TO EVALUATE THE ANESTHETIC EFFECTIVENESS OF MIXTURE OF 2% LIGNOCAINE WITH 1:200,000 EPINEPHRINE, 0.5% BUPIVACAINE AND 7.5 % SODIUM BICARBONATE FOR MANDIBULAR MOLAR EXTRACTIONS UNDER INFERIOR ALVEOLAR NERVE BLOCK - A RANDOMIZED CONTROLLED TRIAL

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LIST OF ABBREVIATIONS

Abbreviations	Full Form
LA	Local Anesthesia
CO_2	Carbon Di-Oxide
H_2O	Water
$NaHCO_3$	Sodium Bicarbonate
HCl	Hydrochloric Acid
IAN	Inferior Alveolar Nerve
VAS	Visual Analog Scale
TACE	Trans arterial chemo embolization

INTRODUCTION

Introduction

Extractions are the most common dental procedures performed since the past few centuries. These extractions were performed without adequate analgesia thereby creating a negative attitude among people towards dentistry. This act of tooth pulling lead to dentophobia which in turn raised a need for an agent-anaesthesia that would make the procedure painless. It was **Karl Koller** who applied Cocaine solution into his own eyes and then pricked it with pins which turned out to be a success. In the very same year cocaine for the first time was used in dentistry by Halstead for mandibular nerve block. Cocaine is the only naturally occurring local anaesthetic agent but with the leap of time, many other agents were synthetically derived. The search continued in the same group and the first local anaesthesia to be used for injection was procaine. Following this many other agents were developed like chloroprocaine and tetracaine. Lignocaine was introduced in 1943 which was the first amide based local anaesthetic agent which had a greater stability compared to ester compounds. Along with the stability, the amide compounds also overcame allergic reactions associated with the ester based anaesthetic agents.[1]

Local anaesthesia is defined as "a local state of loss of sensation without loss of consciousness, in a circumscribed area of the body due to a depression of, excitation in nerve endings or an inhibition of the conduction process in peripheral nerves". The loss of sensation is produced without loss of consciousness. While local anaesthetic agents are the drugs which upon topical application or local injection cause reversible loss of sensory perception, particularly of pain in a localized area of the body.[2]

Mechanism by which the local anaesthesia acts is, in normal physiological process the nerve membrane is partially permeable to potassium and impermeable to sodium ions. There exists a constant negative potential by outwards movement of sodium and inwards movement of potassium ions through this membrane. When the nerve gets excited due to any stimuli the permeability of the nerve membrane takes a shift and causes increase in sodium permeability by influx of these ions into the nerve membrane. This leads to depolarization and causes pain. The local anaesthetic agents blocks the transmission of the sodium ions thus decreasing depolarization and achieving control over pain.[3]

Ideal local anaesthetic agents should be non-irritant, reversible, do not cause any allergic reaction, and have long duration of action and must not cause any allergic reaction, least systemic toxicity and selective to pain pathways.[4] Structure of local anaesthesia consists of three components: 1st – lipophilic aromatic ring, 2nd – intermediate linkage either of ester or amide, 3rd –tertiary amine.[5] These components decide the properties of anaesthetic agent. Basically, local anaesthesia is classified as amino esters or amino amides. Initially ester based was in use. The ester based local anaesthesia is linked to aromatic ring via ester bridge while amide based is linked to aromatic ring via amide bridge. The basic differentiation between the two types is their chemical stability.[6] Esters are unstable and are hydrolyzed readily while amides are comparatively more stable. Cholinesterase hydrolyses ester compounds in the plasma while amide compounds are metabolized in liver. In terms of safety, it is documented well in literature that the allergic reactions are caused more by ester group of local anaesthetic agents when compared with amide group. The possible reason for this allergic reaction is the formation of para-aminobenzoic acid as a by-

product post ester hydrolysis. The following is the basic structural difference between the two types of anaesthesia.[5] (Fig.1)

Ester local anaesthetic agents include Benzocaine, Cocaine, Tetracaine, Procaine and Chloroprocaine while Amide local anaesthetic agents include Ropivacaine, Lignocaine, Mepivacaine, Prilocaine, Etidocaine, Levobupivacaine and Bupivacaine.[6] Amongst these, Lignocaine and Bupivacaine are the most commonly used anesthetics in the recent times. Lignocaine also known as Lidocaine and Xylocaine was introduced in 1948. The formulations of Lignocaine available in market for routine dental use is 2% Lignocaine with 1:50,000 epinephrine, 2% Lignocaine with 1:100,000 epinephrine, 2% Lignocaine with 1:200,000 epinephrine.[4,7] Lignocaine is highly soluble in water and has a rapid onset of action and therefore is used for nerve blocks or local infiltrations in oral cavity. Apart from dental use it is also used in the form of drops for ophthalmic procedures, as a topical anaesthetic agent in post herpetic neuralgia, prior to injection, intravenously for tinnitus and ventricular arrhythmias.[8] When it comes to onset, within 45-90 seconds the action starts and last for a duration of 10-20 minutes with its maximum action after which the effect starts to diminish. From the total amount injected, 60-80% binds to the protein alpha acid glycoprotein giving a bioavailability in oral cavity of 35% and topical of 3%. Around 50% of the Lignocaine injected in the tissues gets metabolized and is eliminated within 90-120 minutes of which 90% is excreted as metabolites and 10% is excreted as unchanged drug.[9]

Bupivacaine, the second most commonly used local anaesthetic agent was introduced in 1963 by **Ekenstam** a chemist from Scandinavian country.[10]

Bupivacaine has a longer chain with four methylene groups. This structure is responsible for different properties between Lignocaine and Bupivacaine. Though the basic form of Bupivacaine is not soluble in water but the acidic form prepared post hydrochloride mixture is highly soluble in water thus available for injection. The market form of Bupivacaine available is 0.5% Bupivacaine, 1:200,000 epinephrine with trade names of Marcaine and Anawin.[4] When compared to Lignocaine, Bupivacaine has a slower onset which takes almost 1-17 minutes for its action to commence. This too depends on the route of administration and the proximity of injection to the area to be anaesthetized. The best feature of Bupivacaine is its duration of action which is around 2-9 hours. This feature makes it ideal for post operative pain control after surgical removal of third molars. The half life of Bupivacaine is 2.7 hours in adults while it is 8 hours in neonates. About 95% of the injected solution binds to protein and is metabolized in liver. 6% is excreted as an unchanged form of drug.[11]

Irony is, the local anaesthesia which is used for controlling pain universally during dental extractions is itself associated with pain during its administration.[12] Various studies report that around 5% of the population are under the fear of pain of local anaesthesia and thus are apprehensive towards their visits to a dentist.[13] This apprehension increases anxiety levels of the patients and may trigger few of the emergencies which occur in dental office like syncope and hyperventilation.[14]As it increases the anxiety of the patient it comes in the way of an effective treatment since anxiety is the biggest barrier to dental procedures. The inferior alveolar nerve anaesthesia is the most common block used in dentistry for routine restorative purpose and dental extractions of the mandibular teeth. Any nerve block has three stages, the first stage is the one wherein the needle is inserted in the tissues; secondly the needle

it advanced to its final position; and thirdly the anaesthetic solution is deposited into the destination site. All these stages are believed to cause pain and discomfort. Apart from these factors, studies have also reported that the type of needle used, the amount of solution deposited as well as the pressure by which the solution gets deposited which determines pain during administration. Smaller the gauge of the needle more is the pain felt, faster the solution is deposited with excessive pressure greater is the discomfort and pain felt. To overcome this clinicians have started using larger gauge needles which cause less trauma to the tissues which insertion and thus less pain. Moreover the solution is also deposited in extremely slow speed. [15, 16]

