factors: The influence of pain can occur but the psychological effect of individuals. The factors seen are anxiety and depression and can have an effect on the individual's level of pain perception [28].

Type of Teeth: Another factor to be considered is the type of teeth, it is seen that molars are shown to have increased incidence of pain compared to other teeth. This could be due to the various nerve innervations present which could potentiate pain [29].

Factors influencing the need for endodontic treatment

The primary cause of endodontic pain arises as a result of reactionary response of the pulp tissue to any causative agents like dental caries or other irritants. The pulp tissue is shown to respond to various external stimuli like dental caries, trauma or even conventional restorative procedures [30]. The progression of bacteria within the canal plays a pivotal role in pain progression. Dental caries are shown to have various microbial and other components which have the capacity to interact with pulp tissue and produce a response [31]. Pain after endodontic treatment is seen to be multifactorial which can be a single cause or multiple causes can associated with pain such as pain with chronic lesion, non-vital tooth, previously opened canal, extension of either the filling material or instrument beyond the apex of the tooth and any leakage in temporary or permanent filling done after endodontic treatment [32].

Quantitative evaluation of pain

The quantitative evaluation of pain is carried out by using special measurement scales to assess the intensity of the pain. The widely used Visual Analogue Scale (VAS) displays a continuous line with numbers from 1 to 100 placed along the line which represent the intensity of pain [33-35]. The intensity of pain can be measured more accurately when more than one scale is used. It is seen that when evaluating on the Visual Analogue Scale, the intensity of post-endodontic pain ranges from 5 to 44 points, lasts less than 72 hours and responds well to non-steroidal anti-inflammatory drugs and acetaminophen [36].

Both NRS and VAS scales are shown to be highly correlated and the most frequently used pain scales for measurement of pain. However, these simple pain scales show some limitations in assessment of pain intensity. They are highly subjective and depend on many more factors than pain, such as mood. This could lead to an imprecise assessment of effectiveness of therapies in daily practice or clinical studies. Moreover, these pain experiences differ for each individual, which influences the frame of reference for each person. As a result, it is shown that differences in pain experiences result in different pain tolerances per person. Pain scores using the VAS and NRS are presumably affected by the patients predetermined levels of pain since participants themselves should indicate pain score, it is not possible to blind participants for the outcome of the VAS or NRS. Therefore, they can (subconsciously) contribute to the success or failure of a therapy, by indicating lower pain scores which overestimate the effect of treatment. From these perspectives, it is difficult to quantify the degree of pain in a precise manner. Therefore, there is a need for a valid, reliable, safe, and low-cost method to determine and quantify patients' pain more objectively [37].

Management of endodontic pain

Management of endodontic pain primarily depends on the accurate diagnosis of the cause of the pain. There are various methods by which an accurate diagnosis can be made, they are clinical examination, peri apical testing, pulp testing, radiographic examination and most importantly the practitioner must be able to differentiate odontogenic pain from non-odontogenic pain.

There are different reasons for an individual to experience pain relief following the administration of an analgesic. This could be due to the efficacy of the drug which was responsible for the alleviation of pain. However, the temporal relationship between the administration of the drug and the dissipation of pain may give patients reason to believe the drug was effective when, in fact, the pain would have abated without any analgesics to begin with. Another reason for pain relief is the placebo effect whereby no pharmacological effect exists. It is purely a psychological effect that accounts for the alleviation of pain. For example, patients often assume that more expensive drugs and prescribed drugs inherently have greater efficacy.

Non-Pharmacological treatment strategies

These strategies include primary dental treatment procedures to relieve pain like pulpectomy and pulpotomy.

Pulpotomy: The pulpotomy is a treatment method done to remove the coronal pulp tissue in the chamber without penetrating pulpal tissue in the root canal systems. It is often performed in cases of acute pain of pulpal origin when there is insufficient time to do a complete pulpectomy. The procedure should be done under adequate isolation with rubber dam being the recommended mode to prevent further microbiological contamination. After access is achieved, slow speed round diamond burs is used to remove pulp tissue to the level of the canal orifice. Slow speed burs are used to prevent obliteration of the natural funnel at the mouth of a canal that makes initial penetration easier. High speed burs can easily destroy that anatomy. Bleeding is typically managed by a cotton pellet placed firmly against the coronal orifices. The pulpotomy, including sealing of sedative and antibacterial dressings in the pulp chamber has been advocated in emergency situations for many years.

