RESEARCH
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EFFECTS OF TEMPERATURE CHANGES ON THE PAIN EXPERIENCED, ONSET AND DURATION OF LOCAL ANAESTHESIA IN PATIENTS UNDERGOING SURGICAL EXTRACTION OF MANDIBULAR THIRD MOLARS: A PROSPECTIVE CLINICAL TRIAL

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Abstract
Background: Lignocaine, a widely used anesthetic, is a weakly basic salt that exists in its unionized form at the ideal temperature and pH. The change in temperature effects the dissociation constant of the drug, which causes more lignocaine to exist in its ionized form. This study explores how temperature changes of the anesthetic agent affect its pharmacodynamics and action, which expresses itself in terms of onset, duration of action, and pain experienced.
Aim and Objectives:
Aim: This study aims to study the effects of using local anesthesia cooled to 4'C as opposed to local anesthesia at room temperature, for the surgical extraction of impacted mandibular molars.
Objectives:
Pain on administration
Onset and duration of action
Material and Methods: This is a prospective, split-mouth study conducted at Saveetha Dental College during a period of 1 month. 40 patients requiring bilateral surgical extraction of mandibular third molars were taken up for the study. Surgical extraction was done using LA at room temperature in the first appointment, and cooled LA in the next appointment. The VAS score, onset and duration of action were recorded and compared.
Results: A small (but significant) change can be observed in the pain experienced during the administration of local anesthesia at 4'C and local anesthesia at room temperature. There was a significant increase in the Onset of action and the duration of action.
Conclusion: Local anesthesia cooled to 4'C has no effect on the pain experienced by the patient, but prolongs the onset and duration of action.
Keyword: Local Anesthesia, Onset Of Action, Duration Of Action, Surgical Extraction, Temperature Changes

INTRODUCTION

Local anesthetics play a pivotal role in modern medicine, facilitating numerous medical procedures by temporarily blocking the sensory and motor functions of nerve cells.
With Ophthalmologist Carl Koller using cocaine to anesthetize his patient's eyes in 1884, [1] the use of local anesthesia has gone through; and will continue to go through several developmental changes. Among these anesthetics, lidocaine stands as one of the most widely used agents for its efficacy and safety. Lidocaine, a member of the amide class of local anesthetics, is known to last around 170 to 190 minutes [2]. It functions by inhibiting voltage-gated sodium channels in neuronal axons and nerve fiber bundles, thereby preventing the conduction of nerve impulses. [3] The practical utility of lidocaine extends to various clinical domains, including surgery, dentistry, and emergency medicine. For decades, healthcare practitioners have sought ways to optimize the pharmacokinetic properties of lidocaine, such as its onset and duration of action, to enhance patient comfort, safety, and procedural outcomes.
Lidocaine, first synthesized in 1943 by Nils Lofgren [4], revolutionized the practice of local anesthesia. It rapidly became a cornerstone of medical and dental procedures due to its efficacy, safety, and versatility. The pharmacological mechanism of lidocaine involves its ability to block sodium channels in nerve cells, preventing the conduction of action potentials and, consequently, the perception of pain. Its use extends to various

medical fields, including surgery, obstetrics, and pain management. [6, 7]

The fundamental property of lidocaine that influences its pharmacodynamics is its ability to dissociate into protonated (non-ionized) and deprotonated (ionized) forms. This dissociation is governed by the drug's pKa, which represents the pH at which half of the molecules exist in each form. [5] A factor that has received less attention but holds significant potential to impact the pharmacokinetics of lidocaine is temperature. Temperature can modulate the pKa of drugs, influencing the ratio of protonated to deprotonated forms, which, in turn, affects the drug's onset and duration of action.

This study aims to investigate the effects of cooling lidocaine solution to 4°C, a temperature lower than typical clinical administration, on the onset and duration of its action. We hypothesize that cooling lidocaine to this temperature will shift the equilibrium between its protonated and deprotonated forms, ultimately influencing its pharmacodynamic properties. Understanding how temperature affects the pharmacokinetics of lidocaine is of paramount importance, as it may provide valuable insights for optimizing its clinical utility and patient outcomes.

Lidocaine is a weak base with a pKa of approximately 7.9. [8, 10] This means that it predominantly exists in its protonated form (LH+) at lower pH values (acidic conditions) and in its deprotonated form (L-) at higher pH values (alkaline conditions). The balance between these forms is essential for the drug's pharmacological activity. The protonated form is hydrophobic and less able to penetrate cell membranes, while the deprotonated form is charged and hydrophilic, facilitating penetration into nerve cells.

