Ref: Ro J Stomatol. 2024;70(2)
DOI: 10.37897/RJS.2024.2.18

Emerging role of cryotherapy and steroids in management of local anaesthetic failure

Aseel Yehia, Khaled Mohamed Abboud, Maram Farouk Obeid

Department of Endodontics, Ain Shams University, Cairo, Egypt

ABSTRACT

Endodontic pain is a disruptive event to all clinicians and patients. When performing dental treatment on teeth with clinically healthy pulps, efficient and adequate local anesthesia is the fundamental basis for dental pain control. Nevertheless, when managing patients with acutely inflamed pulps, local anesthesia is actually much less efficient. Clinical trials have reported that an IANB injection of a local anesthetic solution is inefficient in 30 to 80% of patients diagnosed with acute irreversible pulpitis. Therefore, pain management of lower molars with symptomatic irreversible pulpitis is usually a challenge to the endodontist. Many efforts have been made to implement various pharmaceutical and non-pharmaceutical agents to control the inflammatory processes leading to pulpal pain. These agents chiefly included NSAIDs and synthetic steroids, along with other modalities such as cryotherapy and acupuncture. The effect of steroids and cryotherapy on the success rates on IANBs when treating lower molars with symptomatic acute pulpitis was investigated in a few studies to increase the efficiency and duration of nerve block in these cases. The goal of this review is to highlight the role of steroids and cryotherapy in increasing the success rate of IANB and to point out the clinical studies concerned with both modalities.

Keywords: steroids, cryotherapy, dexamethasone, endodontic pain

Abbreviations

SIP – Symptomatic irreversible pulpitis
NSAIDS – Non steroidal anti-inflammatory drugs
SIP – Symptomatic irreversible pulpitis
IANB – Inferior alveolar nerve block
TTX – Tetrodotoxin
CGRP – calcitonin g related peptide
GMCSF – granulocyte monocyte colony stimulating factor

INTRODUCTION

Symptomatic irreversible pulpitis is an inflammatory disease of the pulp implying that the inflamed pulp is unable to heal (AAE, 2016). Teeth with SIP present with occasional or spontaneous pain that may be throbbing or vague, localized, generalized, or transferred to another site, traditionally accompanied with lingering periods of pain after thermal, specifically cold stimulus. The symptoms in molars diagnosed with acute pulpitis are caused by acute inflammatory process of the pulp and because the pulp is unable to expand due to the surrounding hard tissue, this inflammation causes a marked increase of the intrapulpal pressure. Effective, adequate, efficient, and long-lasting local anaesthesia is an urgent prerequisite because ineffective pain control may lead to a traumatic dental procedure instead of a simple expected one [1]. Nevertheless, local anaesthesia is usually inefficient in those cases, irrelevant of the tooth or the local anaesthetic technique being advocated [2]. Reports on the frequency and seriousness of intraoperative pain vary impressively, and this stamped differences can be attributed to varieties within the test sizes, strategies utilized, and the social and ethnic characteristics of the different populations. Clinical trials

Corresponding authors:
Aseel Yehia
E-mail: aseelabdelzaher@dent.asu.edu.eg

Article History:
Received: 23 April 2023
Accepted: 27 June 2024

have reported that an IANB injection of local anaesthetic solution (1.8 ml) is ineffective in 30 to 80% of patients diagnosed with acute pulpitis so that anaesthetizing those patients fails 8 times higher than healthy unaffected patients [3]. Pain control during endodontic treatment can be accomplished by three main approaches – by decreasing nociceptive impulses from the more distant area, by inhibiting nociceptive impulses transmission in the peripheral neurons and by prohibiting pain perception in the CNS. Local anaesthesia blocks nociceptive impulses that are produced while performing the treatment and this nociceptive input can actually be lowered by administering NSAIDs [3] or steroids [4] as both prohibit prevent the production of prostaglandins at the actual site of insult and/or treatment. Both modalities specifically when a long acting local anaesthetic solution is administered [5] can inhibit pain perception and recognition in the central nervous system after treatment. The present clinical studies report that the using different techniques for pain control are useful; however, there is doubt regarding the most effective anaesthetic protocol to be agreed upon when managing lower molars with pulpitis. Many investigations are still recommended, evaluating patient-based outcomes, to provide evidence-based protocols and more precise protocols. Therefore, the goal of the present review is to have an resolution to this inquiry: "Does the preoperative administration of dexamethasone or cryotherapy increase the efficacy of the standard inferior alveolar nerve block on teeth with symptomatic irreversible pulpitis without the need for premedication?"

