Journal of Advanced Medical and Dental Sciences Research

NLM ID: *101716117*

@Society of Scientific Research and Studies

Journal home page: www.jamdsr.com doi: 10.21276/jamdsr Index Copernicus value = 85.10

(e) ISSN Online: 2321-9599; (p) ISSN Print: 2348-6805

Review Article

Role of Corticosteroids as Endodontic Irrigants: A Review

Pratik Agrawal[1], Syeda Ayesha[2], Godavari Deepak Nagargoje[3], Nitinpreet Kaur[4], Heena Mazhar[5], Heena Tiwari[6]

1. Reader, Dept of Conservative Dentistry and Endodontics, Kalinga Institute of Dental Sciences, KIIT University, Bhubaneswar, Odisha;
2. Intern, Sri Sai College Of Dental Surgery, Vikarabad, Telangana;
3. Senior Lecturer, Department of Conservtive Dentistry & Endodontology, Nanded Rural dental College & Research centre, Nanded, Maharashtra;
4. Dasmesh Institute of Research and Dental Sciences, Faridkot, Punjab;
5. Assistant Professor, Dept Of Oral And Maxillofacial Surgery, Chhattisgarh Dental College And Research Institute, Rajnandgaon, CG
6. BDS, PGDHHM, Ex-Government Dental Surgeon, Kondagaon, Chhattisgarh, India

ABSTRACT:

Researchers have utilized many different modes of delivery for corticosteroids. Dexamethasone has been administered through local infiltration, extra oral intra muscular injections, intra oral intra-muscular injections, oral dosage, and intra canal rinses. Dexamethasone has a plasma half-life of 200 minutes and tissue half-life of seventy-five hours. Systemic absorption of dexamethasone may produce unwanted actions at other sites of the body such as a decrease in the body's healing response. Studies have found that local infiltration of radioactive dexamethasone in the mandibular buccal vestibule of rats was rapidly absorbed in the systematic circulation and deposited throughout the tissues. Within one hour of injection, radioactive dexamethasone was found in the contra-lateral mandible. Although it is difficult to extrapolate conclusions from animal studies, the use of an intra-canal dexamethasone rinse may be an effective means of limiting systematic absorption of the drug.

Key words: Corticosteroids, Endodontic Irrigants, intra-canal dexamethasone.

Received: 02/06/2020 **Modified:** 20/08/2020 **Accepted:** 24/08/2020

Corresponding Author: Dr. Pratik Agrawal, Reader, Dept of Conservative Dentistry and Endodontics, Kalinga Institute of Dental Sciences, KIIT University, Bhubaneswar, Odisha, India

This article may be cited as: Agrawal P, Ayesha S, Nagargoje GD, Kaur N, Mazhar H, Tiwari H. Role of Corticosteroids as Endodontic Irrigants: A Review. J Adv Med Dent Scie Res 2020;8(9):46-52.

INTRODUCTION:

Pain of odontogenic origin has long been a source of anxiety and fear amongst the general population.[1] This fear is so great amongst certain individuals that it actually serves as a barrier to dental treatment.[1,2] Odontogenic pain has also been a common source of frustration amongst dentists whom have difficulties in completely relieving their patient's pain.[3] The ability to relieve such terrible pain amongst patients has been inconsistent, with many patients continuing to experience discomfort after dental treatment is provided.[2] No treatment within the dental profession is as intimately associated with the fear of pain as is root canal therapy. This perception is so prevalent that stating something is "worse than a root canal" is a common way of describing terribly painful experiences.[4] A recent public poll sought to emphasize the unpopularity of members of congress by comparing their favorability ratings to root canals.[5] The ability to predictably treat pulpal and periapical diseases in a

manner that seeks to minimize or even eliminate post-operative discomfort experienced by patients could help improve the image of dentistry within the public realm.[6]