Clinicians frequently note the dramatic effect of opening a chamber and observing the rapid relief that often follows. It seems reasonable to assume that these factors constitute the biological basis

for its highly predictable effect of reducing pain in patients with irreversible pulpitis. Furthermore, by avoiding the canal system, the clinician avoids performing a partial pulpectomy which might traumatize already inflamed tissue. Partial pulpectomy may result in profuse haemorrhage due to the rupture of wide diameter vessels in the central part of the pulp. Less haemorrhage often results when the extirpation of the pulp is made to the apex of the tooth.

Pulpectomy: Pulpectomy is the course of treatment often used in patients who present with symptoms of irreversible pulpitis, or pulp necrosis with or without swelling. Since it is impossible for the clinician to precisely determine the apical extent of pulpal pathosis, a pulpectomy offers the advantage of complete removal of the pulp. Following the pulpectomy it is best to close dressing must be given in order to prevent contamination from the oral cavity. Teeth left open to the environment are often involved in exacerbations during treatment. If there is a flow of exudate from the canal following instrumentation and irrigation, it is best to wait to close the tooth until the flow stops. Infrequently, the flow will continue and, in those instances, a cotton pellet or porous material can be used as a barrier until the patient returns, preferably the next day. The goal is to close the tooth as soon as possible in order to prevent further bacterial penetration.

Pharmacological strategies

Analgesics prescribed during root canal treatment: The analgesics prescribed for root canal treatment can be broadly classified into 2 groups based on the mode of action; Centrally acting drugs act primarily on the central nervous system and are sometimes considered as compound analgesics which is used in combination with nonsteroidal anti-inflammatory drugs. They are classified into 3 categories; sustained-release opioids, immediate-release opioids and long-acting opioids [38].

The use of these analgesics is based on the intensity of pain. Though the use of opioid analgesics is limited in endodontics it is used to some extent due to their centrally acting effect showing adverse effects as well as inhibited localized analgesic effect in localized sites. Some of the opioid's analgesics prescribed are morphine, transdermal fentanyl, oxycodone, oxymorphone, methadone, levorphanol, tramadol and meperidine. Currently, nonsteroidal anti-inflammatory drugs (NSAIDs) are the drug of choice for pain reduction in endodontics. These drugs exhibit less adverse effects but have shown adverse effects such as gastrointestinal disorders, hypertension or kidney disease when used for continuous periods of time for a long run. The most common NSAID option prescribed is ibuprofen 400-600 mg. The second most commonly used drug is acetaminophen (paracetamol) due to its lack of inflammatory activity this drug has shown to be ineffective and has shown some significant side effects on constant usage for instance nausea, dizziness, drowsiness.

Prostaglandins are the main substances that result in the clinical manifestation of inflammation. Erythema and heat are caused by vasodilation in response to prostaglandin E2 (PGE2) primarily and PGI2 to a lesser degree [39]. In the later stages of inflammation, prostaglandins maintain the inflammatory response through chemotaxis of polymorphonuclear cells. Leukocytes at the site of inflammation are responsible for production and activation of a variety of cytokines and inflammatory mediators, most notably interleukins, tumor necrosis factor, histamine, bradykinin, and prostaglandins. In instance to this NSAID's play a crucial role for pain reduction post endodontic treatment.

Nonsteroidal Anti-inflammatory drugs (NSAIDs): They are FDA approved drugs showing antipyretic, anti-inflammatory and analgesic properties. They are commonly used drugs for the treatment of acute pain such as muscle pain, dysmenorrhea, pyrexia, gout, migraines and for acute trauma case scenarios. NSAIDs can be classified in three ways. First, NSAIDs can be broadly classified into two groups based on their chemical structure. Carboxylic acids make up most NSAIDs together with a few enolic acids, most notably phenylbutazone [40-42].

Mechanism of action: Arachidonic acid is metabolized to PGG2 and further to PGH2 by prostaglandin G/H synthase, which has cyclooxygenase and peroxidase activity. Cyclooxygenase catalyses the production of PGG2, whereas peroxidase catalyses the production of PGH2. The NSAIDs exert their actions through specifically inhibiting the enzyme cyclooxygenase without affecting peroxidase [43, 44].