MATERIALS AND METHODS

Material and sources collection

The choice of the papers in this article depended on a manual exploration of the related search engines: Egyptian Knowledge Bank, PubMed, Scopus, and Web of Science .The last activity was in April 2024. The following key words were used: cryotherapy, cold therapy, cryotherapy in root canal treatment, steroids, success of inferior alveolar nerve block, endodontic pain.

Inclusion Criteria

Clinical studies, case reports, with all research that investigated cryotherapy and steroids and written in English and published in scientific dental journals were chosen in this article. The approved articles were electronically selected, and the full references were grouped and filtered. The references list of all articles was manually analyzed for more studies inclusion.

Selection of the Studies

Titles of the selected articles were at first grid separately by all three contributers to select the studies that abide to the inclusion criteria. If controversy occurred between them, a discussion was set for brainstorming, and a final decision was made with the aid of the corresponding author. All articles not matching the inclusion criteria previously decided ruled out.

DISCUSSION

Causes of failure of IANB

Many possible causes were mentioned for local anaesthetic failure during endodontic treatment. These reasons were sorted as anatomical and non-anatomical reasons for ease of recognition. Between the anatomical hypothesis, the mylohyoid nerve theory and the central core theory gained much attention, but failure of anaesthesia to provide anaesthetic success in all teeth has favored the non-anatomical causes [6]. The hypothesis well recognized but least expected to be correct is the lowered pH of the inflamed tissue [7]. This theory proposes that the low pH decreases the availability of the basic form of the anaesthetic solution, therefore decreasing the penetrability to the membrane so, providing inadequate anaesthesia. This is not considered to be the most reasonable clarification for inadequate anaesthesia with IANB where the principal site of inflammation isn't actually injected. The most accepted proposed hypothesis for the decreased success rate of local anesthesia can be the more complicated neural processes. Inflammatory process and bacterial insults cause neurons sprouting, more significant release of neuropeptides like subs. P and CGRP, and the release of inflammatory mediators such as PGE2, PGF2a, IL-1,6, and TNF. This leads to activation and sensitization of nociceptors by reducing their activation thresholds to the point that they discharge in response to the patient's heart beats leading to throbbing pain, and lead as well to stimulation of a larger amount of neurons, leading to a blast of impulse produced from the inflamed tissue to the CNS via many unmyelinated sensory C fibers [8]. A major class of voltage gated sodium channels that are resistant to tetrodotoxin are located on pain receptors. They have higher activation threshold compared to the tetrodotoxin sensitive channels. That's why, they are somehow resistant to many sodium-channel blockers as local anaesthetics [9]. These channels are also sensitized by prostaglandins [10] and they explain the reason why local anaesthesia is less efficient in clinical cases of symptomatic irreversible pulpitis.

Criteria of anaesthetic success

In managing teeth with acute irreversible pulpitis, assessing if adequate and efficient local anaesthesia has been achieved before beginning the treatment is mandatory. Anaesthesia through the IANB has classically been checked subjectively by asking if the patient's lip was numb, and objectively by probing the gum surrounding the tooth to be treated or starting treatment and observing the patient's reaction. Nevertheless, those techniques are not very accurate to evaluate if pulpal anaesthesia has been really achieved [11]. More objective tests can be implemented to determine if the pulp was adequately anaesthetized. The use of electric pulp tester and/ or cold sprays have been agreed upon to precisely assess pulpal anaesthesia in teeth with healthy pulps before the beginning of treatment. If the patient didn't react, at that point pulpal anesthesia is affirmed and the patient isn't anticipated to feel pain during the treatment. Nevertheless, in case of symptomatic acute irreversible pulpitis, a negative response to the stimuli does not warrant pulpal anesthesia [12]. The patient may still report pain while treatment. Therefore, as per Fowler and colleagues, success rates of the inferior alveolar nerve block are estimated as 28% in first molars, 25% in second molars, and 39% in premolars in cases with irreversible pulpitis when patients didn't feel pain or just reported mild pain felt whilst access cavity preparation [13].