Post-operative pain

A substantial amount of research has been published investigating the prevalence of post-operative discomfort after the initiation, continuation, and completion of endodontic therapy. The American Association of Endodontics defines a flare-up as "an acute exacerbation of asymptomatic pulp or peridradicular pathosis after the initiation or continuation of root canal treatment"[7]. Tsesis et al (2008)[8] evaluated the frequency of flare-ups secondary to endodontic therapy through meta-analysis of six studies that included 982 patients. The analysis showed an 8.4% frequency of flare-ups. Nixdorf et al (2010a)[2] published a meta-analysis and systematic review to estimate the presence of odontogenic pain after at least six months following completion of root canal therapy. The analysis included 26 studies and 2,996 teeth qualified for the final analysis. The frequency of persistent odontogenic pain was estimated to be at 5.3% after six months post-treatment (95% CI: 35-7.2%). The authors stated that this is likely a more conservative estimate and that the true figure may be higher, reflecting the widespread occurrence of post-operative pain. One of the challenges facing clinicians is that many patients present with dentoalveolar pain due to a non-odontogenic source, yet they are treated with conventional dental treatments, including root canal therapy. Nixdorf et al (2010b)[9] sought to determine the presence of non-odontogenic pain after at least six months following completion of root canal therapy. They conducted a meta-analysis of 10 qualifying studies including 1,125 teeth. It was determined that possibly up to half of all cases of persistent tooth pain (3.4%; 95% CI: 1.4-5.5%) may be caused in part by non-odontogenic pain. This highlights the importance of proper diagnosis within the dental profession to prevent unnecessary irreversible dental treatments such as root canal therapy and eventually in many cases, extractions. Improved diagnosis and referral for treatment of pain of nonodontogenic origin would ultimately help decrease the frequency of reported cases of post-operative discomfort secondary to endodontic therapy. This in turn could contribute to improved public perceptions regarding discomfort associated with endodontic therapy.[10] The presence of post-operative pain can become especially problematic when it is caused by neuropathic pain. The International Association for the Study of Pain defines neuropathic pain as "pain initiated or caused by a primary lesion in or dysfunction of the nervous system".[11] This type of pain can develop as a result of damage to local neural structures during the root canal procedure itself.[2] The damage causes somatosensory changes in the nerves, which manifests as a constant, burning, and deep ache at the site of treatment with the absence of any clinical signs of pathology. The greatest obstacle that this presents is that this condition is not responsive to analgesics, surgery, or any other dental procedures. This painful condition causes great distress to the patients and much confusion amongst their dental providers.

Neuropathic pain has been reported to affect 3% - 12% of patients after endodontic therapy.The frequency of neuropathic pain after endodontic procedures is higher than that of any other dental procedure.[12] Oshima et al[12] investigated a cohort of sixteen patients and found that neuropathic pain was more likely in females (13 of 16), with a predilection for the maxilla (14 of 16). It was found that tricyclic antidepressants were effective in relieving pain in 68.8% of their patients (11 of 16). However, 25% (4 of 16) of the patients did not report any relief. In order to minimize the risk of neuropathic pain following endodontic treatment, utilization of best endodontic treatment practices, including avoiding overinstrumentation and over extension of obturation materials is critical.[6] Improved practice and techniques may eventually reduce the frequency and development of neuropathic pain secondary to endodontic treatment.[12]

There are numerous, well-documented studies that identify predictors of postoperative pain. These predictors are significant in educating both practitioners and patients. ElMubarak et al (2010)[10] investigated a cohort of 234 patients. They found that patients who undergo root canal therapy with a history of pre-operative pain have a 15.9% incidence of post-operative pain within 24 hours post-treatment, compared to a 7.1% incidence in those with no reported pre-operative pain. It is important to note that numbers of patients evaluated for post-operative pain are too small to attach great value pre-operative as a predictive factor. Rather this study demonstrates that endodontic treatment is an effective means of relieving pain, with patients having an 89% risk of pain free after treatment. The authors found a statistically significant difference in the incidence of post-operative pain between vital teeth, 7.8%, and non-vital teeth, 13.7%. In a meta-analysis published in 2011, Pak & White confirmed that the incidence of postoperative pain was greatest in patients who presented with pre-operative pain. Thus it appears that in order to affect any meaningful change in the incidence of post-operative pain within endodontics that the target population for any pain research be patients with existing pre-operative pain, because they are at greater risk of developing post-operative pain.[13]