In doing so, they suppress the clinical signs of redness, swelling, heat, and ultimately pain. Prostaglandins already present as a result of either physiologic production or pre-existing inflammation are not affected by NSAIDs, and a favourable response to the administration of NSAIDs is not seen until these prostaglandins are no longer active. Certain agents may also possess properties unrelated to cyclooxygenase inhibition that aid their anti-inflammatory effects. These properties include inhibition of superoxide generation by neutrophils, inhibition of phospholipase C, inhibition of neutrophil aggregation, and alteration of B and T cells [45].

Cyclooxygenase exists in two isoforms designated COX-1 and COX-2. Despite their structural similarities, they are encoded by different genes and are distinct in their distribution and expression in various tissues. COX-2 expression is induced in response to bacterial lipopolysaccharide and cytokines, which have an active role in inflammation. Many of the commonly used NSAIDs have been shown to more effectively inhibit COX-1, thereby affecting physiologic cell functions to a greater degree than inflammatory functions. Considering the functions of the COX isoforms, the ideal therapeutic NSAIDs should inhibit the inducible COX-2 without affecting the homeostatic COX-1 [46].

Effect of NSAIDs

A. Analgesic Effect

The main mechanism of action of NSAIDs is known to be **in**hibition of the cyclooxygenase pathway. COX-l is the ubiquitous form produced in normal, quiescent conditions and it is a constitutive protein of normal cells. It is important in the production of prostaglandins that regulate cellular homeostasis, such as renal blood flow, and in circumstances where prostaglandins have a protective function, such as gastric mucus production. COX-2 is the inducible form of the enzyme, expressed in endothelial cells, macrophages, synovial fibroblasts, mast cells, chondrocytes and osteoblasts after tissue trauma, and therefore plays an important role in inflammation. Inhibition of COX-2 represents the most likely mechanism of action for NSAID-mediated analgesia

and there is currently great interest in the possibility that selective COX-2 inhibitors might produce analgesia with fewer adverse effects. Another mechanism of action is inhibition of the lipoxygenase pathway by inhibiting LTB4 and 12-HETE have been consistently detected in inflammation [47].

B. Anti-inflammatory Effect

Cyclooxygenase is one of the major factors to cause inflammation in an individual. NSAIDs are shown to have anti-inflammatory action by inhibiting the cyclooxygenase pathway in reduction of inflammation. Another factor of reduction of inflammation is reduction of lipoxygenase pathway in which arachnoid acid is seen to be the main factor to cause inflammation. NSAIDs are shown to inhibit the lipoxygenase pathway as well and are shown to be a potent anti-inflammatory age [48].

C. Antipyresis Effect

In an event of fever due to various causes such as infection various cytokines are released such as Interleukins, Tumour Necrosis Factor-α, interferons which are shown to increase the prostaglandin production and in turn raising the person's temperature at a point. On administration of NSAIDs these drugs tend to block these productions and in turn reduce the individual's fever.

NSAIDs are widely used for the management of inflammatory-induced pain; however, there is a discrepancy between the extent to which NSAIDs are more useful in control of post-op. Postoperative pain appears to be more decreased with use of indomethacin and Rofecoxib at 24 hrs. Although both indomethacin and Rofecoxib had a similar mechanism of action, small differences in their chemical structure could influence their efficacy and pharmacological properties. However, due to the low number of comparative trials, there is little scientific reason to prefer one NSAID over the other.

D. COX- 2 selective inhibitors

Celecoxib and rofecoxib are the first generation of selective COX-2 inhibitors approved by the Food and Drug Administration (FDA) for pain indications whereas valdecoxib belongs to the second generation of selective COX-2 inhibitors more recently approved by the FDA.

A number of studies have examined the analgesic efficacy of coxibs using the oral surgery model of acute inflammation. However, there are no published reports examining the efficacy of COX-2 inhibitors in orofacial pain of other etiologies such as endodontic pain, pain resulting from orthodontic treatment, and pain following periodontal surgery. Limitations of orally administered selective COX-2 inhibitors, as well as the non-selective NSAIDs for dental pain, include delayed onset when compared to an injectable opioid and the inability to consistently relieve severe pain. The analgesic dose of rofecoxib, 50mg as a single dose over 24 h, is greater than the recommended dose for rheumatoid and osteoarthritis (12.5–25mg), due to concern about a greater incidence of side-effects with repeated doses, such as extremity edema. The best strategy for minimizing pain onset is administration of an NSAID or coxib prior to the postoperative induction of COX-2.

