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# Unveiling Analgesic Arsenal: A Comparative Study of perineural administration of Dexamethasone vs Ketorolac in Conjunction with Articainein Impacted Mandibular Third Molar Surgery

Dr. Prabhu Sankar K[1], Dr. Pavithra M[2], Dr. Vigneswaran T[3],
Dr. Priyadharsana PS[4],Dr. Vigneshwar S[5], Dr. Maneesha Sree GR[6]

[1]*Professor, Department of Oral and Maxillofacial Surgery, RVS Dental College and Hospital, Coimbatore, Tamilnadu, India*
[2]*Postgraduate Student, Department of Oral and Maxillofacial Surgery, RVS Dental College and Hospital, Coimbatore, Tamilnadu, India*
[3]*HOD, Professor, Department of Oral and Maxillofacial Surgery, RVS Dental College and Hospital, Coimbatore, Tamilnadu, India*
[4]*Reader, Department of Oral and Maxillofacial Surgery, RVS Dental College and Hospital, Coimbatore, Tamilnadu, India*
[5]*Senior Lecturer, Department of Oral and Maxillofacial Surgery, RVS Dental College and Hospital, Coimbatore, Tamilnadu, India*
[6]*Senior Lecturer, Department of Oral and Maxillofacial Surgery, RVS Dental College and Hospital, Coimbatore, Tamilnadu, India*

***Abstract:***
***Background****: Impacted mandibular third molar surgery is commonly associated with postoperative pain, swelling, and inflammation. Perineural drug administration has recently gained popularity in clinical practice, posing several advantages over conventional routes of drug administration. Hence, different additives can be used to reduce postoperative discomfort, no studies are comparing Dexamethasone and Ketorolac in Conjunction with Articaine, we have selected this study to evaluate the effect of perineural administration of Dexamethasone and Ketorolac in Conjunction with Articaine in Impacted Mandibular Third Molar Surgery.*
***Materials and Methods****: In this prospective randomized controlled study, 90 patients who needed surgical removal of an impacted mandibular third molar with a similar difficulty were randomly allocated into 3 groups. Group A patients received 1.7 ml of 4% Articaine with 1: 100,000 epinephrine; Group B received 1.7 ml of 4% Articaine with 1: 100,000 epinephrine + 1 ml/4 mg dexamethasone; and Group C received 1.7 ml of 4% Articaine with 1: 100,000 epinephrine + 1 ml/30 mg ketorolac tromethamine for inferior alveolar nerve block. The latency and duration of nerve block, postoperative pain, swelling, and trismus were compared between the groups.*
***Results****: The onset of anesthesia was significantly less in Group B, followed by Group C with a mean value of 58.6±29.6 s and 62.4±30 s, respectively, as compared to Group A. The duration of soft anesthesia was significantly higher in Group B patients, with a mean of 402 ±52 min, followed by 377 ±61 min in Group C and 345 ±17 min in Group A. An inter-group comparison was done between all the groups. When compared to group A, patients in groups B and C experienced significantly less postoperative pain, trismus, and swelling.*
***Conclusion:*** *The clinical performance of perineural dexamethasone with Articaine in controlling post-operative sequelae after mandibular third molar removal was superior to that of perineural ketorolac tromethamine with Articaine.*
***Key Word****: Third Molar, anti-inflammatory agents, dexamethasone, ketorolac tromethamine, Articaine, inferior alveolar nerve block*

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## I. Introduction

Surgical extraction of an impacted mandibular third molar is a procedure frequently performed by oral and maxillofacial surgeons. As the oral cavity is a highly vascularized area, predominantly constituted by loose connective tissue, a series of functional and structural alterations are expected postoperatively, which include pain, trismus, and swelling. Prostaglandins, leukotrienes, and thromboxane-related compounds are inflammatory mediators that cause postoperative swelling and edema. [1] Painless surgery with minimal postoperative discomfort is the ultimate aim of the surgeon.