Most of the local anaesthetic agents are weak bases and are manufactured in powder forms which are usually partially soluble in water and are unstable. To make their solubility perfect they are combined with acid to form a stable hydrochloride salt. The presence of hydrogen chloride salt yields H+ ions and is responsible for the acidic pH of the solution. Higher is the pH more it is basic and lowers the pH more it is acidic in nature. In patients with systemic conditions like hypertension, the clinicians ideally prefer anaesthesia without vasoconstrictor. This solution has a pH in the range of 5 to 6 or more. While in other cases ideally anaesthesia with vasoconstrictor is favored so as to increase the duration of anaesthesia and have a bloodless surgical field. Moreover the use of vasoconstrictor further reduces the pH and makes it more acidic. The pH of anaesthesia with vasoconstrictor ranges between 3.3 to 5.5. This low pH is also contributed because of the presence of preservative agent i.e., an antioxidant sodium bisulfate. Besides, the acidic pH is preferred by the manufacturers as it increases the shelf life of the solution and decreases its oxidation.[17, 18, 19 20]

The acidic nature of anaesthesia is responsible for burning and stinging sensation at the injection site. Moreover, it also has a slow onset of action and traumatizes the tissues post injection.[2] It also has disadvantages the cases where a existing infection is present. When anaesthesia is injected, free base are liberated by the alkalinity of the tissue and this leads to penetration of the local anaesthesia into lipid-rich nerve. This is a natural phenomenon of the body to increase the alkalinity of the solution in vivo. The area of infection is already acidic and injecting local anaesthesia at such sites further reduces free base amount leaving fewer anaesthetic molecules to penetrate the nerve thus leading to failure of anaesthesia in inflamed and infected tissues.[17]

Though few of the above measures like needle size, injecting pressure and speed are undertaken to reduce the pain but still the issue remains unresolved. Recent techniques which are being experimented are the use of buffering agent in the local anaesthesia in addition to vasoconstrictors to reduce pain and discomfort during and also post the procedure to a great extent. The buffering of the solution is done by addition of sodium bicarbonate[17.] The issue is with the buffering of the solution in the cartridges used in dentistry as they were available in prefilled form. But lately, this too was overcome with the introduction of a product by Onpharma which consists of a mixing pen and cartridge connector to increase the pH of solution prior injection. This technique of buffering the solution provides increase in the alkalinity ex vivo. Studies report that the pH of the anaesthetic solution rises from 3.3 to 7.4 by adding $NaHCO_3$ to Lignocaine with epinephrine.[21,22,23]

The mechanism behind increase in pH is; the HCL present in the local anesthesia interacts with sodium bicarbonate (buffering agent). This interaction gives carbon dioxide (CO_2) and water (H_2O) as by-products. The carbon dioxide diffuses

immediately after reaction and continues to do so even after injecting in the tissues. This diffusion of CO_2 in combination with the anaesthetic agent has direct effect on the nerve axon by changing local anaesthetic solution charge and thus increasing the concentration of anaesthesia within the trunk via ion trapping process. This mechanism has been concluded by **Catchlove**, **Bokesch PM et al** and **Raymond S et al**.[24,25,26]

Literature throws light on the studies conducted by experimenting Lignocaine with and without buffering agents. Lignocaine 1% has been compared with Lignocaine 1% buffered with $NCHO_3$, Bupivacaine 0.5% compared with buffered Bupivacaine, Mepivacaine 1% compared with buffered mepivacaine.[27,28,29]

All these studies have been conducted by taking only one anaesthetic agent. Though Lignocaine has been traditionally used but it too comes with its specified disadvantages. To overcome those cons Bupivacaine is used. But, Bupivacaine too has its disadvantage of slow onset of action. Thus there was a need to understand the efficacy of their combined anaesthetic effect on the tissues. Moreover, various studies have been reported on buffering agents but still the topic remains controversial as authors have also reported to have no significant differences in pain and discomfort with and without buffering of anaesthesia. Therefore, to know in depth about the buffering action and the combined effect of the two anaesthetic agents the study was conducted to evaluate the anaesthetic effectiveness of mixture of 2% Lignocaine with 1:200,000 epinephrine, 0.5% Bupivacaine and 7.5 % Sodium Bicarbonate for mandibular molar extractions under Inferior alveolar nerve block through a randomized controlled trial.[30, 31]

AIMS AND OBJECTIVES

Aims and Objectives

Aim of the Study

To compare the effectiveness of buffered mixture of 2% Lignocaine with 1:200000 Epinephrine and 0.5% Bupivacaine with the unbuffered mixture of2% Lignocaine with 1:200000 Epinephrine and 0.5% Bupivacaine for mandibular molar extractions under inferior alveolar nerve block.

Objectives of the study

1. To compare the pain on injection with buffered and unbuffered solution of 2% Lignocaine 1:200000 Epinephrine and 0.5% Bupivacaine by VAS.

2. To compare the time of onset of anesthesia with buffered and unbuffered solution of 2% Lignocaine 1:200000 Epinephrine and 0.5% Bupivacaine.

3. To compare the duration of anesthesia with buffered and unbuffered solution of 2% Lignocaine 1:200000 epinephrine and 0.5% Bupivacaine.

REVIEW OF LITERATURE

Review of Literature

History of local anaesthesia

Braun (1901)[32] demonstrated the "chemical tourniquet" property of epinephrine.

In 1904-1905, procaine was synthesized by German chemist **Einhorn** and **Uhfelder** in Germany. When adrenaline was added, this agent was found to be effective and safe as a local anaesthetic agent for most patients. Procaine was widely used by physicians and dentists till the 1950. **In 1943, Swedish chemist Nils Lofgren** synthesized lignocaine, an amine anaesthetic. It revolutionized the use of local anesthesia in dentistry as it was less allergic and more potent than procaine. By the 1950"s, it became widely accepted.[2]

Ruetsch YA et al (2001)[33] explained about the journey of anaesthesia from cocaine to Ropivacaine. In 1850, around three centuries after the triumph of Peru by Pizzaro, the Austrian von Scherzer brought an adequate quantum of coca leaves to Europe to allow the separation of cocaine. As proposed by his companion Sigmund Freud, depictions of the properties of the coca provoked the Austrian Koller to perform in 1884 the primary clinical activity under local anesthesia, by organization of cocaine on the eye. The utilization of cocaine for local and peripheral anesthesia quickly spread all through Europe and America. The lethal impacts of cocaine were before long distinguished bringing about numerous passings among the two patients and dependent therapeutic staff. Local anesthesia was in a significant emergency until the advancement of present day natural science which prompted the combination of unadulterated cocaine in 1891. New amino ester local anaesthetics were combined somewhere in the range of 1891 and 1930, for example, tropocaine, eucaine, holocaine, orthoform, benzocaine, and tetracaine. Furthermore, amino amide neighborhood soporifics were set up somewhere in the range of 1898 and 1972 including nirvaquine, procaine, chloroprocaine, cinchocaine, lidocaine, mepivacaine, prilocaine, efocaine, bupivacaine, etidocaine, and articaine. These medications were apparently less dangerous than cocaine, however they had contrasting measures of sensory nervous system (CNS) and cardiovascular (CV) health. Bupivacaine proved to be of unique intrigue as a result of its long length of activity and history of clinical

application. Combined in 1957, the presentation of bupivacaine available in 1965 paralleled the dynamic and aggregate reports of CNS and CV effects, prompting the limitation of its utilization and the distinguishing proof of a unique treatment safe CV lethality. Various exploratory investigations were led to distinguish the fine cell system of this effect, which refined comprehension of the activity of local analgesics. The distinguishing proof of optically dynamic isomers of the mepivacaine family prompted the choice of ropivacaine, an unadulterated S-(-) enantiomer, whose toxicology was specifically and widely contemplated before its presentation available in 1996. During the fast and broad utilization of ropivacaine in the facility, undesirable reactions have been seen as constrained.

Chriptopher A (2016)[34] published an article discussing about the history of local anaesthetic agents. The historical backdrop of local anesthesia began in 1859, when cocaine was detached by **Niemann**. In 1884, the ophthalmologist Koller was the primary, who utilized cocaine for topical anesthesia in ophthalmological medical procedure. In 1884, local anesthesia in the oral depression was first performed by the specialist Halsted, when he expelled a intelligence tooth without agony. In many cases, various unfavourable impacts were seen with the clinical utilization of cocaine. In 1905, **Einhorn** revealed the amalgamation of procaine, which was the main ester-type local anaesthetic agent. Procaine was the most usually utilized local anaesthesia for over four decades. In 1943, **Lofgren** incorporated lidocaine, which was the first “present day " local anaesthetic agent, since it is an amide-derivate of diethyl amino acidic corrosive. Lidocaine was showcased in 1948 and is up to now the most generally utilized sedative in dentistry around the world; however other amide Local anaesthetics were brought into clinical use: Mepivacaine 1957, Prilocaine 1960, and Bupivacaine 1963. In 1969, articaine was combined by the scientist **Muschaweck** and was affirmed in 1975 as a nearby sedative in Germany. Today articaine is the most ordinarily utilized nearby sedative in dentistry in Germany, Switzerland, Austria, France, Poland and the Czech Republic.