Preemptive analgesia is based on the principle that pain relief can occur prior to onset of pain in treatment done individuals. This strategy reduces pain during the immediate postoperative period as well as at later time points. As a result, fewer analgesics are consumed, resulting in fewer adverse drug reactions and enhanced recovery. As the most severe postoperative pain often occurs within the first 24 h following endodontic therapy, it can safely be assumed that administration of an NSAID prior to postoperative pain onset is an effective strategy in pain management. Multimodal analgesia is another way of achieving effective postoperative pain control. The combined use of NSAIDs with an opioid is effective in relieving moderate to severe postoperative pain as compared to single-drug regimens. Premedication with celecoxib 200mg and acetaminophen 2000mg was highly effective in reducing postoperative pain as compared to celecoxib 200mg or acetaminophen 2000mg alone. An effective approach in managing moderate to severe postoperative endodontic pain is to prescribe an alternating schedule of an NSAID with an acetaminophen– opioid combination. An advantage of using a multimodal approach is that the combination of these three drugs can have additive analgesic effects.

Adverse effects

Gastrointestinal effects: The primary endpoints were ulcer, perforation, gastric-outlet obstruction, and upper gastrointestinal bleeding. The published data from only the first 6months demonstrated that the incidence of GI effects in the celecoxib group (0.8%) was numerically lower than the NSAID group (1.5%) [49].

Cardiovascular effects: The current clinical data on the cardiovascular effects of coxibs is limited. Thromboxane A2 (TxA2) and prostacyclin I2 (PGI2), products of the cyclooxygenase pathway, are involved in platelet–vascular homeostasis. PGI2, a vasodilator, inhibits platelet aggregation and leukocyte adherence, whereas TxA2, a vasoconstrictor, promotes platelet aggregation. Selective COX-2 inhibitors suppress the synthesis of PGI2 and have no effect on TxA2, shifting the hemostatic balance towards a prothrombotic state with greater potential to initiate adverse occlusive vascular events .[50]

Renal effects: Inhibition of COX-2 can potentially cause hypertension and renal failure. Marketing data for celecoxib and rofecoxib reveals that the incidence of hypertension and edema does not differ from that of the non-selective NSAIDs [51].

While it is clear that COX-2 inhibitors offer some advantages over the non-selective NSAIDs in terms of a lower risk of GI toxicity with long-term use, the effects following short-term use are still unclear. Until more data are available, COX-2 inhibitors should be avoided or used with the same caution as conventional NSAIDs in patients with compromised renal and cardiac function [52].

Corticosteroids: Corticosteroids consist of 2 main categories; glucocorticoids and mineralocorticoids, cortisol is the primary glucocorticoid that is continuously synthesized and secreted from the adrenal cortex. Cortisol and synthetic glucocorticoids circulate in the blood with 90% or more reversibly bound to plasma proteins [53]. The adrenal cortex produces approximately 10mg/day of cortisol in the non-stressed adult. Under severe stress, this level may be increased more than 10-fold. Glucocorticoids inhibit

the production by multiple cells or factors that are important in producing the inflammatory response. This inhibition is a result of the effect of glucocorticoids on gene transcription that produces a decrease in the release of vasoactive and chemo attractive factors, decreased secretion of lipolytic and proteolytic enzymes, decreased extravasation of leukocytes to areas of tissue injury, and ultimately decreased fibrosis. Glucocorticoids have also been shown to produce a protein vasocortin, which has the ability to suppress edema that is not suppressed by NSAIDs. The different glucocorticoids used for reduction of endodontic pain are:

1) Cortisol
2) Cortisone
3) Prednisone
4) Prednisolone
5) 6α-Methylprednisolone
6) Fludrocortisone
7) Triamcinolone
8) Betamethasone
9) Dexamethasone

Corticosteroids have shown varied effect in reduction of pain by acting on the Polymorphic neutrophils (Marshall, 2002) and inhibiting the action of prostaglandin synthesis which is the main causative factor for inflammation and reducing vascular permeability leading to tissue edema (Vyvey, 2010) [54].