The pKa of a compound is temperature-dependent. As the temperature decreases, the pKa tends to decrease as well. [9] This means that cooling lidocaine can alter the equilibrium between its protonated and deprotonated forms. At a lower temperature, there is a greater proportion of protonated lidocaine molecules, which are less likely to penetrate nerve cell membranes efficiently.

Onset of Action:

The onset of action of a local anesthetic is the time it takes for the drug to reach the target site and exert its intended effect. For lidocaine, this means blocking the sodium channels in nerve cells. The rate at which lidocaine can achieve this is influenced by factors like the concentration of the drug and the proportion of lidocaine in its deprotonated form (L-), which is crucial for its cellular penetration. [11]

Duration of Action:

The duration of action of a local anesthetic is the period during which it remains effective at the target site. After achieving the desired effect, the drug must continue to inhibit nerve cell conduction. Factors like metabolism, redistribution, and elimination can influence the duration of action. Cooling lidocaine may influence this parameter by maintaining a greater proportion of protonated molecules, which could resist metabolism and redistribution.

AIM:

This study aims to study the effects of using local anesthesia at 4’C as opposed to conventional local anesthesia for surgical extraction of impacted mandibular molars.

OBJECTIVES:

The objectives of this study are to determine:

The average VAS score in buffered versus unbuffered local anesthetic solution

To determine the average onset and duration of action of local anesthesia

METHODOLOGY:

This is a prospective, single-blinded clinical trial with the cases to control allocation ratio as 1:1. This study was carried out at the Department of Oral and Maxillofacial Surgery at Saveetha Dental College and Hospital. Clearance was obtained from the Institutional Human Ethical Committee, the IHEC number or this study is **IHEC/SDC/OMFS-2207/23/290**

Based on previous studies evaluating similar characteristics, G power version 3.1 0. software was used to calculate the sample size for the power of the study to be 95%.

A total of 40 patients requiring inferior alveolar nerve block for the surgical extraction of impacted mandibular third molars were taken up for the study. All participants were systemically healthy adults, without any co-morbidities who were diagnosed with unilaterally impacted mandibular third molars. Surgical extraction of teeth was done at two different appointments, one week.

Inclusion criteria:

Patient requiring unilateral surgical extraction of impacted mandibular third molars (Pell and Gregory classification- Position A,B,C and Class I,II,III)

Patients within 18 years to 40 years of age.

Patient with no active infection/ associated abscess/ active pus discharge/ trismus

Systemically healing patients without any comorbidities, such as diabetes, hypertension, hepatic or renal disorders, history of peptic ulcers, patients with a history of cardiac disorders.

Exclusion criteria:

Patients with soft-tissue impactions, not requiring any bone-guttering.

Patient requiring non-surgical extraction of mandibular third molars

Patient below 18 years of age or above 40 years of age

Patient with active infection/ associated abscess/ active pus discharge/ trismus

Systemically healing patients without any comorbidities, such as diabetes, hypertension, hepatic or renal disorders, history of peptic ulcers, patients with a history of cardiac disorders.

Randomization and Blinding:

As the patients entered the clinic, they underwent a preliminary examination by a dentist and a thorough medical history and necessary radiographs were taken.

In case the eligibility criterion was met, the patient was explained about the ongoing study and informed consent was taken.

The dentists handed the participants a sealed envelope with a number inside. The numbers were generated and then randomly allocated to the cases or control group using Random Allocation Software (RAS version 3.0)

This study was double blinded and neither the patient, nor the clinician was aware of the group the patient was being allocated to.

METHODOLOGY:

The participants were given local anaesthetic solution as inferior alveolar, long buccal, and lingual nerve block. Immediately after the nerve block was given, the participants were asked to rate the pain experienced on a VAS scale. The onset of action of anesthesia was measured by probing the buccal mucosa on the region of the mandibular first molar and the vermillion border of the ipsilateral side of the lower lip using a blunt periodontal probe by applying gentle pressure. Probing was started 30 seconds after administration of local anaesthesia and done every 5 seconds, till the patient reported complete numbness of both the sites. This time was measured as the time of onset of action of local anesthesia. The procedure was carried out.

Once the procedure was finished, the patient was discharged from the clinic with strict instructions to call and inform the clinician as soon as the effects of the anesthetic agent wear-off and the need for rescue analgesics is felt. This time period was noted as the duration of anesthesia.

Cases: The cases received 2% lignocaine with 1:80,000 adrenaline cooled to 4'C as local anestheisa. This was achieved by placing the lignocaine in a refrigerator with the temperature set at 4'C. The vial was removed right before the solution was loaded in a syringe and injected into the patient.