Lignocaine, bupivacaine, articaine, and ropivacaine are the local anesthetic (LA) agents commonly used

in minor oral surgeries. Among these agents, articaine hydrochloride (Chemically-3-N-Propylamino-propprionylamino-2-carbomethoxy-4-methylthiophene hydrochloride), initially known as carticaine in 1969, is a hybrid molecule belonging to the amide class of LA possessing both amide and ester characteristics, containing a thiophene ring as its lipophilic moiety, and was first marketed in 1976 by Germans. The pharmacological nature of this anesthetic solution is responsible for its principal advantages, which include higher potency (1.5 times that of lidocaine) and improved lipid solubility. [2] In terms of the latency and efficacy of anesthesia, several studies agree that 4% articaine is a safe alternative to 2% lignocaine for the extraction of mandibular third molars and other dental procedures. [3,4,5]

Various adjuvants, like dexmedetomidine, fentanyl, dexamethasone, clonidine, ketorolac, magnesium sulfate, etc., were added to localanesthetics to improve their latency and efficacy. [6,7]Among these, dexamethasone and ketorolac tromethamine are used effectively to reduce postoperative complications after impacted third molar surgery in the field of oral surgery in various dosages and administration routes. [8,9,10]

Dexamethasone is a long-acting corticosteroid that has a potent anti-inflammatory effect and aids in promoting the synthesis of regulatory proteins such as lipocortin and vasocortin during the inflammatory process.[11-13] Non-steroidal anti-inflammatory drugs (NSAIDS) are drugs that act by inhibiting the cyclooxygenase (COX) enzyme involved in the synthesis of chemical mediators of inflammation. [14,15] Nsaids are the most effective anti-inflammatory agents and are commonly used in oral surgery to decrease postoperative swelling and trismus, delay the onset, and reduce the intensity of pain following minor oral surgery with fewer undesirable adverse effects. [16-18] Ketorolac tromethamine is a nonselective COX inhibitor and has analgesic, anti-inflammatory, and antipyretic properties. [19]

To potentiate the effect of local anesthetics, site-specific drug delivery to the operative site by administering local anesthetic agents mixed with steroidal agents and NSAIDS has also been reported in the literature.[20-24]Our study was designed to assess and compare the effectiveness of perineural administration of Dexamethasone vs. Ketorolac in conjunction with Articaine in surgical removal of impacted mandibular third molar surgery.

## II. Material and Methods

**Subjects and selection method**: The study population was drawn from patients who presented to the Department of Oral and Maxillofacial Surgery at RVS Dental College and Hospital, Kumaran Kottam Campus, Kannampalayam, Coimbatore, for surgical removal of impacted teeth from September 2023 to November 2023. Patients who met up inclusion criteria were randomly divided into three groups.

Group A: 1.7 ml of 4% articaine (Septanest, Septodont Healthcare) with 1: 100,000 epinephrine

Group B: 1.7 ml of 4% articaine (Septanest, Septodont Healthcare) with 1: 100,000 epinephrine + 1 ml/4 mg dexamethasone (Decdon,Wockhardt, India).

Group C: 1.7 ml of 4% articaine (Septanest, Septodont Healthcare) with 1: 100,000 epinephrine + 1 ml/30 mg ketorolac tromethamine(NEON Laboratories Ltd.)

**Inclusion criteria:**

The inclusion criteria were ASA [American Society of Anaesthesiologists] Class I subjects aged between 18 and 28 years with impacted mandibular third molars of similar difficulty index, Class II and position B according to Pell and Gregory's classification, and willing to take part in the study were included.

**Exclusion criteria:**

The exclusion criteria were the presence of acute infection or swelling at the time of surgery, a previous history of allergy to LA solution or NSAIDS, associated pathology with impacted third molars, pregnant or lactating females, subjects with any systemic disease, and also those who used non-trial drugs during the study period.

**Procedure methodology**

Following approval from the institutional ethical committee, a randomized prospective clinical trial was carried out. After receiving written informed consent, 90 patients who needed surgical removal of an impacted mandibular third molar with a similar difficulty index were enrolled in the study.

All 90 subjects were randomly allocated into three groups (n = 30 in each group).