Pulp Physiology and Inflammation

The understanding of pulp physiology and the body's inflammatory processes within the context of the human dental pulp is critical to the development of effective

therapeutic approaches to reducing post-operative pain after root canal treatment.[14] The pulp is very unique in the human body in that the physical environment of the dental pulp is a low-compliance environment through encasement by dentin. The pulp consists of loose connective tissue that contains nerves, blood vessels, lymph vessels, interstitial fluids, and a wide array of immune and connective tissue cells. Odontoblasts form the border between the pulp and dentin. Fibroblasts are located throughout the pulp that function in maintaining the fibrous extra cellular matrix of the pulp.[15]

Blood flow to the pulp is provided by very small arterioles, approximately 100 μm in diameter that enters through the apical foramen. Blood from the arterioles are distributed through an extensive network of branching capillaries, which provides an efficient pathway for the distribution of nutrients. This system is so efficient that every minute the pulp is able to replace the entire blood volume within the vasculature five to fourteen times. Lymph vessels that are located in the central part of the pulp is the only mechanism to remove proteins that leak from the blood vessels, and this becomes of critical importance during reversible pulpitis.[16] It is important to note however that there is no source of collateral circulation to the pulp, a fact that has significant consequences in the presence of inflammation.[15]

There are both autonomic and sensory nerves present in the dental pulp. Sympathetic autonomic nerves have been found to have a regulatory effect on pulpal blood flow, with stimulation causing vasoconstriction of the arterioles. There are two types of sensory nerve fibers: A-fibers and C-fibers. Nearly 90% of pulpal A-fibers are A-delta fibers, which are myelinated, fast conducting, low threshold nerve fibers that are unable to survive in hypoxic environments. The remaining 10% of pulpal A-fibers are A-beta fibers that provide propioceptive feedback. C fibers are unmyelinated, slow conducting, and high threshold nerve fibers that are able to survive in hypoxic environments. Responses to A-delta fibers are characterized by an immediate and sharp, sometimes stabbing-like pain, were as responses to C fibers are characterized by a prolonged dull type of pain.[14]

External irritants initiate the inflammatory process in the pulp. These irritants can be mechanical irritants such as the friction and heat that is generated when a bur cuts on tooth structure. These irritants could also be chemical, which includes bacteria, bacterial by-products, and even chemical rinses such as concentrated phosphoric acid utilized during cavity preparation. However, the penetration of bacteria and their by-products are by far the most common cause of inflammation to the pulp.[17] The inflammatory process in the pulp is the same as in the rest of the body, and is mediated by the same cells and pathways, with the only difference being the pulp's low compliance environment.[15] Dendritic cells present in the pulp release interleukin-8 (IL-8), which serves as a powerful chemotactic agent for other inflammatory cells, including neutrophils, macrophages, and mast cells.[17] Histamine, a potent vasodilator, is released from mast cells, resulting in vasoldilation of the arterioles and leakage of the venules. This leads to a further increase in inflammatory infiltrate in the pulp as well as their chemical mediators. There are two main consequences as a result of this increase in infiltrate, both of which are synergistic: Increase in tissue pressure, and increase in inflammatory infiltrate.[18] The first is that the increased osmotic pressure, a result of the increased protein concentration released from inflammatory cells within the pulp, quickly leads to an increase in tissue pressure. The low-compliance environment of the pulp prevents the dissipation of the increased tissue pressure. As a result, pulpal blood flow is decreased. In high-compliant tissues, increased blood flow allows the removal of inflammatory mediators and cells, thus limiting any excessive damage to the local site. As a result of the pulp's decreased blood flow, there is instead a rapid accumulation of inflammatory cells and mediators, which only leads to greater vascular damage.[19] This vicious cycle eventually leads to tissue necrosis. The second main consequence is the cascade of pro-inflammatory mediators and their subsequent effects on pulpal tissue throughout the progression of the inflammatory process. These mediators are released from multiple cells and include in part: histamine, serotonin, prostaglandins, leukotrienes, platelet activating factor (PAF), substance P (SP), and a wide host of enzymes that activate several different pro-inflammatory pathways.[17] Histamine and serotonin are released from mast cells and platelets respectively, yet both act on local vasculature to cause increased permeability through the contraction of the blood vessels' smooth muscle.[20]