Controls: The controls received 2% lignocaine with 1:80,000 adrenaline at room temperature, which is 22'C as local anestheisa.

Outcomes measured:

Primary Outcome Measured:

Pain experienced by the participants at the time of injection.

Pain experienced during the procedure.

Secondary Outcomes Measured:

Onset of action of local anesthesia

Duration of Action of local anesthesia.

The Visual Analog Scale (VAS) was used for the measurement of pain.

The VAS is a validated tool for measuring pain intensity, with scores ranging from 0 to 10, where 0 represents no pain and 10 represents the worst pain imaginable. Participants were instructed to mark their pain intensity on a 10 cm horizontal line corresponding to their perceived level of pain. Figure 1 shows the VAS scale for pain measurement.

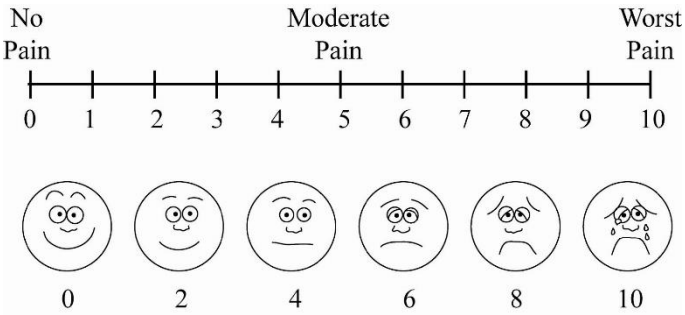


Figure 1: VAS scale for pain measurement

STATISTICAL ANALYSIS:

IBM SPSS statistics version 23 was used to analyse the collected data. Descriptive statistics were used to summarize the demographic characteristics of the participants. The mean VAS scores at each time point were compared between the experimental and control groups using independent t-tests. The significance level was set at $p < 0.05$.

Mann-Whitney U Test was done to analyse the data and draw out conclusions.

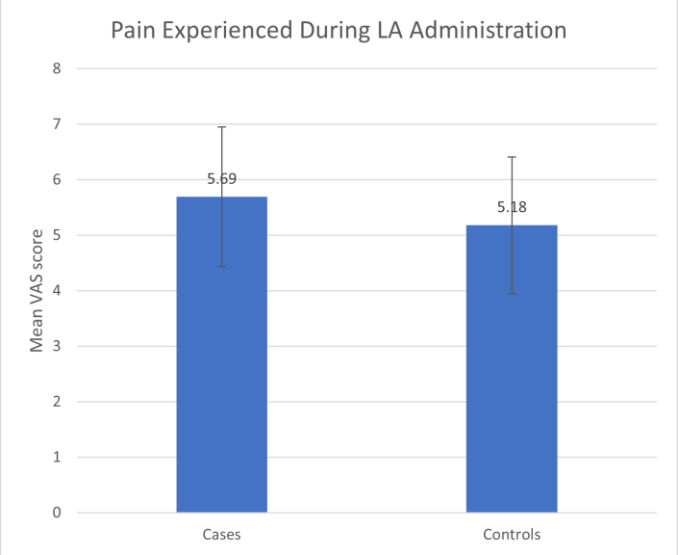
RESULTS

Table 1: VAS score after LA administration

Group	Minimum	Maximum	Mean	SD
Cases	3.00	8.00	5.69	1.26
Controls	4.00	8.00	5.18	1.23

The table 1 shows the VAS score after LA administration.

Graph 1: Pain experienced during LA administration



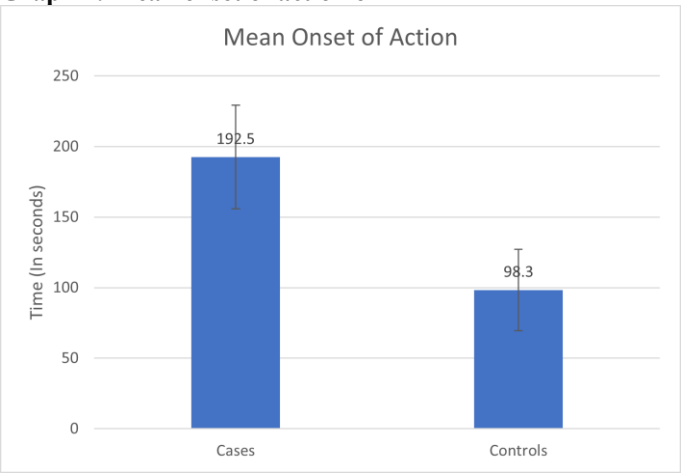
It can be observed that the mean VAS score after the administration of LA is 5.18 for controls, while it is 5.69 for cases. Hence cooling of the vial to 4'C causes a mild increase in the pain experienced by the patient (graph1).