Pharmacology of local anaesthesia

Covino BG (1986)[6] in his study reported that the most important clinical properties of local anaesthetic agents are potency, onset, duration of action and relative blockade of sensory and motor fibres. These qualities are related primarily to the physicochemical properties of the various compounds. In general, lipid solubility determines the relative intrinsic potency of the various agents, while protein binding influences the duration of anaesthesia and *pKa* is correlated with the onset of action. In general, the local anaesthetics for infiltration, peripheral nerve blockade, and extradural anaesthesia can be classified into three groups: (1) agents of low potency and short duration, for example procaine and chloroprocaine;(2) agents of moderate potency and duration, for example lignocaine, mepivacaine and prilocaine;and (3) agents of high potency and long duration, for example amethocaine, bupivacaine and etidocaine. These local anaesthetics also vary in terms of onset: chloroprocaine, lignocaine, mepivacaine, prilocaine and etidocaine have a rapid onset, while procaine, amethocaine and bupivacaine are characterized by a longer latency period.

Moore PA and Hersh EV (2010)[4] reported that the amide local anesthetic agents currently available in dentistry were extremely safe and effective. The availability of various formulations of lidocaine, mepivacaine, prilocaine, articaine, and bupivacaine permits a practitioner to select agents that can meet treatment requirements. Many advances in local anesthesia therapeutics and armamentarium have become available to the dental practitioner in recent years. Through careful selection of agents and proper adjustment of dosing, most serious adverse reactions associated with dental local anesthetic agents can be prevented.

Becker DE and Reed KL (2012)[5] reported that local anaesthetics have an impressive history of efficacy and safety in medical and dental practice. Their use is so routine, and adverse effects are so infrequent, that providers may understandably overlook many of their pharmaco therapeutic principles. In their review they discussed about onset of anaesthesia, duration of action, metabolism and elimination of the agent from the body, toxicity associated with local anaesthesia and interaction of these agents with other drugs. The review helped to update essential pharmacology for the various local anaesthetic formulations.

Giovannitti JA et al (2013)[35] provided a comprehensive review of the pharmacology of local anesthetics as a class, and provided details of the individual drugs available in dental cartridges. Maximum recommended doses of local anesthetics and vasoconstrictors are presented for healthy adult and pediatric patients, and for patients with cardiovascular system impairments. Various complications and reasons for failure of local anesthesia effectiveness were discussed, and current and future trends in local anesthesia were presented to provide an overview of current researches in local anesthesia. It was reported that local anesthesia remained the foundation of pain control in dentistry especially when combined with moderate-deep sedation for invasive and painful procedures in the contemporary oral and maxillofacial surgical model. Local anaesthetics also are the safest and most effective drugs in medicine and dentistry to relieve intra operative and postoperative pain. It is only with a thorough understanding of pharmacology and anatomy that clinicians have the basic clinical foundation to enhance the care of patients.

Mumba JM et al (2017)[36] presented a summary of the findings which jotted few points that local anaesthetics block the transmission of pain from the nerve endings into the central nervous system. Chemically, they are classified as esters and amides depending on the intermediate chain between the lipophilic aromatic ring and the hydrophilic amine group. The primary mode of action is blockade of the fast voltage-gated sodium channels. To achieve this effect, the unionised fraction of the drug crosses the lipid bi layer of the axoplasm and blocks the channel intracellularly. The duration and density of the block depend on both the volume and concentration of the agent used. Factors that influence the efficacy of local anaesthetics are the pH, pKa, lipid solubility, protein binding and the length of the intermediate chain. Efficacy can be augmented by use of adjuncts such as adrenaline, opioids, alpha 2-adrenergic agonists (clonidine) and alkalinisation. Toxicity is related to the site of injection, the vascularity of the site and the injected dose. The use of vasoconstrictors may reduce toxicity due to reduction in systemic absorption. From the local anaesthetics in clinical use, racemic bupivacaine has the highest affinity for the sodium channels and is the most difficult to manage in the event of systemic toxicity

Local anaesthesia implications

Chapman PJ and Macleod AWG (1985)[37] conducted a clinical trial comparing bupivacaine to lidocaine in 20 patients undergoing the surgical removal of bilateral impacted mandibular third molar teeth at separate appointments. A combination analog and category pain scale was used to assess pain on four occasions over the first 24 hours following the operation. Results showed a marked reduction in postoperative pain experienced over this time and almost unanimous patient preference for bupivacaine. The study concluded that many oral surgical operations are technically difficult and prolonged, resulting in considerable postoperative pain and discomfort, especially over the first 8-12 hours. Long-acting local anesthetics like bupivacaine can eliminate a considerable amount of this unwanted experience.

Ribotsky BM et al (1996)[38] conducted a study to assess the advantages of using a 50/50 mixture of lidocaine and bupivacaine with respect to onset and duration of local anesthesia instead of using the solutions independently were evaluated. In a double-blind randomized experiment, 12 subjects, each volunteering both feet, were studied. One foot was injected with 1 ml of one of the following three solutions: 1% plain lidocaine, 0.25% plain bupivacaine (Marcaine), or a 50/50 mixture of 1% lidocaine and 0.25% bupivacaine; and in the other foot, a 1-ml injection of normal saline as a blinded control. A 5.07 (10 g) Semmes-Weinstein monofilament wire was used for testing for sensory blockade and the onset and duration of anesthesia was recorded for each subject. It was determined that there was no significant difference in the mean onset times for the three solutions, and no significant difference between the durations of anesthesia of plain lidocaine and the 50/50 mixture. Additionally, it was determined that bupivacaine had a prolonged duration of anesthesia compared with the other two solutions. The results of this preliminary study suggest that there is no clinical advantage, with respect to onset and duration of local blockade, to using a 50/50 mixture of plain lidocaine and plain bupivacaine in place of their independent use.

OZMEN O et al (2013)[39] conducted a study to investigate whether a 2% lidocaine addition to 0.5% bupivacaine that is used in a lateral sagittal infraclavicular block, when administered in an upper extremity surgery, decreases the block onset time,

drug effect time, and drug activity when compared with bupivacaine alone. This study was performed on 120 American Society of Anaesthesiology classification I–II patients who were 18–65 years old and scheduled to undergo an upper extremity surgery. The group testing in the study was as follows: 20 mL (5 mg/mL) bupivacaine, 10 mL (5 mg/mL) bupivacaine + 10 mL (20 mg/mL) lidocaine, and 20 mL (20 mg/mL) lidocaine were used respectively in the bupivacaine group, bupivacaine + lidocaine group, and lidocaine groups. It was found that the block onset time was very long in the bupivacaine group. Motor block developed the fastest in the lidocaine group and the bupivacaine + lidocaine group. Motor block regression was the fastest in the lidocaine group and the slowest in the bupivacaine + lidocaine group. Loss of cold and touch sense was the fastest in the bupivacaine + lidocaine group and the lidocaine group. Loss of sense of pain was the fastest in the bupivacaine + lidocaine group. Postoperative analgesia requirement time was the longest in the bupivacaine + lidocaine group. There were no differences among the satisfaction scores. It was concluded that lidocaine addition to bupivacaine significantly lowered the block onset time and extended the postoperative analgesia requirement time compared to bupivacaine alone and had no effect.