Prostaglandins and leukotrienes are very important pro-inflammatory chemical mediators that orginate from the same precursor, arachidonic acid. Cycloxygenase enzymes convert arachidonic acid to prostaglandins and thromboxanes and lipoxygenase convert arachidonic acid to leukotrienes).[20] Prostaglandins function to cause vasodilation in local vessels, promote chemotaxis of inflammatory cells, and sensitize the receptors of pain fibers to stimulation by other mediators such as bradykinin.[14] Leukotrienes are from amongst the most potent chemotactic agents, attracting neutrophils and macrophages that produce extensive tissue and cellular damage through the release of degradative enzymes such as lyzozymes.[17] Leukotrienes also have profound effects on vascular permeability and increase pain through prolonged stimulation of nerve fibers.

Platelet activating factor is released from various immune cells and acts as a chemotactic agent, acts on blood vessels to increase vascular permeability, and acting on other cells to increase the production of other chemical mediators such as serotonin and leukotrienes.[17] SP is a pro-inflammatory neuropeptide that is released by C fibers upon stimulation and causes vasodilation, increased vascular permeability, and pain by lowering the threshold of sensory nerves.[21] Calcitonin gene related peptide, CGRP, is another neuropeptide released by C-fibers upon stimulation that acts in a similar fashion as SP.[22] The actions of these chemical mediators directly and indirectly cause pain at the site of inflammation. This is done directly through lowering the excitability threshold of the A-delta and C-fibers or indirectly by way of an increase in edema and tissue pressure. Thus it can be seen that the accumulation of pro-inflammatory mediators in the dental pulp quickly leads to a cycle of increased vascular permeability, pain, and ultimately tissue necrosis.[14] Many recent studies have demonstrated increased levels of inflammatory mediators in inflamed pulpal tissues. Bowles et al (2003)[23] measured the concentration of SP in normal and inflamed pulps through the insertion of micro-dialysis probes into the pulp. The concentrations of SP were eight times higher in teeth clinically diagnosed with irreversible pulpitis in comparison to those teeth diagnosed with normal pulps.[23] Tuncer et al found elevated levels of SP in inflamed periradicular tissues, highlighting the role that it plays in the spread of inflammation from the pulp to the periradicular tissues.[21] Lepinski et al (2000)[24] used the same microdialysis probe technique as Bowles et al[23] to evaluate pulpal concentrations of bradykinin, a potent pain mediator, in teeth with a clinical diagnosis of irreversible pulpitis as compared to normal pulps. Bradykinin concentrations were thirteen times greater in teeth with irreversibile pulpitis as compared to normal pulps.[24] Karapanou et al (2008) obtained gingival crevicular fluid samples from teeth diagnosed with irreversible pulpitis as well as adjacent and contralateral teeth with normal pulpal tissues to evaluate the concentration of IL-8, an important inflammatory chemotactic agent. It was found that interleukin-8 was significantly elevated in the gingival crevicular fluid of those teeth with irreversibile pulpitis.[25] Caviedies-Buchelli et al (2004)[22] found significantly higher levels of CGRP in pulpal tissues collected from teeth with irreversible pulpitis as compared to normal teeth. A recent article by Yingchun et al (2013) evaluated the expression of EphA7 receptors, a tyrosine kinase found on the membranes of inflammatory cells, in teeth with normal pulps and teeth with irreversible pulpitis. Higher expressions of the receptors were found in inflamed pulps as compared to normal pulps.[26] All of these recent high-level clinical studies suggest an active role of inflammatory mediators in pulpal inflammation. Post-operative pain develops when the integrity of the periapical tissues is compromised. This can occur during endodontic treatment from mechanical irritants such as hand instruments and obturation materials protruding beyond the minor foramen. Chemical irritation can occur if any of the solution is extruded beyond the apex. Sealers used in obturation are often both mechanical and chemical irritants since many commercially available sealers are cytotoxic.[17] In response to the tissue irritation, an inflammatory response is initiated, leading to an influx of inflammatory cells and mediators as described above, ultimately resulting in postoperative pain.