Management strategies of local anaesthetic failure

Many clinical trials have suggested approaches to overcome the inadequacy of IANBs for controlling pain in teeth with acute pulpitis, for example implementing different anaesthetic techniques targeting other anatomical landmarks [2,14], using different types and/or increasing the amount of the solution injected [11,15], preoperative prescription of an oral drug as NSAIDs or steroids [16], injecting preoperative submucosal tramadol [4], cryotherapy [17], low-level laser therapy [18], acupuncture [19] and the administration of supplemental buccal and lingual infiltration injections [20], intra-ligamentary [21], and intra-bony injections [22,23]. Our review focuses on 2 anti-inflammatory approaches and discusses their rationale in enhancing the success rate of IANB in lower molars with irreversible pulpitis.

Steroids

Physiological effect of steroids

A recognized approach to antagonize the inflammation and manage pain is drugs prescription that can be either preoperatively to attain precautionary analgesia or rather postoperatively after treatment to lessen the expected or present pain. These drugs include NSAIDs [16], paracetamol [24], and steroids [25]. Steroids have a significant powerful antiinflammatory effect (for instance, 25 times as that of hydro-cortisone on pain happening due to sensitization and activation of nociceptors due to multiple inflammatory mediators) [26,27]. Glucocorticoids have various sites of action, and they inhibit the phospholipase enzyme so, they are considered to be strong inhibitors of COX and LOX pathways of arachidonic acid metabolism [28].

Glucocorticoids mediate this inhibition by a variety of cells and factors which are critical in exacerbating the inflammation. This action is due that glucocorticoids affect gene transcription that leading to a decrease in the production of many chemo attractive factors, decrease migration of white blood cells to sites of insult, and finally minimal tissue fibrosis. Steroids as well show significant effects on the immunity by inhibiting the production of cytokines, especially interferon G, GM-CSF, IL-1, IL-2, IL-3, IL-6 and TNFa. Therefore, this pharmacological action of steroids antagonizes the inflammatory process that cause pain of pulpal origin.

Glucocorticoids also reduce bradykinin mediators via promoting the formation of angiotensin converting enzyme. Bradykinin activates the action of pain receptors and leads to the release of substance P, and CGRP that mediate pain. Moreover, glucocorticoids inhibit the release of neuropeptides thus, inhibit neurogenic inflammation [29]. Glucocorticoids also produce vasocortin that suppresses edema, unlike NSAIDs that cannot mediate this action [30]. The corticosteroids family includes dexamethasone, methylprednisolone and prednisolone. Methylprednisolone and Prednisolone are intermediate-action drugs (relative potency of 5,4 respectively) but, dexamethasone is a long-action one with a relative potency of 25 more than that of endogenous cortisol [31].

Effect of dexamethasone on the success rate of IANB

The effect of dexamethasone on the success rate on IANBs when treating lower molars with symptomatic irreversible pulpitis was investigated in a few studies to enhance the efficiency and duration of nerve block in these cases. Aggarwal et al [32] concluded that buccally supplementally infiltrating 1 mL/4 mg of dexamethazone didn't enhance the success rate of IANB in mandibular molars, and that it didn't significantly differ compared to the control group. Also, Mai Mohamed et al 2020 [33] showed that administrating one dose of 0.5 mg dexamethasone preoperative did not alter the magnitude of pain postoperatively nor the success anesthesia of IANB by administering 2% mepivacaine with 1:100,000 epinephrine in patients with acute irreversible pulpitis.

Kaushik et al [34] assessed the efficiency of anesthesia with 2% lidocaine with 1:200,000 epinephrine against a mixture of 2% lidocaine, 1:200,000 epinephrine and 1 mL of 4 mg dexamethasone (Twin mix) for IANBs in patients with acute irreversible pulpitis affecting the lower molars in a randomised controlled trial. This clinical study showed that the anaesthetic efficiency of Twin mix has been similar to that of 2% lidocaine for IANB.

On the other hand, in a randomized, parallel, clinical study, Aggarwal et al. 2021 [25] concluded that intraligamentary administration of dexamethasone increased the success rate of anaesthesia. In another double-blinded, controlled trial, Aksoy et al. 2021 [4] concluded that dexamethasone administration extended the time interval of anaesthetic action when it was in comparison to that of saline. It was concluded as well in the this study that administering dexamethasone by submucosal infiltration provides analgesia rather than an anaesthetic action. Moreover, the administration of dexamethazone in lower molars with symptomatic irreversible pulpitis by this way has been shown to show efficient pain control in management of pain of endodontic origin.