Yadav A et al (2013)[40] aimed to demonstrate if 2% lidocaine hydrochloride with 1 : 200,000 epinephrine could provide palatal anesthesia in maxillary tooth removal with a single buccal injection. The subjects included in the clinical study were those requiring extraction of the maxillary third molar of either side. For the purpose of comparison, the sample was randomly divided into 2 main groups: group 1 (study group) included 100 subjects who were to receive a single injection before extraction, and group 2 (control group) included 100 subjects who were to receive a single buccal injection and a single palatal injection before extraction. After 5 minutes the extraction was performed. All patients were observed for Faces Pain Scale during extraction and asked for the same on a 100-mm visual analog scale after extraction. According to visual analog scale and Faces Pain Scale scores, when maxillary third molar removal without palatal injection (study group) and with palatal injection (control group) were compared the difference was not statistically significant. It was concluded that removal of maxillary third molars without palatal injection is possible by depositing 2 mL of 2% lidocaine hydrochloride with 1 : 200,000 epinephrine to the buccal vestibule of the tooth.

Balakrishnan K et al (2015)[41] conducted a literature review which discussed about the analgesic and anaesthetic abilities of the bupivacaine versus lignocaine during surgical removal of impacted third molars. It was found that both bupivacaine and lignocaine have their merits and demerits but beyond any doubt it has been proven by the clinical trials that bupivacaine provides better and prolonged analgesia and anesthesia post operatively during minor surgical procedures done at chair side along with surgical removal of impacted third molars. Hence, bupivacaine can be regularly used as the anaesthetic solution along with adrenaline 1:200,000 for surgical removal of impacted third molars provided care being taken regarding the dosage and the cardio depressant property of bupivacaine. Right now, further studies are going on.

Dhanrajani P and Chung P (2016)[42] conducted a study to compare the effectiveness and duration of action of two concentrations of bupivacaine with adrenaline for postoperative pain in patients undergoing surgical removal of four third molars under general anesthesia.

60 patients undergoing surgical removal of four wisdom teeth received bupivacaine 0.5% (n = 30) or 0.25% (n = 30). The severity of pain in the immediate recovery period and at 2 and 24 h after surgery was recorded using the visual analogue scale. Differences were assessed by box and whisper plot and the Student's *t*-test. It was found that the analgesic effects of the 0.25% and 0.5% doses were significantly different at 30 min after surgery but not after 2 and 24 h. The difference of mean of 0.25% and 0.5% was much higher after 0.5 h but less after 2 and 24 h. The study concluded that bupivacaine 0.5% was statistically better for pain control during the immediate postoperative period, but there was no significant difference in pain control between the two dose strengths at 2 and 24 h after surgery.

Agarwal P et al (2017)[43] conducted a study to compare bupivacaine and lignocaine use in surgical extraction of impacted mandibular third molars. This was a prospective, randomized, double blind study. 50 patients requiring surgical removal of impacted mandibular third molars were randomly divided into two equal groups. 0.5% Bupivacaine without any vasoconstrictor and 2% lignocaine with 1:80,000 adrenaline were used in a double blind manner. All required parameters were noted during surgery and questionnaires given to all patients, to assess onset of anaesthesia,

the time of complete disappearance of numbness, pain perception and postoperative analgesic requirement. It was found that longer duration of action and longer painless period postoperatively, lesser pain intensity and decreased postoperative analgesic requirement were observed for bupivacaine with statistical significance. However, the onset of anaesthesia was earlier for lignocaine as compared to bupivacaine. Study concluded that bupivacaine has better pain control, increased duration of anaesthesia, lesser postoperative pain and decreased analgesic requirement postoperatively than lignocaine. The application of bupivacaine to minor oral surgical procedures like removal of impacted teeth is desirable.

Kulkarni S and Palkar MI (2018)[44] conducted a study to evaluate efficacy of 2% lignocaine with two different dilutions of epinephrine in equal volumes (1ml), used as infiltration anaesthesia in the extraction of mandibular anteriors and premolars. The following parameters were evaluated: onset, depth and duration of anaesthesia, hemostasis during the procedures, and complications, if any. 40 patients underwent extractions of mandibular teeth (anteriors and premolars) using local infiltration anesthesia of 2% lignocaine. 20 patients received 2% lignocaine with 1:80000 adrenaline and another 20 patients received 2% lignocaine with 1:200000 adrenaline. It was found that there was statically significant difference in the onset of anesthesia and the duration of action of local anesthesia in study group but not in efficacy and depth of anesthesia. The study concluded that longer duration of anaesthesia can be achieved with the use of local infiltration 2% lignocaine with 1:80000 dilution of adrenaline when compared with equal volume of 2% lignocaine with 1:200000 dilution of adrenaline.

Adelusi EA et al (2019)[45] conducted a study to evaluate the post-extraction pain control of 0.5% Bupivacaine compared with 2% Lidocaine following intra-alveolar tooth extraction. This study was a double blind randomized controlled trial on patients who underwent intra-alveolar tooth extraction. There were two groups of 126 subjects per Bupivacaine and Lidocaine group respectively. Pain experience was assessed using Numeric Rating Scale (NRS). Data were analyzed using SPSS and $P<0.05$ was considered statistically significant. When post-operative pain was recorded in Lidocaine group between 3 to 12 hours post-extraction there was a significant improvements afterward while in the Bupivacaine group, there was almost pain-free

period for the first 8 to 9 hours postoperatively. A significant reduction in the need for post-operative analgesics was noted in the Bupivacaine group. Overall patient satisfaction was significantly higher for the Bupivacaine group.
The study concluded that bupivacaine appears to offer more effective post-operative pain control following intra-alveolar tooth extraction.

Buffering of local anaesthesia and its implications

The history of alkalinisation/buffering of local anesthetics goes way back as 1910, when **Gros and Lawen in 1910** carried out alkalinisation of 1% procaine with 0.5% sodium bicarbonate and noted an increased potency of buffered procaine.[46]

Bromage PR (1965)[47] was the first to use pH adjusted lignocaine. He used carbonated lignocaine for epidural analgesia and proved decreased latency of onset by one third as compared to plain lignocaine solution.42 since then; many more studies have been conducted over years to study the efficacy of buffering local anesthetic solutions.

Bartfield JM et al (1990)[48] carried out a randomized, double-blind, prospective clinical trial on 91 adult patients (68 men and 23 women) in age group of18- 86 years with simple linear lacerations to compare buffered lignocaine with plain lignocaine as a local anesthetic for simple lacerations repair. Each wound edge was anesthetized with either plain or buffered lignocaine using a randomized, double-blind protocol. The pain of infiltration was measured with a previously validated visual analog pain scale. The results showed that buffered lignocaine was significantly less painful than plain lignocaine during infiltration. The study concluded that buffered lignocaine is preferable to plain lignocaine as a local anesthetic agent for the repair of simple lacerations.

Orlinsky M et al (1992)[49] conducted a prospective, randomized, double blinded study on 61 patients to compare the pain level experienced upon subcutaneous infiltration of unbuffered lignocaine with pH buffered lignocaine in a traumatic laceration. Solutions of unbuffered 1% lignocaine and buffered 1% lignocaine were randomly assigned to Site I or Site II of a single laceration for each subject, with the

18 patient serving as self-control. Pain scores were recorded for each site, and anesthetic preference was determined for each patient. The result showed that buffered lignocaine had a preference over unbuffered lignocaine. The study concluded that that buffered lignocaine is preferred over unbuffered lignocaine with a preference ratio of 3.0 and that the order of injection is an important factor in trials that involve multiple sequential injections, in the same patient.

Barnett TA et al (1992)[50] performed a randomized prospective double blind trial on 25 patients (2 male and 23 female) to verify the efficacy and potentially reduced local irritative effects of buffered lignocaine in hyperthermia (HT) as well as to delineate what role, if any, the pH of the local anesthetic had in the development of nodules. A total of 146 catheter placements were performed on 54 fields in 25 patients (64 placements with the buffered anesthetic preparation Y, 82 with the control, Z).Visual Analog Scale was used to evaluate the pain. Patients were scored both for the pain noted during the infiltration of lignocaine and the pain noted with subsequent catheter placement. In addition, the development of subcutaneous nodules at the sites of catheter placement was monitored at the time of 3-week follow-up. A statistically significant difference in the level of pain associated with infiltration of buffered versus unbuffered lignocaine preparations was observed. The results of this trial support the use of buffered lignocaine prior to catheter placement for hyperthermia treatments as a method of reducing pain at infiltration and reducing the rate of subsequent development of subcutaneous nodules.