Table 2: Onset of action (in seconds)

Group	Minimum	Maximum	Mean	SD
Cases	40	300	192.5	36.74
Controls	35	180	98.3	28.76

The table 2 shows the Onset of action (in seconds)

Graph 2: Mean onset of action of LA



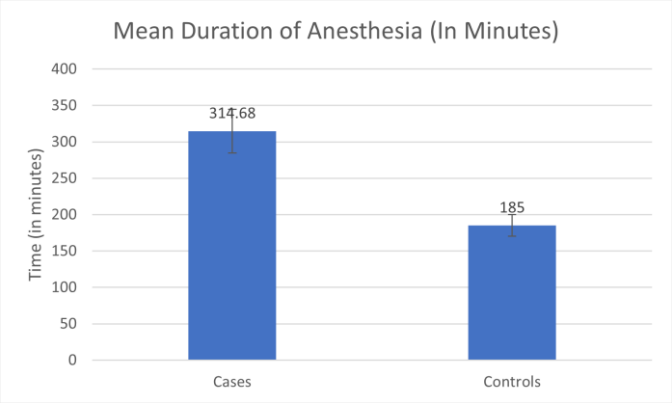
The mean onset of action is 192.5 for cases, while it is 98.3 for the controls. Hence there is a drastic increase in the time taken for the local anesthetic agent to act when it is cooled to 4'c as opposed to when it is at room temperature (graph 2).

Table 3: Duration of action (in minutes)

Group	Minimum	Maximum	Mean	SD
Cases	140	360	314.68	30.24
Controls	120	250	185.00	14.80

The table 3 shows the Duration of action (in minutes)

Graph 3: Duration of action of LA



The Mean duration of anesthesia is also increased when the anesthetic vial is cooled to 4'C. The mean duration of action is 185 minutes for cases, while it is 314.68 minutes for the controls. Hence lidocaine cooled to 4'C has a much longer duration of action as compared to lidocaine at room temperature. Graph 3 shows the Duration of action of LA

TABLE 4: Comparison between study and control groups using Mann-Whitney U test

Parameter	Mean Difference	Mann-Whitney U test	Z-value	p-value
VAS score during anesthesia	-0.51	1375	6.778	<0.001
Onset of Action (in seconds)	94.2	468	8.564	<0.001
Duration of Anesthesia (in minutes)	129.68	1576	10.378	<0.001

The table 4 shows the Comparison between study and control groups using Mann-Whitney U test

DISCUSSION:

The results of our randomized controlled trial investigating the effects of cooling lidocaine to 4°C compared to room temperature (22°C) have provided valuable insights into the impact of temperature on the onset and duration of action of the local anesthetic. These findings hold significant clinical relevance, as they may influence the practice of local anesthesia across various medical fields.

A systemic review done by Tirupathi SP et al [12] show that heating up lidocaine can help reduce pain perception by the patient. Similar results were obtained by studies done by Goodman A et al, Gandhi et al [13-15] showed that an increase in the temperature decreases the onset of action of lignocaine. Our study yielded intriguing results regarding the onset and duration of action of lidocaine when cooled to 4°C. We observed that cooling lidocaine led to a significant increase in the onset of action compared to lidocaine administered at room temperature. Additionally, the duration of action was prolonged when lidocaine was cooled.

The observed increase in the onset and duration of action when lidocaine is cooled can be explained by its pH-dependent dissociation, which is influenced by temperature. Cooling lidocaine to 4°C results in a shift of the equilibrium between protonated (LH+) and deprotonated (L-) forms toward the protonated form. At lower temperatures, a greater proportion of lidocaine exists as LH+, which is less likely to penetrate nerve cell membranes efficiently. This delayed cellular penetration of the protonated form accounts for the increased onset of action, as it takes more time for the drug to reach its target site, i.e., the sodium channels in nerve cells.

Additionally, the prolonged duration of action can be attributed to the increased proportion of protonated lidocaine. This form is less likely to be metabolized and redistributed, which allows it to persist at the target site for a longer period, continuing to block nerve cell conduction.

The implications of these findings for clinical practice are noteworthy. Optimal onset and duration of action of local anesthetics are critical for the comfort of patients and the success of various medical and dental procedures. The observed effects of cooling lidocaine could have significant clinical advantages,

While the findings of this study present intriguing possibilities for enhancing the clinical utility of lidocaine through cooling, safety remains a paramount concern. It is essential to consider the potential risks and challenges associated with implementing cooled lidocaine in clinical practice.