Compared to NSAIDs, Shokri et al 2018 [35] showed that administration of 4 mg of dexamethasone preoperatively or 400 mg ibuprofen 60 minutes before the IANB led to a marked increase in the success of anaesthesia when managing lower molars with acute irreversible pulpitis.[35] This agrees with previous studies by Shahi et al 2012 [36] and Bidar et al 2017 [37]. Moreover, Kumar et al [38] concluded that the administration of a combination of ibuprofen and dexamethasone preoperatively improved the success rate of IANB in mandibular molars with symptomatic acute irreversible pulpitis.

In another prospective randomised, double blinded clinical trial, Aggarwal et al [39] proposed to assess the anaesthetic effect of adding 2 mg of dexamethasone (4 mg/ml) to 2% lidocaine solution (plain, or with 1:80,000 epinephrine). They concluded that adding dexamethasone to 2% lidocaine with epinephrine, when given as an IANB, can increase the anaesthetic success rate when managing lower molars with acute irreversible pulpitis.

Cryotherapy

Physiological action of Cryotherapy

Cryotherapy is a popular approach that is widely used in sport injuries and in surgeries for management of pain and providing postoperative care. Cryotherapy techniques that provide faster cooling of tissues offer some advantage when compared to slower cooling techniques [40]. Likewise, it is generally thought that greater reduction of temperature leads to stronger suppression of metabolism, therefore suggesting that cryotherapy approaches that provide lower temperatures are more efficient. Thermodynamic properties, especially the change of physical state, have a great effect. Ice-based techniques, going through a change of state from the solid to liquid one, absorb greater amount of heat. In a study by Bleakley et al [41], they showed that optimum levels of pain control can be practically obtained by using crushed ice for intervals of 5–15 minutes and that all different approaches of cryotherapy may demand longer periods of time to lower the skin's temperature to necessary levels. In root canal therapy, cryotherapy is recommended following periapical apicectomies and during root canal irrigation to control the inflammatory processes, therefore, decreasing postoperative pain [42].

The therapeutic effects of cryotherapy are achieved by affecting metabolic, hemodynamic, neuromuscular processes [43]. The hemodynamic effect can be explained by that cold promotes vasoconstriction with an antiedematous effect, leading to a decrease in inflammation by decreasing the number of white blood cells adhering to the capillary endothelial cells and minimizing their transfer to the site of tissue injury [44]. The second is cellular in nature and has to do with slowing down metabolism. By cryotherapy, blood flow to the tissues is well reduced. Therefore, cells use less amount of oxygen and blood flow is decreased due to vasoconstriction, leading to minimal generation of oxygen radicals in tissue, and prevention of hypoxia and extra damage of tissue [45]. The final effect is neurological, such that temperature reduction induces analgesia by slowing nerve conduction velocity. Nevertheless, this affects more the myelinated A-delta neurons which are deactivated completely at approximately 7°C when compared to the unmyelinated °C that are deactivated totally at around 3°C as shown by Franze and Iggo [46]. It was as well suggested that gate control theory is accountable for pain reduction caused by cryotherapy as the larger myelinated A fibers provide a faster more pronounced sensory input which temporarily closes the gate and inhibits the unmyelinated °C fibers from transmitting the more painful impulses leading to minimal pain sensation.

Effect of cryotherapy on success rate of IANB

The effect of cryotherapy on the success rate on IAN blocks when providing treatment for lower molars with acute irreversible pulpitis has been investigated in a few studies. Intraoral approaches took different forms being applied to the soft tissue or hard tooth structure.

Intraoral soft tissue cryotherapy application in the facial vestibule of lower molars in the form of

ice blocks wrapped in gauze increased the efficiency of IANB relative to the control groups as concluded by Topcuoglo et al [17], Gupta et al [47] and El-Heeny et al [48]. However, Endo-ice being sprayed to the crowns of teeth did not provide much efficient pain control during pulp chamber penetration compared to buccal infiltration injection by articane as concluded by Koteeswaran et al [49]. This was agreed upon later by Gopakumar et al[12] who concluded that the application of Endo-ice and intrapulpal ice after IANB significantly increases the effectiveness of pulpal anaesthesia in lower second molars with symptomatic irreversible pulpitis. Aggarwale et al[50] assessed if cooling 2% lidocaine solution with 1:200,000 epinephrine had an analgesic effect, when given as an intraligamentary supplemental injection after a failed IANB. They concluded that cooling didn't affect the anaesthetic efficiency of intraligamentary supplemental injections, administered after a failed IANB.