Bancroft JW et al (1992)[51] conducted a prospective blind study on 20volunteers to compare the effect of pH neutralization on the pain experienced during intra dermal administration of lignocaine. A plain solution (pH = 6.1) and three different buffered solution of 1% lignocaine (pH values of 6.8, 7.0, and 7.2) were prepared, and a 0.5-mL of each of the four solutions was then injected intradermally into the velar aspect of one forearm over 2.5 seconds. The pain of each injection was measured on a visual analog scale (VAS). The result demonstrated a dramatic reduction in the pain associated with lignocaine infiltration by buffering the pH above6.8. However, among the buffered lignocaine solutions, there was no significant difference in the reduction of the pain associated with lignocaine infiltration. The study concluded that buffering

of 1% lignocaine above a pH of 6.8 significantly reduces the mean quantitative pain estimates compared with the non buffered controls.

Bartfield JM et al (1993)[27] carried out a randomized, double-blind, prospective clinical trial on 31 patients (19 men and 12 women) in the age group of 18to 59 years to test whether buffered lignocaine is less painful to administer as a digital nerve block than plain lignocaine. Subjects received digital nerve blocks by injection of buffered lignocaine on one side and plain lignocaine on the other in a pre determined, randomized order. Pain of infiltration was assessed by visual analog pain scale. The results showed that Buffered lignocaine was significantly less painful to administer than plain lignocaine. Thus the study concluded that buffered lignocaine is preferable to plain lignocaine for digital nerve blocks in adults because it causes less pain and is equally efficacious.

Matsumoto AH et al (1994)[52] did a randomized, prospective, double-blind study on 150 patients undergoing diagnostic angiography or interventional radiology to evaluate the effect of using a buffered lignocaine solution on the perception of pain experienced by a patient during its intra dermal injection. 150 patients were divided into 3 subgroups of 50 each. 1mL of one of three lignocaine solutions (plain 1%lignocaine, 1% lignocaine diluted with normal saline in a 10:1 ratio, and 1%lignocaine diluted with 8.4% sodium bicarbonate in a 10:1 ratio) were administered to each group intradermally over 10-15 seconds. The pain on injection was measured on a visual analogue scale (VAS). The result showed that mean pain score for the buffered solution was significantly lowered than other two solutions and there was significant reduction in the perception of pain associated with the administration of a buffered 1% lignocaine solution regardless of the age of the patient or the anatomic location of skin infiltration. The study concluded that buffering lignocaine significantly decreases the discomfort associated with its administration as a local anesthetic.

Sinnot CJ et al *(*2000)[53] studied the effect of adding sodium bicarbonate to lidocaine with and without epinephrine versus equivalent alkalinisation by sodium hydroxide (NaOH) on onset, degree, and duration of peripheral nerve block. Part I examined alkalinisation by sodium bicarbonate versus NaOH to pH 7.8 on 0.5% lidocaine, with

and without epinephrine (1:100,000), prepared from crystalline salt. Part II examined 0.5% and 1.0% commercial lidocaine solutions, with and without epinephrine, either unalkalinized or alkalinized with sodium bicarbonate or NaOH. With NaOH, pH was adjusted to 7.8, but with sodium bicarbonate, no pH adjustments were made to simulate clinical conditions. Results revealed that in part I, addition of either NaOH or sodium bicarbonate to 0.5% lidocaine without epinephrine produced a faster onset than did unalkalinized lidocaine, without effecting degree or duration of block. In solutions with epinephrine there were no differences in onset, degree, or duration between lidocaine alkalinized with sodium bicarbonate versus NaOH. In part II, addition of sodium bicarbonate or NaOH to 1.0% commercial lidocaine without epinephrine did not accelerate onset compared with the unalkalinized solution. However, adding sodium bicarbonate decreased the degree and duration of block by 25% and more than 50%, respectively, compared with lidocaine unalkalinized and alkalinized with NaOH. With epinephrine, sodium bicarbonate hastened onset without effecting degree and duration compared with the unalkalinized solution. Study concluded that 1% commercial lidocaine without epinephrine, sodium bicarbonate decreases the degree and duration of block. However, in solutions with epinephrine, sodium bicarbonate hastens onset, without effecting degree or duration.

Davies RJ (2003)[54] conducted a review to provide evidence that buffering of local anaesthetics with sodium bicarbonate reduces the pain of injection whilst not affecting efficacy. Medline search from 1966 to December 2001 was conducted. Articles in all languages were included. Bibliographies were examined for papers. The search identified 63 publications of which all were retrieved. Of these, 22 were human prospective randomized controlled trials directly assessing the pain of infiltration. Three papers were based on observations. No case series, case reports, or retrospective studies were identified. One animal study was found. The review concluded that buffering with sodium bicarbonate significantly reduces the pain of local anaesthetic injection. The buffered solutions retain the efficacy of local anaesthetics and are stable in the mixtures used in the trials. Adrenaline-containing buffered solutions need refrigeration in closed containers for storage. Buffering will be particularly useful where pain of local anaesthetic injection may not be well tolerated such as in large areas of infiltration, sensitive areas such as the face and in

children. Study recommended that sodium bicarbonate and tables of stable dilutions are readily available in the emergency department to facilitate this.

Brandis K et al (2011) [55] commercial local anaesthetic solutions have an acidic pH to maximise their water solubility and chemical stability. This increases their shelf-life. Immediately before injection, alkali can be added to raise the pH towards the physiological pH. This is called 'alkalinisation' or 'buffering' of the solution. Anaesthetic activity is dependent on having both the ionised and non-ionised forms of the drug present after injection. Alkalinisation increases the proportion of non-ionised drug and this could be advantageous. Care must be taken, because if too much alkali is added, the local anaesthetic will precipitate. When used for infiltration anaesthesia or block of small nerves, alkalinised solutions of local anaesthetic are less painful when injected. The onset of local anaesthesia may also be slightly quicker. For epidural anaesthesia or block of large nerves the amount of time saved is minimal and so alkalinisation is not practically useful for these procedures.

Frank SG and Lalonde DH (2012)[56] conducted a study to determine the acidity of lidocaine and the correct ratio of bicarbonate that should be added to neutralize lidocaine to achieve body pH. 50 samples each of commonly used anesthetics (lidocaine 1% and 2%, with and without epinephrine 1:100,000) were obtained and tested for pH. Data were also analyzed according to whether the vials had been previously opened. 10 additional samples of lidocaine 1% with 1:100,000 epinephrine were titrated against sodium bicarbonate 8.4% and tested for pH and the presence of precipitate. Results reported were, 1% lidocaine with 1:100,000 epinephrine had a mean (± SD) pH of 4.24±0.42, and 2% lidocaine with 1:100,000 epinephrine had a mean pH of 3.93±0.43. Plain 1% lidocaine had a pH of 6.09±0.16, and plain 2% lidocaine had a pH of 6.00±0.27. Epinephrine-containing solutions were more acidic when they had been previously opened. One per cent lidocaine with epinephrine required 8.4% sodium bicarbonate at a ratio of 1.1 mL:10 mL to 1.8 mL:10 mL to achieve the target tissue pH of 7.38 to 7.62. It was concluded that lidocaine with epinephrine was approximately 1000 times more acidic than subcutaneous tissue. The addition of bicarbonate to the local anaesthetic solution is simple to perform and is inexpensive. The proper volume ratio of 8.4% sodium bicarbonate to 1% lidocaine with 1:100,000 epinephrine is approximately 1 mL: 10mL.

Afolabi O et al (2013)[57] conducted a double-blind, randomized trial to investigate the effect of buffering lidocaine on the pain of injection and duration of anesthetic effect. The study involved 44 healthy volunteers. The upper lip was injected with a solution of: lidocaine 1% (Xylocaine, AstraZeneca, Canada, Inc) with epinephrine; and lidocaine 1% with epinephrine and 8.4% sodium bicarbonate. Volunteers reported pain of injection and duration of anaesthetic effect. Results were, 26 participants found the unbuffered solution to be more painful. 15 participants found the buffered solution to be more painful; the difference was not statistically significant. 21 volunteers reported duration of anaesthetic effect. The buffered solution provided longer anaesthetic effect than the unbuffered solution. The study concluded that although buffering increased the duration of lidocaine's anaesthetic effect in this particular model, a decrease in the pain of the injection was not demonstrated, likely due to limitations of the study.