Group A: 1.7 ml of 4% articaine with 1: 100,000 epinephrine
Group B: 1.7 ml of 4% articaine with 1: 100,000 epinephrine + 1 ml of 4 mg dexamethasone.
Group C: 1.7 ml of 4% articaine with 1: 100,000 epinephrine + 1 ml of 30 mg ketorolac tromethamine

The patients and operator were blinded regarding the type of LA used, and a single qualified operator performed all the surgical procedures.Each patient was administered the inferior alveolar nerve block with the local anesthetic solution according to the allotted group. The LA solution was injected using an Unolok aspirating leur-lock syringe (HMD, India) fitted with a 26-gauge needle at a rate of 1 ml/min by the same surgeon, depending upon the groups.The latency was measured from the time after full needle withdrawal until the onset of subjective signs of anesthesia, and the duration of anesthesia was recorded as the time between the initialpatient perception of the anesthetic effect and the moment as the effect began to fade, using a 10-point Visual Analog Scale. The need to re-anesthetize the site was also recorded.

**Surgical procedure and clinical study parameters**

Under standard aseptic conditions, a Ward's incision was placed using a no-15 blade, the mucoperiosteal flap was elevated, and bone guttering was done using a 702-surgical carbide fissure bur (SS White, Lakewood, NJ, USA) on a straight surgical handpiece and micro-motor with copious saline (0.9 percent) irrigation. Tooth sectioning was done if required. Wound closure with a simple interrupted 3-0 black braided silk suture. The time required for the surgical procedure was recorded, from incision placement to wound closure, using a digital stopwatch. Post-extraction measures were instructed, followed by prescribing 500 mg amoxicillinthrice a day and 400 mg ibuprofen twice a day for 5 days.

Postoperative pain was measured using a 10-point VAS score, facial swelling was measured from the tragus to the angle of the mouth,and mouth opening (MO) was recorded using a Vernier caliper for all the patients preoperatively and postoperatively on the 1st, 3rd, and 7th days.

**Statistical analysis**

The data was assessed using analysis of variance (ANOVA) to analyze the significance of the collected data with a significant p-value ($P < 0.05$).

## III. Result

A total of 90 patients were included in this study, of whom 39 were females and 51 were males. The mean procedural time for patients in Groups A, B, and C was 25±5 minutes, 25 ±4 minutes, and 24±6 minutes, respectively, with no statistical difference. All90 inferior alveolar nerve blocks were successful without the need for re-anesthesia. The onset of anesthesia was significantly less in Group B, followed by Group C with a mean value of 58.6±29.6 s and 62.4±30s respectively, as compared to the control groups. (Graph 1, Table 1) The duration of soft anesthesia was significantly higher in Group B patients, with a mean of 402 ±52 min, followed by 377±61 min in Group C, and 345 ±17 min in Group A (Graph 2, Table 2). An inter-group comparison was done between all the groups. Postoperative VAS was higher in patients from Group A, followed by Group B and Group C. (Graph 3, Table 3) In the study groups, facial swelling reached its peak on the 1st postoperative day and gradually decreased until the 7th postoperative day, in contrast to the control group, where there was a gradual increase in swelling up to the 3rd postoperative day, followed by a reduction on the 7th postoperative day (Graph 4, Table 4). There was a marked reduction in MO among patients in group A when compared to groups B and C. (Graph 5, Table 5) All the patients had a complete recovery from anesthesia without any complications in all the groups.