The Use of Glucocorticosteroids in Dentistry and Disruption of the inflammatory cycle has long been the focus of pain research. The primary target sites for pharmacological approaches have been two classes of enzymes: phospholipase, which synthesizes arachidonic acid from phospholipids, and cyclooxygenase, which synthesizes prostaglandins. Steroidal anti-inflammatory drugs (SAID), also known as glucosteroids, are a class of drugs that function by inhibiting phospholipase A2, thus reducing the production and concentrations of prostaglandins and leukotrienes. Non-steroidal anti-inflammatory drugs (NSAIDS), are a class of drugs that function by inhibiting cyclooxygenase enzymes, which reduces prostaglandins but does not affect leukotriene production.[20]

Histology has been used frequently to evaluate the direct anti-inflammatory effects of corticosteroids on periapical inflammation and pathology. Metzger et al (2002)[27] studied the effect of dexamethasone on the size of periapical lesions in rats. Bone resorption is modulated by inflammatory cytokines, thus they hypothesized that pharmacological modulation of bone resorption is possible. Periapical lesions were induced in molars of rats in two groups, a control group and an experimental group administered intramuscular injections of dexamethasone. None of the rats in the experimental group developed any abscess or overt sign of infection. Histologic evaluation of the periapical lesions of both groups showed that lesions in the dexamethasone group were significantly smaller than those of the control group. This suggested that the systemic administration of dexamethasone inhibited at least partially, the development of inflammatory periapical lesions. It is possible that dexamethasone had an inhibitory effect on osteoclasts. The authors found that in the experimental dexamethasone group, osteoclasts were more likely to undergo apoptosis, ultimately reducing the number of osteoclasts and limiting the potential for greater resorption.[27] Nobuhara et al (1993)[28] also used rats to observe any histologic changes due to the application of dexamethasone in inflamed periapical tissues of molars. The distal roots of

vital and non-vital first molars were over-instrumented with hand files, followed with the deposition of either saline or dexamethasone via buccal infiltration. The amounts of neutrophils for each specimen were counted at three time points: 6, 24, and 48 hours, and at three different locations within the periodontal ligament: adjacent to the apical foramen, the middle of the ligament, and adjacent to the cancellous bone. For both vital and non-vital cases, the dexamethasone groups demonstrated significantly less neutrophil infiltrate at 48 hours at the apical portion of the periodontal ligament as well as the middle of the ligament space. Neutrophils are the hallmark cells of acute inflammation, and any potential method to locally decrease neutrophil concentrations may have profound impacts on clinical symptoms following endodontic treatment. One of the effects of periapical inflammation is the presence of neural sprouting into the periodontal ligament, leading to increased sensitivity upon stimulation of the periodontal ligament.[28] Holland (1996)[29] sought to determine if systemic dexamethasone affects neural sprouting. Twenty ferrets had root canal treatment completed on mandibular canines, with the experimental group administered oral dexamethasone at the time of treatment. After three months, the ferrets were killed and specimens were prepared for histological evaluation. It was found that innervation density in the apical region, as well as the total innervation density of the periodontal ligament, were significantly lower in the dexamethasone group as compared to the control group.[29]