Logothetis DD (2013)[58] reported that local anaesthetics are the safest drugs used in dentistry for pain management, but cause undesirable qualities such as stinging and burning upon injection, relatively slow onset of action, and unreliable or no anesthesia when injected into infected tissues. Buffering of local anaesthetics has been demonstrated to counteract these undesirable qualities of local anaesthetics. Recent advances in technology have made buffering of local anaesthetics practical for use to alkalinize dental local anaesthetic cartridges chair side immediately prior to injection, making the anaesthetic's onset quicker, more reliable, and more comfortable for the patient. This article provided an overview of neurophysiology, pharmacology of local anaesthetics, and the role and benefits of local anesthetic buffering.

Gupta S et al (2013)[59] conducted a double-blind randomized case control study to validate the addition of sodium bicarbonate in local anesthetics to increase its effectiveness as local infiltrations in maxillary teeth associated with per apical infections. The subjects were divided in two groups. One group received local infiltration with 2% lignocaine 1:80,000 adrenaline, and other group received local infiltration with the buffered counterpart. Intra-alveolar extraction was performed. Onset of anesthesia and pain during extraction were assessed by VAS and Verbal Response Scale. Average onset time in the buffered group was 72.03 sec less than that of the non-buffered group, which was 144.22 sec. The mean value of the sum of ranks

in the VAS was 6,091.50 for control group and 14,0088.50 for the test group. The sum of ranks in the VRS for the control group was 6,336 and 13,764 for the test group, and repeated injections were 12 with the control group and 4 with the test group. They concluded that the action of sodium bicarbonate in local anaesthetics increases the pH of the solution, thus making them more effective in an acidic environment.

Madan SG (2014)[60] conducted a study to know the exact amount of 7.5%W/V B.P sodium bicarbonate (NaHCO3)necessary to get buffering pH of 2% lignocaine without adrenaline ,with 1:80,000 adrenaline and with 1:2,00,000 adrenaline. 10 ml of Type:1 (2% lignocaine without adrenaline), Type:2(2% lignocaine with 1:80,000) and Type:3 (2% lignocaine with 1:2,00,000 adrenaline) were selected for study. In laboratory 7.5% W/V BP NaHCO3 was added in each anaesthetic solution until pH of each mixture reaches body physiologic pH-7.2.pH was measured with pH measurement strips and confirmed by digital pH meter. Same procedure was performed for ten time and mean value was obtained. It was found that required amount of 7.5% W/V B.P NaHCO3 to get physiologic pH of local anesthetic solution was 1.6ml for Type:1, 2.1ml for Type:2 and 2.5ml for Type:3. Solution got precipitated at 0.4ml , 1.9ml, 2ml of 7.5% W/V BP NaHCO3 for Type:1, Type:2 and Type:3 respectively. Conclusion: Precise amount of buffering agent require to obtain buffered pH of local anaesthetic solution is 0.1ml for Type: 1, 1.8ml for Type: 2, 1.5ml for Type:3. These values are just smaller value at which solution get precipitates. There is no major pH changes for Type: 1 so it was not advised to buffer Type:1 local anesthetic solution. Anesthetic – to – bicarbonate solution ratio is 10:1.8 for Type:2 and 10:1.5ml for Type:3.

Abusedera MA et al (2014)[61] did a prospective randomized controlled study for 21 consecutive patients in age group of 52–78 (19 male and 2 female) to assess the efficacy of intra-arterial buffered lignocaine on peri and post-procedural pain in hepatocellular carcinoma patients undergoing chemoembolization. Thirty-nine Trans arterial chemoembolization (TACE) procedures were carried out in which buffered lignocaine was used in 20 TACE and normal saline in 19 TACE. Visual analog scoring was used to assess pain (VAS). The study concluded that Intra-arterial administration of buffered lignocaine before infusing the embolization particle of

TACE is safe and effective, in doses as low as 50 mg for reducing peri and post procedural pain.

Harreld TK et al (2015)[62] carried out a prospective , randomized, double blind study to compare the pain of infiltration and the pain of an incision and drainage procedure of buffered versus a non buffered 4% lignocaine formulation in symptomatic emergency patients presenting with a diagnosis of pulpal necrosis, associated periapical area, and an acute clinical swelling. Eighty-two emergency patients were randomly divided into 2 groups to receive 2 intraoral infiltration injections of either 4% lignocaine with 1:1,00,000 epinephrine buffered with 0.18 ml8.4% sodium bicarbonate using the Onpharma (Los Gatos, CA) buffering system or4% lignocaine with 1,1:00,000 epinephrine. Subjects rated the pain of needle insertion, needle placement, and solution deposition for each injection using a 170- mm visual analog scale. An incision and drainage procedure was performed, and subjects rated the pain of incision, drainage and dissection on VAS. They found no significant differences between the buffered and non-buffered 4% lignocaine formulations for needle insertion, placement and solution deposition of the infiltration injections or for the treatment phases of incision, drainage and dissection. The study concluded that buffering 4% lignocaine formulation did not significantly decrease the pain of infiltration or significantly decrease the pain of incision and drainage procedure when compared with a non buffered 4% lignocaine formulation in asymptomatic patients with a diagnosis of pulpal necrosis and associated swelling.

Saatchi M et al (2015)[63] did a prospective, randomized, double-blind study on80 patients aged between 20 – 55 years to compare the anesthetic efficacy of buffered versus non buffered 2% lignocaine with 1:80,000 epinephrine solution for inferior alveolar nerve (IAN) block in patients with symptomatic irreversible pulpitis in the mandibular posterior teeth. The patients received 2 cartridges of either 2% lignocaine with 1:80,000 epinephrine buffered with 0.18 ml, 8.4% sodium bicarbonate or 2%lignocaine with 1:80,000 epinephrine with 0.18 ml sterile distilled water using conventional IAN block injections. Endodontic access preparation was initiated 15minutes after injection. Each patient was asked to rate his or her initial pain on a Heft-Parker visual analog scale (HP-VAS). The results showed that IAN block success rate was 62.5% for the buffered group and 47.5% for non buffered group

though the values were not statistical significant. The study concluded that buffering the 2% lignocaine containing 1:80,000 epinephrines with 8.4% sodium bicarbonate did not improve the success of the IAN block in patients with symptomatic irreversible pulpitis.

Best CA et al (2015) [64] used injectable local anesthetic solutions to facilitate pain-free surgery is an integral component of many procedures performed by the plastic surgeon. In many instances, a solution that has both rapid onset and prolonged duration of analgesia is optimal. A combination of lidocaine and bupivacaine, plain or with epinephrine is readily available in most Canadian health care settings where such procedures are performed, and fulfils these criteria. However, commercially available solutions of both medications are acidic and cause a burning sensation on injection. Buffering to neutral pH with sodium bicarbonate is a practical method to mitigate the burning sensation, and has the added benefit of increasing the fraction of no ionized lipid soluble drug available. The authors report on the proportions of the three drugs to yield a neutral pH, and the results of an initial survey regarding the use of the combined solution with epinephrine in hand surgery. The combined solution of 2% lidocaine with 1:100,000 epinephrine and 0.5% bupivacaine with 1:200,000 epinephrine in a 1:1 ratio, buffered with $NaHCO_3$, may be the ideal LA solution for practitioners to use in many clinical applications. A practical clinical application of the laboratory investigations did not investigate the chemical stability of epinephrine in buffered solutions over time.