**Graph no 1:** Graph showing latency of the local anaesthetic (LA) solution among groups

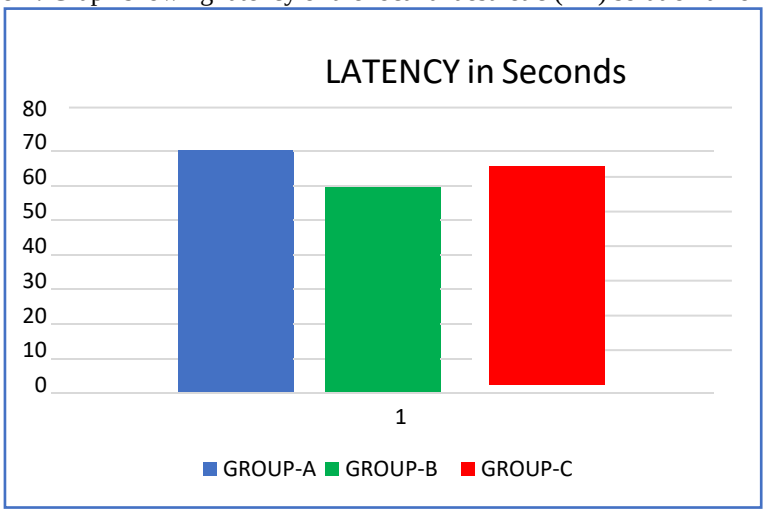

**Table no 1:** Inter-group comparison to assess the latency of anaesthesia using Analysis of variance (ANOVA) between the groups.

| ANOVA | | | | | |
|---|---|---|---|---|---|
| | Sum of Squares | Degree of freedom | Mean Square | F | Sig. |
| Between Groups | 2745.867 | 2 | 1372.933 | 3.380 | 0.039 |
| Within Groups | 35340.533 | 87 | 406.213 | | |
| Total | 38086.400 | 89 | | | |

**Graph no 2:** Graph showing the duration of soft tissue anaesthesia among groups

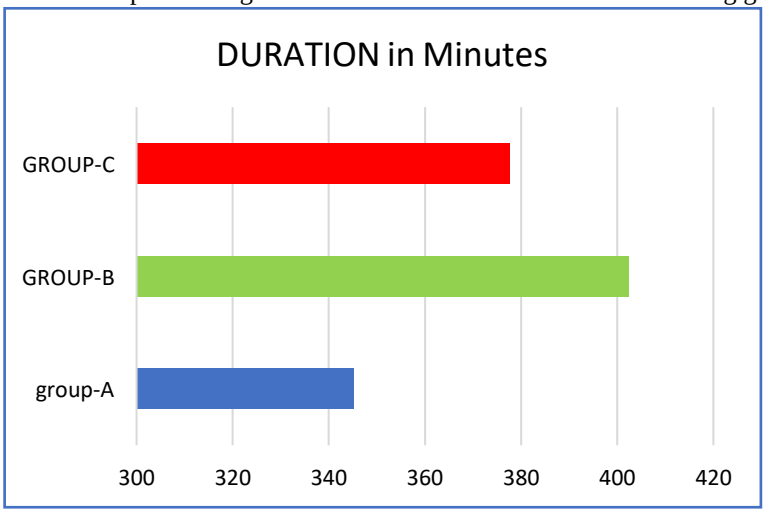


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**Table no 2:** Inter-group comparison to assess the duration of anesthesia using Analysis of variance (ANOVA) between the groups

| **ANOVA** | | | | | |
|---|---|---|---|---|---|
| | Sum of Squares | Degree of freedom | Mean Square | F | Sig. |
| Between Groups | 49431.267 | 2 | 24715.633 | **28.399** | **0.000** |
| Within Groups | 75717.233 | 87 | 870.313 | | |
| Total | 125148.500 | 89 | | | |

**Graph no 3:** Graph showing the post-operative pain among groups.

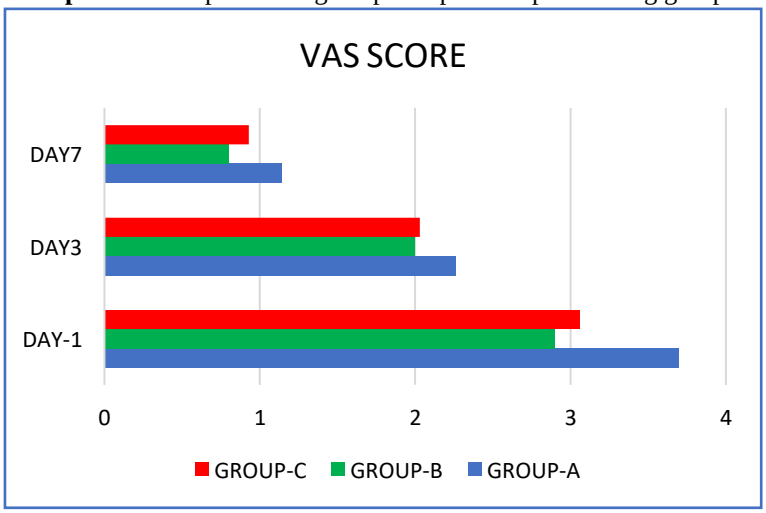

**Table no 3**: Inter-group comparison to assess the post-operative VAS score using Analysis of variance (ANOVA) between the groups