Isett et al (2003)[30] conducted a double-blind, randomized clinical study to investigate the effect of methylprednisolone (depo-medrol) on pulpal concentrations of PGE2 and IL-8. Forty patients with diagnoses of irreversible pulpitis participated. After being anesthetized, patients were given either intraosseous methylprednisolone or saline. The teeth were extracted anywhere from 24 hours to 72 hours after the intraosseous injection. The pulp tissues were extracted from the teeth and the concentrations of the PGE2 and IL-8 determined via enzyme immunoassay. The pulpal concentrations of PGE2 were significantly reduced at 24 hours post injection, but not at seventy-two hours.[30]

Much clinical research also has been produced on the use of SAIDS and their effect on inflammation and postoperative pain. Various modes of administration have been used, ranging from intramuscular injections to intra canal medications. [31, 32, 33, 34, 35, 36] A recent study by Jalalzadeh et al (2010)[34] administered a prednisolone pill 30 minutes before treatment to both vital and non-vital teeth in patients completed in one visit. 40 patients participated in this double blind study with patients divided equally between the placebo group and the prednisolone group. Prednisolone resulted in a statistically significant reduction in post-endodontic pain at 6, 12, and 24 hours following treatment. Marshall and Leisenger (1993)[33] carried out a double blind study evaluating the effect of 4 mg dexamethasone i.m. on post-operative pain in patients with both vital and non-vital teeth. Fifty patients were included in the placebo controlled experiment. Pain levels were recorded at 4 hours, 24 hours, and 48 hours postoperatively. Patients in the experimental group had significantly lower pain levels at 4 hours post-operatively compared to the placebo group.[33] Rogers et al (1999)[37] investigated the analgesic effects of a dexamethasone rinse in symptomatic vital cases in treatments completed in two visits. Forty-eight patients participated and were divided into four groups: placebo pills to be taken post-operatively, oral ibuprofen to be taken postoperatively, dexamethasone (4 mg/ml) intra canal rinse, and ketorolac intra canal rinse. The patients recorded their pain levels at 6, 12, 24, and 48 hours post-operatively. Dexamethasone provided statistically significant pain relief at 12 hours as compared to placebo, but the difference between dexamethasone and ketorolac and ibuprofen was not significant statistically.

Ehrmann et al (2003)[36] sought to evaluate whether Ledermix, a corticosteroid and antibiotic paste, reduced the incidence of post-operative pain in necrotic teeth. Two hundred and twenty one patients were randomized to treatments: ledermix, calcium hydroxide (CaOH), and no medication. Patients in the Ledermix group had consistently less post-operative pain at all observed time points as compared to patients in the CaOH and placebo groups (2003). In 2001, Negm et al (2001)[38] published a double blind, randomized study evaluating the efficacy of dexamethasone as an intra-canal medicament in the treatment of inter-appointment pain in patients undergoing root canal therapy on vital teeth. Postoperative pain levels were evaluated up to 48 hours. 480 Patients who needed endodontic therapy received either the corticosteroid-antibiotic medicament, or a placebo. Over 93% of the patients assigned to the steroid group had complete relief of pain within the first 24 hours, compared to only 22% in the placebo group. The most significant factor in this study was the large size of participants in each group, with over 248 patients in the experimental group and 232 patients in the control group.[7] A weakness in the Negm study is that the SAID and antibiotic were mixed into one medicament, making it difficult to draw conclusions about the efficacy of either component alone. It would have been more appropriate to have two experimental groups: a SAID group, and an antibiotic group.

CONCLUSION:

Although, Standard of care root canal therapy causes significant reduction in post-operative pain,

corticosteroids like dexamethasone may be used as medicaments or endodontic irrigants to the process of root canal treatment more pleasant for the patient.