CONCLUSION

The previous findings showed that steroids and cryotherapy effectively enhance the success rates of IANBs and improve pain management in patients with symptomatic acute irreversible pulpitis. Nevertheless, the success rates yet aren't sufficient as needed to guarantee thorough anaesthesia, the same as concluded by the former studies. It is recommended that more clinical research be done using various pain management strategies on participants with various diagnoses (such as apical periodontitis, pulp necrosis, and so forth).

Conflict of interest: none declared
Financial support: none declared

REFERENCES

1. Avinash, Sheikh AB, Rashid S, Ali M, Siddiqui KN, Mujeeb F. Anesthetic Efficacy of Intraligamentary Injection Techniques on Mandibular Posterior Teeth Diagnosed with Asymptomatic Irreversible Pulpitis. *Pak Armed Forces Med J.* 2022;72(5):1550-4. https://doi.org/10.51253/pafmj.v72i5.4005.
2. Aggarwal V, Singla M, Kabi D. Comparative evaluation of anesthetic efficacy of Gow-Gates mandibular conduction anesthesia, Vazirani-Akinosi technique, buccal-plus-lingual infiltrations, and conventional inferior alveolar nerve anesthesia in patients with irreversible pulpitis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2010;109(2):303-8. https://doi.org/10.1016/j.tripleo.2009.09.016
3. Mittal R, Swiah JME. Anaesthetising Painful Pulp in Endodontics-A Review. *J Oral Health Community Dent.* 2011;5(3). https://doi.org/10.5005/johcd-5-3-145
4. Parirokh M, Ashouri R, Rekabi AR, Nakhaee N, Pardakhti A, Askarifard S, et al. The effect of premedication with ibuprofen and indomethacin on the success of inferior alveolar nerve block for teeth with irreversible pulpitis. *J Endod.* 2010;36(9):1450–4. https://doi.org/10.1016/j.joen.2010.05.007
5. Aksoy F, Ege B, Tosun S. The effect of pre-operative submucosal administration of dexamethasone, tramadol, articaine on the success rate of inferior alveolar nerve block on mandibular molars with symptomatic irreversible pulpitis: A randomized, double-blind placebo-controlled clinical trial. *Int Endod J.* 2021;54(11):1982-92. https://doi.org/10.1111/iej.13604
6. Parirokh M, Yosefi MH, Nakhaee N, Manochehrifar H, Abbott P V., Reza Forghani F. Effect of bupivacaine on postoperative pain for inferior alveolar nerve block anesthesia after single-visit root canal treatment in teeth with irreversible pulpitis. *J Endod.* 2012;38(8):1035-9. https://doi.org/10.1016/j.joen.2012.04.012
7. Parirokh M, Abbott P V. Present status and future directions—Mechanisms and management of local anaesthetic failures. *Int Endod J.* 2022;55:951-94. https://doi.org/10.1111/iej.13697
8. Drum M, Reader A, Nusstein J, Fowler S. Successful pulpal anesthesia for symptomatic irreversible pulpitis. *J Am Dental Assoc.* 2017;148(4):267-71. https://doi.org/10.1016/j.adaj.2017.01.002
9. Goodis HE, Poon A, Hargreaves KM. Tissue pH and temperature regulate pulpal nociceptors. *J Dent Res.* 2006;85(11):1046-9. https://doi.org/10.1177/154405910608501114