| **Day 1** | | | | | |
|---|---|---|---|---|---|
| | Sum of squares | Degree of freedom | Mean square | F | Sig. |
| Between groups | 12.689 | 2 | 6.344 | **5.311** | **.007** |
| Within groups | 103.933 | 87 | 1.195 | | |
| Total | 116.622 | 89 | | | |
| **Day-3** | | | | | |
| | Sum of squares | Degree of freedom | Mean square | F | Sig. |
| Between groups | 1.089 | 2 | .544 | **0.431** | **0.651** |
| Within groups | 109.800 | 87 | 1.262 | | |
| Total | 110.889 | 89 | | | |
| **Day 7** | | | | | |
| | Sum of squares | Degree of freedom | Mean square | F | Sig. |
| Between groups | .822 | 2 | .411 | **0.717** | **0.491** |
| Within groups | 49.900 | 87 | .574 | | |
| Total | 50.722 | 89 | | | |

**Graph no 4:** Graph showing the post-operative swelling among groups

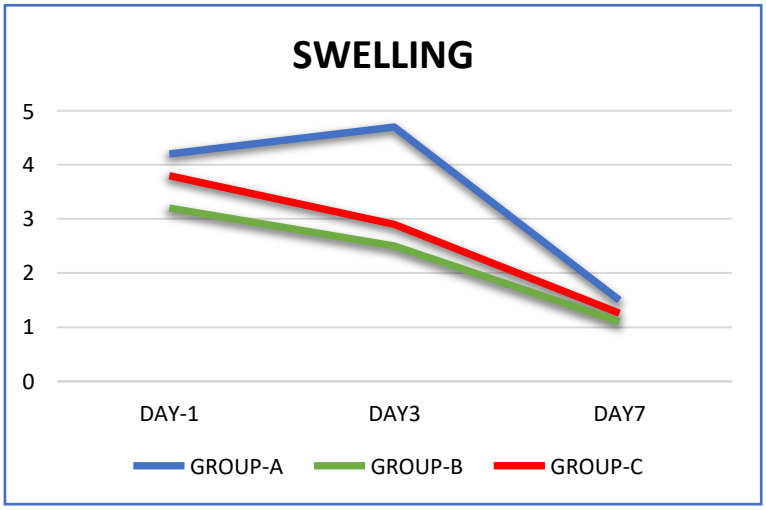


**Table no 4**: Inter-group comparison to assess the post-operative swelling using Analysis of variance (ANOVA) between the groups

| **Day-1** | | | | | |
|---|---|---|---|---|---|
| | Sum of squares | Degree of freedom | Mean square | F | Sig. |
| Between groups | 9.756 | 2 | 4.878 | **5.267** | **0.007** |
| Within groups | 80.567 | 87 | .926 | | |
| Total | 90.322 | 89 | | | |
| **Day-3** | | | | | |
| | Sum of squares | Degree of freedom | Mean square | F | Sig. |
| Between groups | 83.356 | 2 | 41.678 | **36.987** | **0.000** |
| Within groups | 98.033 | 87 | 1.127 | | |
| Total | 181.389 | 89 | | | |
| **Day-7** | | | | | |
| | Sum of squares | Degree of freedom | Mean square | F | Sig. |
| Between groups | 3.356 | 2 | 1.678 | **2.811** | **0.066** |
| Within groups | 51.933 | 87 | .597 | | |
| Total | 55.289 | 89 | | | |