CONCLUSION:

In conclusion, our randomized controlled trial has demonstrated that cooling lidocaine to 4°C can significantly increase the onset and duration of action of the local anesthetic. While this holds substantial promise for clinical practice, safety concerns and logistical challenges must be considered when implementing cooled lidocaine. Future research should focus on optimizing temperature, conducting clinical trials, and exploring combination therapies to further enhance anesthesia. Ultimately, this study has opened the door to potential improvements in local anesthesia, with the potential to benefit both patients and healthcare providers.

Through this study, it can be safely concluded that lowering the temperature of local anesthesia to 4'C increases the pain perception by the patient, increases the onset and duration of action of the anesthetic agent.

References

1. *Haas DA: An update on local anesthetics in dentistry. J Can Dent Assoc. 2002, 68:546-51.*
2. *Best CA, Best AA, Best TJ, Hamilton DA: Buffered lidocaine and bupivacaine mixture - the ideal local anesthetic solution. Plast Surg (Oakv). 2015, 23:87-90. 10.4172/plastic-surgery.1000913*
3. *Singh P: An emphasis on the wide usage and important role of local anesthesia in dentistry: a strategic review. Dent Res J (Isfahan). 2012, 9:127-32. 10.4103/1735-3327.95224*
4. *Calatayud J, González A. History of the development and evolution of local anesthesia since the coca leaf.*

Anesthesiology. 2003 Jun;98(6):1503-8. doi: 10.1097/00000542-200306000-00031. PMID: 12766665.

5. *Scarfone RJ, Jasani M, Gracely EJ: Pain of local anesthetics: rate of administration and buffering. Ann Emerg Med. 1998, 31:36-40. 10.1016/s0196-0644(98)70278-1*
6. *Momsen OH, Roman CM, Mohammed BA, Andersen G: Neutralization of lidocaine-adrenaline. A simple method for less painful application of local anesthesia (Article in Danish). Ugeskr Laeger. 2000, 162:4391-4.*
7. *Martin AJ: pH-adjustment and discomfort caused by the intradermal injection of lignocaine. Anaesthesia. 1990, 45:975-8. 10.1111/j.1365-2044.1990.tb14636.x*
8. *Dollery C: Therapeutic drugs. Churchill Livingstone, Edinburgh, UK; 1999.*
9. *Tirupathi SP, Rajasekhar S. Effect of warming local anesthesia solutions before intraoral administration in dentistry: a systematic review. J Dent Anesth Pain Med. 2020 Aug;20(4):187-194. doi: 10.17245/jdapm.2020.20.4.187. Epub 2020 Aug 27. PMID: 32934984; PMCID: PMC7470999.*
10. *Ibusuki S, Katsuki H, Takasaki M: The effects of extracellular pH with and without bicarbonate on intracellular procaine concentrations and anesthetic effects in crayfish giant axons. Anesthesiology. 1998, 88:1549-57. 10.1097/00000542-199806000-00019*
11. *Al-Shayyab MH, Baqain ZH. Factors predictive of the onset and duration of action of local anesthesia in mandibular third-molar surgery: a prospective study. Eur J Oral Sci. 2018 Apr;126(2):110-117. doi: 10.1111/eos.12406. Epub 2018 Feb 16. PMID: 29450917.*
12. *Tirupathi SP, Rajasekhar S. Effect of warming local anesthesia solutions before intraoral administration in dentistry: a systematic review. J Dent Anesth Pain Med. 2020 Aug;20(4):187-194. doi: 10.17245/jdapm.2020.20.4.187. Epub 2020 Aug 27. PMID: 32934984; PMCID: PMC7470999.*
13. *Gandhi N, Shah N, Wahjuningrum DA, Purnomo S, Nooshian R, Arora S, Pawar AM. Evaluation of pulpal anesthesia and injection pain using IANB with pre-heated, buffered and conventional 2% lignocaine in teeth with symptomatic irreversible pulpitis-a randomized clinical study. PeerJ. 2022 Oct 19;10:e14187. doi: 10.7717/peerj.14187. PMID: 36281366; PMCID: PMC9587718.*
14. *Goodman A, Reader A, Nusstein J, Beck M, Weaver J: Anesthetic efficacy of lidocaine/meperidine for inferior alveolar nerve blocks. AnesthProg. 2006, 53:131-9. 10.2344/0003-3006(2006)53[131:AEOMFI]2.0.CO;2*
15. *Colaric KB, Overton DT, Moore K: Pain reduction in lidocaine administration through buffering and warming. Am J Emerg Med. 1998, 16:353-6. 10.1016/s0735-6757(98)90126-7*