Phero JA et al (2016)[65] conducted a study to assess outcomes for peak blood levels for buffered 2% lidocaine with 1:100,000 epinephrine compared with non-buffered 2% lidocaine with 1:100,000 epinephrine. It was a prospective, randomized, double blinded, crossover trial, wherein the clinical impact of buffered 2% lidocaine with 1:100,000 epinephrine was compared with the non-buffered drug. Venous blood samples for lidocaine were obtained 30 minutes after a mandibular nerve block with 80 mg of the buffered or unbuffered drug. Two weeks later, the same subjects were tested with the alternate drug combinations. Subjects also reported on pain on injection with a 10-point Like rt-type scale and time to lower lip numbness. The explanatory variable was the drug formulation. Outcome variables were subjects' peak blood lidocaine levels, subjective responses to pain on injection, and time to

lower lip numbness. Serum lidocaine levels were analyzed with liquid chromatography-mass spectrometry. Results revealed that48% of subjects were women, half were Caucasian, 22% were African American, and 13% were Asian. Median age was 21 years (interquartile range [IQR], 20-22 yr), and median body weight was 147 lb (IQR, 130-170 lb). Median blood levels (44 blood samples) at 30 minutes were 1.19 mg/L per kilogram of body weight. Mean blood level differences of lidocaine for each patient were significantly lower after nerve block with the buffered drug compared with the non-buffered agent. Mean score for pain on injection for nerve block was 3.3. 78% of subjects reported lower or the same pain scores with the buffered drug; 61% of subjects reported a shorter time to lower lip numbness with the buffered drug. Study concluded that buffering 2% lidocaine with epinephrine can produce clinical outcomes favourable for subjects and clinicians without clinically detrimental peak blood lidocaine levels.

Guo J et al (2018)[66] conducted a systematic review which evaluated the use of buffered versus non-buffered lidocaine to increase the efficacy of inferior alveolar nerve block (IANB). Inclusion criteria were randomized, double-blinded studies from PubMed, Web of Science, Cochrane Library, Embase, and ProQuest. Two of the authors assessed the studies for risk of bias. Outcomes included onset time, injection pain on a visual analog scale (VAS), percentage of painless injections, and anesthetic success rate of IANB. The search strategy yielded 19 references. Eleven could be included in meta-analyses. Risk of bias was unclear in ten and high in one study. Buffered lidocaine showed 48 seconds faster onset time, and 5.0 units lower (on a scale 0–100) VAS injection pain than non-buffered. No significant difference was found on percentage of people with painless injection, nor success rate. The review concluded that buffered lidocaine significantly decreased onset time and injection pain (VAS) compared with non-buffered lidocaine in IANB. But since heterogeneity was high, sample size was low, quality of the evidence was low to moderate, and additional studies with larger numbers of participants and low risk of bias were needed to confirm these results.

Goodchild JH and Donaldson M (2019)[67] conducted a study wherein multiple buffered samples of four different commercially available local anaesthetic solutions were prepared. The buffered samples were mixed to 9:1, 19:1, and 18:1 ratios (local

anaesthetic to 8.4% sodium bicarbonate). Sample pH was recorded using a pH meter. Two samples of each local anaesthetic at each ratio were prepared and sequentially pH tested. The pH was recorded via the same pH meter, which was cleaned between each test. Results revealed that the pH change between unbuffered solutions and all buffered samples was statistically different. There was no final pH difference between the 9:1 and 19:1, and 19:1 and 18:1 buffering ratios; however, a statistical difference was seen between the final pHs of the solutions resulting from the 9:1 and 18:1 buffering ratios. After correction for multiple comparisons, the difference between the 9:1 and 18:1 ratio was marginally significant. The study concluded that each of the buffering ratios tested can be used to alkalinize dental local anaesthetic solutions. For practical purposes, a direct injection chair side of 0.1 mL of 8.4% sodium bicarbonate into any of the four local anaesthetics tested is easy, simple, and safe compared to the more complex remove and replace method.

Kattan S et al (2019)[68] conducted a systematic review that addressed the question of "In adults requiring dental therapy with pulpally involved teeth, what is the comparative efficacy of buffered local anesthetics (LAs) compared with that of non buffered LAs in achieving anesthetic success?" Search was performed on MEDLINE, Scopus, Cochrane Library, ClinicalTrials.gov, World Health Organization International Trials Registry Platform, OpenGrey, Google Scholar Beta, and 2 textbooks to identify double-blinded randomized controlled trials in which researchers directly compared the efficacy of buffered and non buffered LAs in adult participants, as well as any associated side effects. Furthermore, reference lists of all included and excluded studies to identify any further trials was done. Weighted anesthesia success rates were estimated and compared by using a random-effects model. A total of 14,011 studies were initially identified from the search; 5 double-blinded randomized clinical trials met inclusion criteria. Buffered LAs were more likely to achieve successful anesthesia than non buffered LAs (odds ratio, 2.29; 95% confidence interval, 1.11 to 4.71; P = .0232; I^2 = 66%). The review concluded that buffered LAs are more effective than non buffered LAs when used for mandibular or maxillary anesthesia in pulpally involved teeth. Buffering of LAs has 2.29 times greater likelihood of achieving successful anesthesia.

MATERIALS AND METHOD

Materials and Method

An experimental study was designed to evaluate the anesthetic effectiveness of mixture of 2% Lignocaine with 1:200,000 epinephrine, 0.5% Bupivacaine and 7.5 % Sodium Bicarbonate for patients undergoing mandibular molar extractions using Inferior alveolar nerve block.

Study design

Randomized, double blind, prospective and comparative in nature.

Study area

The study was conducted in the Department of Oral & Maxillofacial Surgery.

Study population

Patients requiring extraction of mandibular molar extraction as per inclusion criteria.

Sample size

The sample size calculation was done with the use of ‘n master software 1.0 version’. The sample size calculation was based on proportions in which the groups were divided into 2. From the previous literature which gave two values for group A and group B. The power of the study was stated at 80% which could give statistically significant result and the alpha error was set at 5%. The hypothesis was a two sided hypothesis which gave a sample size of 45 in each group.

Sampling technique

All selected patients according to inclusion criteria divided into two treatment groups, each group containing 45 patients using a computer generated random list.

Group A- Trial group (Buffered 2% Lignocaine with 1:200,000 Epinephrine and 0.5% Bupivacaine)

Group B- Control group (2% Lignocaine with 1:200,000 Epinephrine and 0.5% Bupivacaine)

Inclusion criteria

- Patients in the age group of 18-60 years and either gender.
- Patients requiring extraction of mandibular molar.
- Patient in good health and with controlled systemic disease.

Exclusion criteria

- Periodontally compromised mandibular molars
- Patients with impacted mandibular molar (Pederson difficulty index moderate to severe)
- Patient with known allergy to local anesthetic agent
- Mentally challenged patients.
- Patients with any systemic disease.
- Pregnant females
- Patient not willing to give informed consent.

Preoperative procedure:

A complete case history was taken preoperatively using a standard case history proforma **(Annexure I)**. This included a careful documentation of their medical history and history of allergy (particularly in relation to local anesthesia). Intraoral periapical radiographs of the tooth to be extracted were taken prior to the procedure to ensure that the tooth could be extracted under local anesthesia. Hematological assessments were done if necessary. These included random blood sugar levels, bleeding time, clotting time etc. in case if the values of these assessments were beyond the normal range, further assessments were carried out and physician consent obtained prior to the extraction procedure. The entire procedure and nature of study was explained to the patient in a language understood by the patient. The patient was also explained about the visual analogue scale and how to record pain scores on it. **(Annexure II)** Signatures/thumb impression on the consent forms **(Annexure III)** were taken thereafter.

Materials

1. Diagnostic instruments- Mouth mirror, straight probe, tweezer.

2. Dispovan, Luer lock - 2ml disposable syringes 0.45 X 38 mm

3. LOX 2% (manufactured by Neon Laboratories Limited) -lignocaine Hydrochloride with 1:2, 00,000 adrenaline available in 30ml vials. **(Fig.2)**

4. 0.5% Bupivacaine (manufactured by Neon Laboratories Limited) available in 30ml vial. **(Fig.3)**

5. 7.5% sodium bicarbonate **(Fig.4)**

6. Stop watch

7. Digital pH meter

8. Armamentarium for tooth extraction for mandibular molar extraction **(Fig.5)**

9. Emergency drug kit.

Preparation of anesthetic buffer

4.5ml of 2%lignocaine with 1:2, 00,000 epinephrine and 0.5% bupivacaine was taken in a sterile beaker and drop by drop 0.6ml of 7.5% sodium bicarbonate was mixed beyond which a white precipitate could be seen. This solution was prepared freshly. The pH of conventional solution and the freshly prepared local anesthetic solution was measured using digital pH meter. The pH of the conventional solution was 3.39 **(Fig.6)** and that of buffered solution was 6.88 **(Fig.7)** at ambient room temperature of 37 degree Celsius.