10. Modaresi J, Dianat O, Soluti A. Effect of Pulp Inflammation on Nerve Impulse Quality with or without Anesthesia. *J Endod.* 2008;34(4):438-41. https://doi.org/10.1016/j.joen.2008.01.014.
11. Henry MA, Hargreaves KM. Peripheral Mechanisms of Odontogenic Pain. *Dent Clin North Am.* 2007;51:19-44. https://doi.org/10.1016/j.cden.2006.09.007
12. Vreeland DL, Beck M, Meyers W, Weaver J. An Evaluation of Volumes and Concentrations of Lidocaine in Human Inferior Alveolar Nerve Block. vol. 15. 1989
13. Gopakumar R, Jayachandran M, Varada S, Jayaraj J, Ezhuthachan Veettil J, Nair NS. Anesthetic Efficacy of Endo-Ice and Intrapulpal Ice Sticks After Inferior Alveolar Nerve Block in Symptomatic Irreversible Pulpitis: A Randomized Controlled Study. *Cureus.* 2023. https://doi.org/10.7759/cureus.42135
14. Fowler S, Drum M, Reader A, Beck M. Anesthetic success of an inferior alveolar nerve block and supplemental articaine buccal infiltration for molars and premolars in patients with symptomatic irreversible pulpitis. *J Endod.* 2016;42(3):390–2. https://doi.org/10.1016/j.joen.2015.12.025
15. Saatchi M, Shafiee M, Khademi A, Memarzadeh B. Anesthetic Efficacy of Gow-Gates Nerve Block, Inferior Alveolar Nerve Block, and Their Combination in Mandibular Molars with Symptomatic Irreversible Pulpitis: A Prospective, Randomized Clinical Trial. *J Endod.* 2018;44(3):384-8. https://doi.org/10.1016/j.joen.2017.10.008
16. Eskandarinezhad M, Ghasemi N, Rostami P, Abdollahi AA. Comparison of the success of inferior alveolar nerve anesthesia in the mandibular first molars with symptomatic irreversible pulpitis using two anesthetic solutions of prilocaine and mepivacaine: A randomized controlled clinical trial. *Dent Res J (Isfahan).* 2023;20(1). https://doi.org/10.4103/1735-3327.372661
17. Aggarwal V, Singla M, Rizvi A, Miglani S. Comparative evaluation of local infiltration of articaine, articaine plus ketorolac, and dexamethasone on anesthetic efficacy of inferior alveolar nerve block with lidocaine in patients with irreversible pulpitis. *J Endod.* 2011;37(4):445-9. https://doi.org/10.1016/j.joen.2011.01.016
18. Topçuoğlu HS, Arslan H, Topçuoğlu G, Demirbuga S. The Effect of Cryotherapy Application on the Success Rate of Inferior Alveolar Nerve Block in Patients with Symptomatic Irreversible Pulpitis. *J Endod.* 2019;45(8):965-9. https://doi.org/10.1016/j.joen.2019.05.001.
19. Topçuoğlu HS, Akpınar B. The effect of low-level laser therapy on the success rate of inferior alveolar nerve blocks in mandibular molars with symptomatic irreversible pulpitis: A randomized clinical trial. *Int Endod J.* 2021;54(10). https://doi.org/10.1111/iej.13596
20. Jalali S, Moradi Majd N, Torabi S, Habibi M, Homayouni H, Mohammadi N. The Effect of Acupuncture on the Success of Inferior Alveolar Nerve Block for Teeth with Symptomatic Irreversible Pulpitis: A Triple-blind