Pharmacology of corticosteroids: The adrenal cortex synthesises fat-soluble corticosteroids from cholesterol. These steroids contain 21 carbon atoms in a four membered hydrocarbon ring system. Corticosteroids comprise glucocorticoids and mineralocorticoids. In humans, cortisol is the primary glucocorticoid that is continuously synthesised and secreted from the adrenal cortex [55]. This process is under the control of the hypothalamus and anterior pituitary. Along with the adrenal cortex, they make up the hypothalamic-pituitary-adrenal (HPA) axis, a system that regulates glucocorticoid level. The hypothalamus produces corticotropin-releasing hormone (CRH), which travels to the anterior pituitary via the hypothalamic-hypophyseal portal system and stimulates the release of adrenocorticotropic hormone (ACTH) by pituitary corticotrophs [56]. ACTH, a peptide of 39 amino acids, is the main regulator of cortisol secretion. In turn, glucocorticoids inhibit ACTH secretion via direct and indirect actions inhibiting (CRH) neurons resulting in decreased CRH release, and via direct effects on corticotrophs.

Investigations on the effects of GCS on pain after RCT have used various routes of administration for the medications, either by injection (intra-periodontal ligament, supra-periosteal, intraosseous, parental), systemic ingestion, or as an intracanal medicament. All investigations except four have used the medication either as a root canal dressing or as a prescribed medication to be taken after RCT. The three exceptions used glucocorticoids as a premedication prior to commencing treatment. The intra-canal use of GCS may be considered to be safe as only a very small amount of GCS can be inserted into the root canal and therefore there can only be very limited, if any, systemic side effects. In addition, placing the active medicament into the root canal enables it to work directly on the inflamed tissues around the apex of the tooth root by diffusing from the canal; in this situation, the root canal acts as a drug delivery system. On the other hand, oral ingestion, and particularly injection, of GCS will produce higher doses of the drug which may provide more anti-inflammatory effects in the periapical tissues and therefore effectively reduce post-operative pain, although the systemic side effects may be greater. In addition, studies that employed systemic GCS used known doses of the GCS.

Other Analgesic Used

NMDA based analgesics: Flupirtine is a derivative of triaminopyridine available in the form of maleate salt. It is a non-centrally acting, non-opioid analgesic with N-methyl-D aspartate (NMDA) receptor and is shown to be effective in management of postoperative pain. The analgesic action of flupirtine includes analgesia, muscle relaxation and neuroprotection properties [57]. Its administration is done either orally or rectally and undergoes biotransformation in the liver. Its excretion is seen 72% in the urine and rest through the faeces. It is well tolerated and has less side effects [58]. The analgesic action of these drugs is quite different when compared to NSAIDs. This is by the indirect antagonist action of potassium channels with the activation of these channels leading to hyperpolarization of the neuronal membrane and the neuron. These drugs activate this channel are selective neuronal potassium channel openers (SNEPCO) and flupirtine being a prototype drug [59]. The use of flupirtine maleate is used extensively in the medical field for various applications such as for pain reduction. It is seen that 100mg of flupirtine maleate has a similar action when compared to 1gm paracetamol for treatment of acute attack of migraine[60]. Several studies have shown its analgesic efficacy with various other analgesics such as diclofenac sodium, piroxicam and has shown to effectively reduce pain in all this patient. [61].

Benzodiazepines: Benzodiazepines are among the other drugs that can be used as adjuvant drugs in times of pain that may enhance the analgesic effects of NSAIDs for postendodontic pain reduction. They are shown to have antianxiety effects, anticonvulsant activity, antidepressant activity and muscle relaxant properties[62]. Benzodiazepines act as positive modifiers and potent activators of GABA receptors in the CNS.

GABA receptor agonists showed significant analgesic properties in the animal pain studies. The GABA receptor agonists are clinically effective in the treatment of pain, especially when combined with other analgesics. Benzodiazepines reduces the pain intensity by reducing the pain-induced anxiety, insomnia and muscle spasms. The other possible mechanism of action of alprazolam can be stimulating in the release of endogenous opioids, such as enkephalins in CNS areas involved in pain processing. Some patients of the ibuprofen group reported nausea and vomiting more than the patients of ibuprofen + alprazolam group; this effect might be due to the anti-nausea effect of benzodiazepines such as alprazolam [63].