REFERENCES:

1. Sohn W, Ismail W. Regular Dental Visits and Dental Anxiety in an Adult Dentate Population. The Journal of the American Dental Association 2005; 136(1): 58-66.
2. Nixdorf D, Moana-Filho E, Law A, McGuire L, Hodges J, John M. Frequency of Persistent Tooth Pain after Root Canal Therapy: A Systematic Review and Meta-Analysis. Journal of Endodontics 2010a; 36(2): 224-30.
3. Nobuhara WK, Carnes DL, Gilles JA. Anti-Inflammatory Effects of Dexamethasone on Periapical Tissues following Endodontic Overinstrumentation. Journal of Endodontics 1993; 19(10): 501-07.
4. Wong M, Lytle WR. A Comparison of Anxiety Levels Associated with Root Canal Therapy and Oral Surgery Treatment. Journal of Endodontics 1991; 17(9): 461-65.
5. Public Policy Polling. Poll Results. Congress Less Popular than Cockroaches, Traffic Jams. N.p., 8 Jan. 2013. Web. 15 Jan. 2013. <http://www.publicpolicypolling.com/main/2013/01/congress-less-popular-thancockroaches-traffic-jams.html>.
6. Seltzer S, Naidorf I. Flare-ups in Endodontics: I. Etiological Factors. Journal of Endodontics 2004a; 11(11): 472-78.
7. Glossary of Endodontic Terms. 8th ed. N.p.: American Association of Endodontists, 2012. Glossary of Endodontic Terms. American Association of Endodontists. Web. <http://www.nxtbook.com/nxtbooks/aae/endodonticglossary/index.php>.
8. Tsesis I, Faivishevsky V, Fuss Z, Zukerman O. Flare-ups after Endodontic Treatment: A Meta-analysis of Literature. Journal of Endodontics 2008; 34(10): 1177-181.
9. Nixdorf D, Moana-Filho E, Law A, McGuire L, Hodges J, John M. Frequency of Nonodontogenic Pain after Endodontic Therapy: A Systematic Review and Meta-Analysis. Journal of Endodontics 2010b; 36(9): 1494-498.
10. ElMubarak A, Abu-bakr N, Ibrahim Y. Postoperative Pain in Multiple-visit and Singlevisit Root Canal Treatment. Journal of Endodontics 2010; 36(1): 36-39.
11. Merskey H, Bogduk N. "Part III: Pain Terms, A Current List with Definitions and Notes on Usage. Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. 2nd ed. Seattle: IASP, 1994: 209-14.
12. Oshima K, Ishii T, Ogura Y, Aoyama Y, Katsuumi I. Clinical Investigation of Patients Who Develop Neuropathic Tooth Pain After Endodontic Procedures. Journal of Endodontics 2009; 35(7): 958-61.
13. Pak JG, White SN. Pain Prevalence and Severity Before, During, and after Root Canal Treatment: A Systematic Review. Journal of Endodontics 2011; 37(4): 429-38.
14. Kim, S. Neurovascular Interactions in the Dental Pulp in Health and Inflammation. Journal of Endodontics 1990; 16.(2): 48-53.
15. Ingle J, Bakland L, Baumgartner J. Ingle's Endodontics. Hamilton, Ont.: BC Decker, 2008. Print.
16. Oehmke M, Knolle E, Oehmke HJ. Lymph Drainage in the Human Dental Pulp. Microscopy Research and Technique 2003; 62(3): 187-91.
17. Siqueira J. F, Barnett F. Interappointment Pain: Mechanisms, Diagnosis, and Treatment. Endodontic Topics 2004; 7(1): 93-109.
18. Caviedesbucheli J, Munoz H, Azueroholguin M, Ulate E. Neuropeptides in Dental Pulp: The Silent Protagonists. Journal of Endodontics 2008; 34(7): 773-88.
19. Heyeraas K. Pulpal Microvascular and Tissue Pressure. Journal of Dental Research 1985; 64: 585
20. Seltzer S, Naidorf I. Flare-ups in Endodontics: II. Therapeutic Measures. Journal of Endodontics 2004b; 11(12): 559-67.
21. Tuncer L, Alacam T, Oral B. Substance P Expression Is Elevated in Inflamed Human Periradicular Tissue. Journal of Endodontics 2004; 30(5): 329-32.
22. Caviedesbucheli J, Camargobeltran C, Gomezlarotta A, Cristinatrujillomoreno S, Morenoabello G, Gonzalezescobar J. Expression of Calcitonin Gene-Related Peptide (CGRP) in Irreversible Acute Pulpitis. Journal of Endodontics 2004; 30(4): 201-04.
23. Bowles W, Withrow J, Lepinski A, Hargreaves K. Tissue Levels of Immunoreactive Substance P Are Increased in Patients with Irreversible Pulpitis. Journal of Endodontics 2003; 29(4): 265-67.
24. Lepinski A, Hargreaves K, Goodis H, Bowles W. Bradykinin Levels in Dental Pulp by Microdialysis. Journal of Endodontics 2000; 26(12): 744-47.
25. Karapanou V, Kempuraj D, Theoharides T. Interleukin-8 Is Increased in Gingival Crevicular Fluid from Patients with Acute Pulpitis. Journal of Endodontics 2008; 34(2): 148-51.
26. Yingchun D, Weidong L, Wu W. Increased Expression of EphA7 in Inflamed Human Dental Pulp. Journal of Endodontics 2013; 39(2): 223-27.
27. Metzger Z, Klein H, Klein A, Tagger M. Periapical Lesion Development in Rats Inhibited by Dexamethasone. Journal of Endodontics 2002; 28(9): 643-45.
28. Nobuhara WK, Carnes DL, Gilles JA. Anti-Inflammatory Effects of Dexamethasone on Periapical Tissues following Endodontic Overinstrumentation. Journal of Endodontics 1993; 19(10): 501-07.
29. Holland G. Steroids Reduce the Periapical Inflammatory and Neural Changes after Pulpectomy. Journal of Endodontics 1996; 22(9): 455-58.
30. Isett J, Reader A, Gallatin E, Beck M, Padgett D. Effect of an Intraosseous Injection of Depo-Medrol on Pulpal Concentrations of PGE2 and IL-8 in Untreated Irreversible Pulpitis. Journal of Endodontics 2003; 29(4): 268-71.
31. Shariar S, Mokhtari H, Rahimi S, Yavari HR, Narimani S, Abdolrahimi M, Nezafati S. Effect of Premedication with Ibuprofen and Dexamethasone on Success Rate of Inferior Alveolar Nerve Block for Teeth with Asymptomatic Irreversible Pulpitis: A Randomized Clinical Trial. Journal of Endodontics 2012; 39(2): 160-162.