**Graph no 5:** Graph showing the restricted mouth opening among groups.

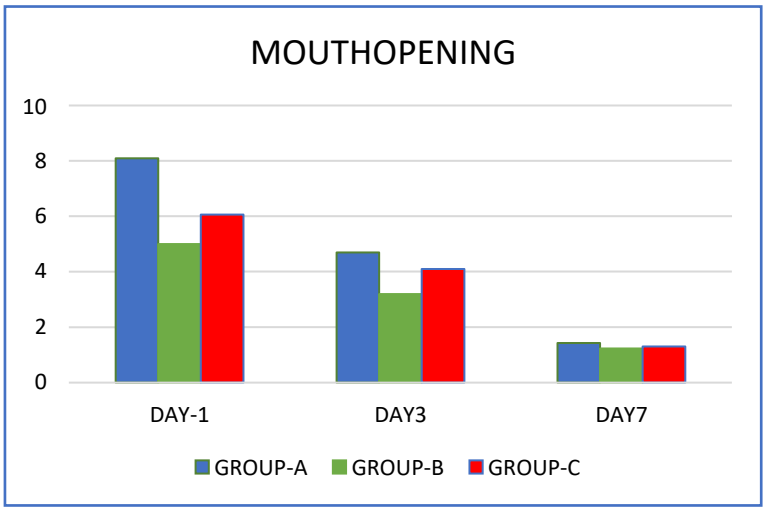


**Table no 5:** Inter-group comparison to assess the post-operative mouth opening using Analysis of variance (ANOVA) between thegroups

| **Day-1** | | | | | |
|---|---|---|---|---|---|
| | Sum of squares | Degree of freedom | Mean square | F | Sig. |
| Between groups | 148.822 | 2 | 74.411 | **31.340** | **0.000** |
| Within groups | 206.567 | 87 | 2.374 | | |
| Total | 355.389 | 89 | | | |
| **Day-3** | | | | | |
| | Sum of squares | Degree of freedom | Mean square | F | Sig. |
| Between groups | 34.200 | 2 | 17.100 | **14.907** | **0.000** |
| Within groups | 99.800 | 87 | 1.147 | | |
| Total | 134.000 | 89 | | | |
| **Day-7** | | | | | |
| | Sum of squares | Degree of freedom | Mean square | F | Sig. |
| Between groups | .622 | 2 | .311 | **0.361** | **0.698** |
| Within groups | 75.033 | 87 | .862 | | |
| Total | 75.656 | 89 | | | |

## IV. Discussion

From the results, it is evident that admixing 4mg dexamethasone and 30 mg ketorolac tromethamine to conventional articaine proved to be beneficial to the patients compared to conventional articaine alone, especially in terms of faster onset, longer duration of anesthesia, and the other parameters assessed. On comparing the perineural administration of 4mg dexamethasone admixed with articaine, 30 mg ketorolac tromethamine admixed with articaine, and articaine alone, it was found that the dexamethasone group was superior to the ketorolac group in all evaluated parameters.

Dexamethasone, which is a synthetic glucocorticoid and potent anti-inflammatory agent, has gained interest recently for its role as an adjuvant analgesic along with perineural blockade as well as other regional and general anesthesia techniques.[25] Several potential mechanisms of action included suppression of C-fiber transmission of pain signals and reduction of neuronal discharge by the nerve cell. [26] Several RCTs have evaluated the effects of perineural as well as intravenous dexamethasone as adjuvants to peripheral nerve blocks and demonstrated that both perineural and intravenous dexamethasone caused prolonged sensory blockade and prolonged duration of postoperative analgesia when compared to placebo. [27,28]

Ketorolac is a perineural NSAID that provides analgesia by inhibiting prostaglandin synthesis. Studies have proven that ketorolac alone produces adequate pain relief when administered parenterally or via wound infiltration. [29] Some clinical studies proved the efficacy of ketorolac to prolong the duration of analgesia when administered as an adjuvant with LA in perineural blockade and also IVRA. [30]

Dexamethonized LA solution is a novel method of intra-space drug administration to achieve anesthesia and analgesia that was popularized by Bhargava et al. Is known to have several advantages over conventional

routes. Administration of steroids following third molar surgery has beneficial effects postoperatively as corticosteroids are involved in suppressing the inflammatory mediators at the injury site, suppressing acute inflammation. [20.] Literature evidence highlights the effectiveness of dexamethasone after third molar surgery. [21,31,32] In the present study, it was observed that patients who received dexamethasonized LA showed improved quality of life postoperatively, as demonstrated by the decreased VAS score and facial swelling as compared to the ketorolac group and control group.