Opioid Analgesics: Opioids produce analgesia by activation of opioid receptors. Three major families of opioid receptors have been cloned: the mu, kappa and delta opioid receptors. Three major families of opioid receptors have been found: the mu, kappa and delta opioid receptors. The mu opioid receptor is activated by most clinically used opioids including codeine hydrocodone, oxycodone, hydrocodone, tramadol and morphine. The kappa opioid receptor is activated by drugs such as pentazocine and buprenorphine. No currently approved drugs are selective for the

delta receptor. Opioid analgesia occurs by activation of opioid receptors expressed on neurons in supraspinal sites, spinal sites and in peripheral tissue [64, 65].

In general, the opioid receptors are thought to inhibit neuronal activity and their analgesic efficacy is attributed in part to the observation that opioid receptors are expressed at most of the major pain processing areas in the central nervous system [66, 67]. Consequently, systemic administration of opioids produces analgesia by inhibiting pain transmission at multiple areas of the pain site. Opioid analgesia occurs by activation of opioid receptors expressed on neurons in supraspinal sites, spinal sites and in peripheral tissue. In general, the opioid receptors are thought to inhibit neuronal activity and their analgesic efficacy is attributed in part to the observation that opioid receptors are expressed at most of the major pain processing areas in the central nervous system. Consequently, systemic administration of opioids produces analgesia by inhibiting pain transmission at multiple areas in the neuraxis. Opioids are well recognized to produce variable responses in patients, with some patients reporting considerably greater analgesia than others, even after administration of identical doses [68, 69].

In addition, several polymorphisms to the opioid receptors have been discovered and are associated with altered responses to opioid analgesics or altered reports of pain intensity. Gender is another interesting genetic factor associated with altered opioid responsiveness. Several studies have reported that women demonstrate significantly greater analgesia to kappa opioids (e.g., pentazocine) than men. The adverse effect profile of the opioids is well recognized and includes nausea, emesis and respiratory depression. Concern has also been raised about opioid abuse and its impact in the dental setting.

Caffeine: Caffeine has shown recent evidence of pain reduction in endodontics which is used as adjuvant with acetaminophen. It is given to patients who are intolerant to NSAIDs and has shown adequate effect in relieving pain.

Caffeine's role in pain management is among questionable yet attractive subjects in this regard. The effects of caffeine on pain control are somewhat complex yet understanding such effects is valuable. Before addressing the role of caffeine in pain control, first we must be familiar with a substance called adenosine. Adenosine is an inhibitor of neuronal activity in the central nervous system (CNS) and peripheral nervous system (PNS). There are four subtypes of adenosine receptors in human bodies including A1, A2A, A2B, and A3, which are expressed in different parts of the CNS and PNS [70].

The endogenous compound adenosine has various modulatory effects in the central and peripheral nervous systems and its receptors have been known to be involved in antinociception. Enhancing these receptors could lead to arousal, concentration and vigilance. The structure of caffeine is similar to adenosine and therefore Caffeine competes with adenosine for A2a receptors causing their inhibition. Despite this, caffeine does not alter dopamine release and therefore does not have abuse potential like other adenosine blocking agents, such as cocaine. Caffeine could reduce pain sensation through its effects on adenosine receptors. Caffeine seems to express its direct effect via central blocking of adenosine receptors that influence pain signaling or by blocking of peripheral adenosine receptors on sensory afferents but a clear mechanism of action is still unknown. Antagonism of adenosine receptors, as well as inhibition of cyclooxygenase activity at some sites, may explain caffeine antinociceptive effects and its adjuvant actions. Interestingly, some researchers claim that genetics can influence the response of individuals to caffeine consumption. sOur institution is passionate about high quality evidence based research and has excelled in various fields [71-81].

Conclusion

The use of different strategies for management of endodontic pain is known to be used for many ways and is shown to be multifactorial in nature. The clinician should judiciously assess the cause of endodontic pain and come to a final decision on which mode of treatment modality should be considered for pain relief. The most common analgesics prescribed by clinicians is seen to be NSAIDs but the recent evidence also suggests other analgesics showing similar or better analgesic effect with lesser side effects. The clinician should judiciously consider all recent evidence and come to an adequate conclusion for the accurate diagnosis and lesser incidence of endodontic pain.

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