32. Marshall J, Walton R. The Effect of Intramuscular Injection of Steroid on Posttreatment Endodontic Pain. Journal of Endodontics 1984; 10(12): 584-88.
33. Liesinger A, Marshall F, Marshall J. Effect of Variable Doses of Dexamethasone on Posttreatment Endodontic Pain. Journal of Endodontics 1993; 19(1): 35-39.
34. Jalalzadeh S, Mamavi A, Shahriari S, Santos F, Pochapski M. Effect of Pretreatment Prednisolone on Postendodontic Pain: A Double-blind Parallel-randomized Clinical Trial. Journal of Endodontics 2010; 36(6): 978-81.
35. Chu F, Leung W, Tsang P, Chow T, Samaranayake L. Identification of Cultivable Microorganisms from Root Canals with Apical Periodontitis Following Two-Visit Endodontic Treatment with Antibiotics/Steroid or Calcium Hydroxide Dressings. Journal of Endodontics 2006; 32(1): 17-23.
36. Ehrmann E, Messer H, Adams G. The Relationship of Intracanal Medicaments to Postoperative Pain in Endodontics. International Endodontic Journal 2003; 36(12): 868-75.
37. Rogers M, Johnson B, Remeikis N, Begole R. Comparison of Effect of Intracanal Use of Ketorolac Tromethamine and Dexamethasone with Oral Ibuprofen on Post Treatment Endodontic Pain. Journal of Endodontics 1999; 25(5): 381-84.
38. Negm M. Intracanal Use of a Corticosteroid-antibiotic Compound for the Management of Posttreatment Endodontic Pain. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology & Endodontics 2001; 92(4) 435-39.