Randomized Clinical Trial. *J Endod.* 2015;41(9) https://doi.org/10.1016/j.joen.2015.04.026
21. Aggarwal V, Jain A, Kabi D. Anesthetic Efficacy of Supplemental Buccal and Lingual Infiltrations of Articaine and Lidocaine after an Inferior Alveolar Nerve Block in Patients with Irreversible Pulpitis. *J Endod.* 2009;35(7):925-9. https://doi.org/10.1016/j.joen.2009.04.012
22. Aggarwal V, Singla M, Miglani S, Kohli S. Efficacy of Articaine Versus Lidocaine Administered as Supplementary Intraligamentary Injection after a Failed Inferior Alveolar Nerve Block: A Randomized Double-blind Study. *J Endod.* 2019;45(1):1-5. https://doi.org/10.1016/j.joen.2018.09.012
23. Saber SM, Hashem AA, Khalil DM, Pirani C, Ordinola-Zapata R. Efficacy of four local anaesthesia protocols for mandibular first molars with symptomatic irreversible pulpitis: A randomized clinical trial. *Int Endod J.* 2022;55(3):219–30. https://doi.org/10.1111/iej.13667
24. Nusstein J, Kennedy S, Reader AI, Beck M, Weaver J. Anesthetic efficacy of the supplemental X-tip intraosseous injection in patients with irreversible pulpitis. *J Endod.* 2003;29(11). https://doi.org/10.1097/00004770-200311000-00010
25. Kumar U, Rajput A, Rani N, Parmar P, Kaur A, Aggarwal V. Addendum: Effect of pre-operative medication with paracetamol and ketorolac on the success of inferior alveolar nerve block in patients with symptomatic irreversible pulpitis: a double-blind randomized clinical trial. *J Dent Anesth Pain Med.* 2023;23(1). https://doi.org/10.17245/jdapm.2023.23.1.57
26. Aggarwal V, Singla M, Saatchi M, Gupta A, Hasija M, Meena B, et al. Preoperative Intraligamentary Injection of Dexamethasone Can Improve the Anesthetic Success Rate of 2% Lidocaine during the Endodontic Management of Mandibular Molars with Symptomatic Irreversible Pulpitis. *J Endod.* 2021;47(2):161–8. https://doi.org/10.1016/j.joen.2020.11.023
27. Mehrvarzfar P, Shababi B, Sayyad R, Fallahdoost A, Kheradpir K. Effect of supraperiosteal injection of dexamethasone on postoperative pain. *Aust Endod J.* 2008;34(1):25–9. https://doi.org/10.1111/j.1747-4477.2007.00076.x
28. Mehrvarzfar P, Esnashari E, Salmanzadeh R, Fazlyab M, Fazlyab M. Effect of dexamethasone intraligamentary injection on post-endodontic pain in patients with symptomatic irreversible pulpitis: A randomized controlled clinical trial. *Iran Endod J.* 2016;11(4):261-6. https://doi.org/10.22037/iej.2016.2
29. Nath R, Daneshmand A, Sizemore D, Guo J, Enciso R. Efficacy of corticosteroids for postoperative endodontic pain: A systematic review and meta-analysis. *J Dent Anesth Pain Med.* 2018;18(4):205. https://doi.org/10.17245/jdapm.2018.18.4.205
30. Donnerer J, Holzer-Petsche U. The Inhibition of Neurogenic Inflammation. *NeuroImmune Biology.* 2009;8:169-89. https://doi.org/10.1016/S1567-7443(08)10408-2.
31. Marshall JG. Consideration of steroids for endodontic pain. *Endod Topics.* 2002;3(1):41-51. https://doi.org/10.1034/j.1601-1546.2002.30105.x.
32. Zoorob RJ, Gender D. A different look at corticosteroids. *Am Fam Physician.* 1998;58(2):443-5.
33. Aggarwal V, Singla M, Rizvi A, Miglani S. Comparative evaluation of local infiltration of articaine, articaine plus ketorolac, and dexamethasone on anesthetic efficacy of inferior alveolar nerve block with lidocaine in patients with irreversible pulpitis. *J Endod.* 2011;37(4):445–9. https://doi.org/10.1016/j.joen.2011.01.016
34. Mohamed Safei Eldin M, Nabil Roshdy N, Yehia Fouda M. A Comparative Assessment of the Effect of Pretreatment Dexamethasone Versus Placebo on Post-Endodontic Pain and Success of Inferior Alveolar Nerve Block in Mandibular Molars with Symptomatic Irreversible Pulpitis: A Blinded Randomized Clinical Trial Therapeutic Study. *Acta Scientific Dental Sciences.* 2020;4(5):60–6. https://doi.org/10.31080/asds.2020.04.0836
35. Kaushik M, Sharma R, Moturi K, Podugu UK, George A, Mehra N. Comparing the Efficacy of Twin Mix and Lidocaine for Inferior Alveolar Nerve Blocks in Patients with Symptomatic Irreversible Pulpitis. *Anesth Prog.* 2020;67(4):207-13. https://doi.org/10.2344/anpr-67-03-11
36. Shokri M, Rafiee Node S, Mortazavi S. P71: The Effect of Pretreatment with Ibuprofen and Dexamethasone on the Effect of Nerve Block Lower Alveolar Marked in Irreversible Pulpitis Teeth. 2018.