LA solutions with a vasopressor have a pH of approximately 3.5. Malammed SF emphasized that the LA must be deposited near the nerve membrane through a proper injection technique, and it must cross the nerve membrane to block sodium channels to obtain adequate anesthesia. The solution should exist in RN, the uncharged form that is lipid-soluble and able to penetrate the neural sheath and membrane. Alkalinization or buffering of LA solution alters its pH to a more basic solution, which will increase the RN as compared to the charged RNH+, which is water-soluble, resulting in various advantages such as a lesser sting on injection and an enhanced onset of anesthesia.[33] The present study showed similar results that the patients in the dexamethasone group and the ketorolac group had a faster onset and longer duration of anesthesia, with improved quality of life postoperatively.

The chemical stability of dexamethonized LA has been validated using a double-beam ultraviolet (UV) spectrometry study. It was observed that physical compatibility and pH between LA and dexamethasone solutions were similar, along with no change in the properties or stability of the active molecules (LA component, epinephrine, and dexamethasone). [34] The author also opined that intra- space administration of dexamethasone can achieve plasma concentrations similar to those achieved when the drug is administered intramuscularly. [35,36]

Available studies point to the efficacy of ketorolac tromethamine in controlling moderate to severe pain, with an effective reduction ofPGE2 and TxB2 levels in the first hours of the postoperative period. However, none of these studies evaluated their analgesic effect ata single dose for a period greater than 12 hours. [37,38] Other clinical trials comparing the analgesic effects of NSAIDs and corticosteroids in several pharmacological protocols showed statistically similar results for both classes [39,40,41] or higher for corticosteroids [42], in agreement with the results obtained in this study. The formation of swelling after surgical trauma is mainly related to the vascular events of the inflammatory process, which promote vasodilation and increase vascular permeability, with consequent changes in the local hydrostatic and osmotic pressures. [43]. The expected peak for swelling usually occurs between 48 and 72 hours after the procedure. [40,42], similar results to those shown in the present study.

Corticosteroids are more effective than NSAIDs in controlling swelling. [11] This is probably due to the combined action of lipocortin promotion, which acts on the inhibition of phospholipase A2, and vasocortin, a histamine release inhibitor, which provides wider suppression of the inflammatory process in addition to inhibiting the synthesis of eicosanoids [11]. Corticosteroids with intermediate action duration did not present a significant difference in reducing swelling when compared to NSAIDs [40]. However, dexamethasone, which has a longer-lasting action, provides a greater reduction of swelling even when compared to methylprednisolone[44]. In this sense, the long-term anti-inflammatory action seems to play an important role in controlling swelling in view of its late developmentin acute inflammation.

The mechanism by which dexamethasonized LA improves postoperative outcomes has been proposed by Bhargava et al. Dexamethasone blocks superoxide production and lysosomal enzyme release in human neutrophils, inhibiting the functional degranulation response. Admixing it with LA causes the solution to become basic (pH = 6) as compared to the conventional LA with vasoconstrictor, which is more acidic (pH range = 3.5–4.5), enhancing the onset and duration of anesthesia. It was also proposed that there is an increase in the activity of inhibitory potassium channels through glucocorticoid receptors on nociceptive fibers and the vasoconstriction property of dexamethasone. [45]

To support this evidence, Williams et al. have concluded that lower doses of dexamethasone administered perineurally can cause significant clinical outcomes, and larger doses did not exhibit additional benefits, and the adverse effects on neural conduction were dose-dependent.[46,47,48] No known incidence of neurotoxicity, complications, or adverse effects in humans has been documented in the literature for the use of peri-neural dexamethasone. [49]Further studies need to be conducted involving a larger study population to establish definitive results along with the chemical stability of articaine when mixed with dexamethasone and ketorolac, which is beyond the scope of this study.

## V. Conclusion

The clinical performance of dexamethasone in controlling postoperative inflammatory events was superior to that of ketorolac tromethamine in all evaluated parameters, which seems to be related to the particularities of its broad anti-inflammatory action mechanism and prolonged half-life. Thus, it is a more accessible and suitable option for preemptive administration in oral surgery.

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