37. Shahi S, Mokhtari H, Rahimi S, Yavari HR, Narimani S, Abdolrahimi M, et al. 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. *J Endod.* 2013;39(2):160-2. https://doi.org/10.1016/j.joen.2012.10.011
38. Bidar M, Mortazavi S, Forghani M, Akhlaghi S. Comparison of Effect of Oral Premedication with Ibuprofen or Dexamethasone on Anesthetic Efficacy of Inferior Alveolar Nerve Block in Patients with Irreversible Pulpitis: A Prospective, Randomized, Controlled, Double-blind Study. *Bull Tokyo Dent Coll.* 2017;58(4):231-6. https://doi.org/10.2209/tdcpublication.2016-0050
39. Kumar M, Singla R, Gill GS, Kalra T, Jain N. Evaluating Combined Effect of Oral Premedication with Ibuprofen and Dexamethasone on Success of Inferior Alveolar Nerve Block in Mandibular Molars with Symptomatic Irreversible Pulpitis: A Prospective, Double-blind, Randomized Clinical Trial. *J Endod.* 2021;47(5):705-10. https://doi.org/10.1016/j.joen.2021.01.005
40. Aggarwal V, Ahmad T, Singla M, Gupta A, Saatchi M, Hasija M, et al. Addition of 2 mg dexamethasone to improve the anesthetic efficacy of 2% lidocaine with 1:80,000 epinephrine administered for inferior alveolar nerve block to patients with symptomatic irreversible pulpitis in the mandibular molars: a randomized double-blind clinical trial. *J Dent Anesth Pain Med.* 2022;22:305. https://doi.org/10.17245/jdapm.2022.22(4).4.305.
41. Merrick MA, Jutte LS, Smith ME. Cold Modalities With Different Thermodynamic Properties Produce Different Surface and Intramuscular Temperatures *J Athl Training.* 2003:38(1):28-33.
42. Bleakley CM, Hopkins JT. Is it possible to achieve optimal levels of tissue cooling in cryotherapy? *Phys Ther Rev.* 2010;15(4):344–50. https://doi.org/10.1179/174328810X12786297204873
43. Al-Nahlawi T, Hatab TA, Alrazak MA, Al-Abdullah A. Effect of intracanal cryotherapy and negative irrigation technique on postendodontic pain. *J Contemp Dent Pract.* 2016;17(12). https://doi.org/10.5005/jp-journals-10024-1969
44. van der Westhuijzen AJ, Becker PJ, Morkel J, Roelse JA. A randomized observer blind comparison of bilateral facial ice pack therapy with no ice therapy following third molar surgery. *Int J Oral Maxillofac Surg.* 2005;34(3):281-6. https://doi.org/10.1016/j.ijom.2004.05.006
45. Schaser KD, Disch AC, Stover JF, Lauffer A, Bail HJ, Mittlmeier T. Prolonged superficial local cryotherapy attenuates microcirculatory impairment, regional inflammation, and muscle necrosis after closed soft tissue injury in rats. *Am J Sports Med.* 2007;35(1):93-102. https://doi.org/10.1177/0363546506294569
46. Vera J, Ochoa J, Romero M, Vazquez-Carcaño M, Ramos-Gregorio CO, Aguilar RR, et al. Intracanal Cryotherapy Reduces Postoperative Pain in Teeth with Symptomatic Apical Periodontitis: A Randomized Multicenter Clinical Trial. *J Endod.* 2018;44(1):4–8. https://doi.org/10.1016/j.joen.2017.08.038
47. N Franz BD, Iggo A. Conduction failure in myelinated and non-myelinated axons at low temperatures. vol. 199. 1968.
48. Prakash P, Gupta R. Cryotherapy as an adjunct to inferior alveolar nerve block in Symptomatic Irreversible Pulpitis: A randomised controlled clinical trial. IP Indian *J Conserv Endod.* 2022;7(1):16-23. https://doi.org/10.18231/j.ijce.2022.004
49. Elheeny AAH, Sermani DI, Saliab EA, Turky M. Cryotherapy and pain intensity during endodontic treatment of mandibular first permanent molars with symptomatic irreversible pulpitis: A randomized controlled trial. *Clin Oral Investig.* 2023;27(8):4585-93. https://doi.org/10.1007/s00784-023-05084-1
50. Koteeswaran V, Ballal S, Natanasabapathy V, Kowsky D. Efficacy of Endo-Ice followed by intrapulpal ice application as an adjunct to inferior alveolar nerve block in patients with symptomatic irreversible pulpitis—a randomized controlled trial. *Clin Oral Investig.* 2019;23(9):3501-7. https://doi.org/10.1007/s00784-018-2768-4
51. Aggarwal V, Singla M, Saatchi M, Gupta A, Hasija M, Meena B. Effect of Cooling of Lidocaine with Epinephrine on the Anesthetic Success of Supplementary Intraligamentary Injection after a Failed Primary Inferior Alveolar Nerve Block: A Randomized Controlled Trial. *Eur Endod J.* 2023;8(4):239-45. https://doi.org/10.14744/eej.2023.41275