Data Collection

Patients visiting Oral and Maxillofacial Surgery Department of for mandibular molar extraction under the inclusion criteria were randomly allocated to either group A or B. After obtaining informed written consent, under all aseptic precaution procedure was started and the inferior alveolar nerve block **(Fig.8)**, lingual nerve block and long buccal nerve block on the desired side was given using freshly prepared mixture of anesthetic solution containing -

For **Group A (buffered)**

- 4.5ml of 2% lignocaine with 1:200,000 epinephrine
- 4.5ml of 0.5% bupivacaine
- 0.6ml of 7.5 % sodium bicarbonate

For **Group B (Non buffered)**

- 2% Lignocaine with 1:200,000Epinephrine
- 0.5% Bupivacaine

Keeping the speed of injection same for every patient, local aesthetic mixture was administered. Following this the surgical site was checked for the subjective and objective signs of anaesthesia after achievement of which the surgical procedure was started. All the patients were operated by a single operator. After achieving haemostasis, post operative instructions and medications were given.

1. Cap. Amoxicillin 500mg thrice a day, for 5 days.
2. Tab. Diclofenac sodium twice a day, for 5 days.
3. Tab. Ranitidine 150 mg twice a day, for 5 days.

The patient was followed up over a telephonic call.

Assessment of Parameters

- Pain on injection was noted for every patient using Visual Analog Scale (VAS)

  Pain during injection was defined as pain described by the patient on Visual Analogue Scale (VAS) during injection of the solution and not on the needle-prick. The VAS composed of continuous, horizontal, 10-mm line, anchored by the end points of "no pain" on the right and "extreme pain" on the left.
- Time of onset will be recorded using a stop watch from the time of retrieval of needle to up to first sign of anesthesia (numbness in lower lip of respective side).
- The time of administration was noted for each patient. They were asked to make a note of when they perceive pain at their surgical site and were followed-up the next day over a telephonic call to note the duration of anesthesia.

Statistical analysis

Randomization

Numbers were assigned to patients visiting Department of oral and maxillofacial surgery and falling into inclusion criteria of the study and randomization was done through computer generated system as seen in Table no.1

Allocation concealment

The local anesthetic solution administered to the patient was of same colour and was not mixed in front of them.

Blinding

To avoid bias in the study a double blinding was performed. The patients were not aware to which group they belong because of allocation concealment. Secondly, the person recording the parameters of pain, duration of onset and duration of action of local anesthesia was kept unaware about the group he is recording

Duration of study

The study was performed for a period of 18 months from January 2018 to July 2019.

Ethics clearance

The scientific and ethical clearance was obtained from the institutional review, Scientific and ethical committee.

Informed consent

A brief outline of the purpose of study along with the inclusion criteria was explained in the informed consent. The linguistics of the informed consent was as per the convenience of the patients. It was explained to the patients that their participation

is voluntary, all the personal details are strictly confidential and their anonymity would be maintained. They were asked to raise their doubts or queries before signing the informed consent.

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RESULTS

Results

The present study was undertaken to evaluate the anaesthetic effectiveness of mixture of 2% Lignocaine with 1:200,000epinephrine, 0.5% Bupivacaine and 7.5 % Sodium Bicarbonate for mandibular molar extractions under IAN block through a randomized controlled trial. The pain intensity during administration of local anaesthesia was assessed using Visual Analog pain rating scale in both the groups. Mean seconds required for the onset of action as well as mean hours of duration of anaesthesia for both buffered and non-buffered anaesthesia was also measured. Unpaired t-test was applied to know the statistical significant difference between the groups for pain intensity, mean time for onset of action and mean duration of action. The results obtained in the two groups for the above three parameters are as below:

Demographic details

A total of 45 patients were allocated in Group A from 18 years to 60 years of age. Out of 45 patients, 17 patients were males and remaining 28 patients were females. Table no.2 & Graph no.1a shows the distribution of patients based on their age group in Group A wherein, 12 patients belonged to age group 21-25 years, 11 into 26-30 years, 8 into 31-35 years, 7 into 36-40 years, 3 into 41-45 years, 1 into 46-50 years, 3 into 51-55 years age group. The maximum patients were found from 21-25 years and the least were 45-50 years of age group. The mean age in this group was found to be 32.42 years with a deviation of 8.32.

A total of 45 patients were allocated in Group B from 18 years to 60 years of age. Out of 45 patients, 20 patients were males and remaining 25 patients were females. Table no.2 and Graph no.1b shows the distribution of patients based on their age group in Group B. In Age group,1 patient was in 16-20 years age group, 10 patients belonged to age group 21-25 years, 8 into 26-30 years, 4 into 31-35 years, 6 into 36-40 years, 8 into 41-45 years, none into 46-50 years, 3 into 51-55 years age group, 4 into 56-60 and 1 into 61-65 years of age group. The maximum patients were found from 21-25 years and the least were in 16-20 and 61-65 years age group. The mean age in this group was found to be 36.3 years with a deviation of 12.4.

Pain intensity

Buffered solution group

The table no.4 and graph no.3 represents the mean score of pain intensity of patients at the time of administration of local anaesthesia for molar extraction. The mean score of pain intensity during administration was 3.67±1.21. The intensity was in the range with minimum of score 1 on visual analog scale and maximum score of 8.

Non buffered solution

The pain intensity determined by visual analog scale for non-buffered anaesthetic solution at the time of administration of local anaesthesia for molar extraction is presented in table 4. The mean score of pain intensity during administration was 3.69±1.02. The intensity was in the range with minimum of score 2 on visual analog scale and maximum score of 7.The bar diagram in graph no.3 represents the mean values of pain intensity in the graphical form showing a higher pain score with the buffered anaesthetic solution followed by non-buffered anaesthetic solution.

Between the groups

When statistical test was applied to know the difference between the two groups it was found that no significant difference was present in pain intensity between the group administered with buffered anaesthetic solution and the group administered with non-buffered anaesthetic solution for molar extraction (Table no.7). A mean difference of 0.02 with t-value of 0.094 and p=0.92 was present which shows insignificant difference between the groups.Graph no.6 represents a bar regarding the mean difference in the intensity of pain of the two groups i.e., with and without buffering agent in the anaesthetic solution.

Onset of action

Buffered solution group

The table no.5 & graph no.4 represents the mean time required for the onset of action of local anaesthesia in group of patients administered with buffered solution for molar

extraction. The mean time taken for the onset of anaesthesia was 99.20±31.22 seconds. The onset of action in 45 patients was in a range of 56 seconds being minimum to upto 220 seconds being maximum.

Non buffered solution

The table no.5 & graph no.4 represents the mean time required for the onset of action of local anaesthesia in group of patients administered with non-buffered solution for molar extraction. The mean time taken for the onset of anaesthesia was 168.76±54.56 seconds. The onset of action in 45 patients was in a range of 80 seconds being minimum to 316 seconds being maximum to show its action.

The bar diagram in graph no.4 represents the mean values of time taken by both buffered and non-buffered anaesthetic solutions for the onset of action. It can be observed that the buffered solution mean time for the onset of action is quite more than that of non-buffered solution.

Between the groups- When statistical test was applied to know the difference between the two groups it was found that significant difference was observed between the duration of onset in patients anaesthetised with buffered solution than that of non-buffered solution. The patients anesthetised with buffered solution showed a statistically significant less time to initiate the action of local anaesthesia as compared to the ones subjected to non- buffered solution. A mean difference of 69.56 seconds was observed between the two groups with t-value of 7.42 and p=0.0001 was present which shows a significant difference between the groups as shown in table no 8. Graph no.6 represents a bar showing regarding the mean difference in the onset of action of the two groups namely with and without buffering agent.

Duration of action

Buffered solution

The table no.6 & graph no.5 represents the mean time about how long the anaesthesia with buffering agent showed its effects. The mean time regarding duration of local anaesthesia was 5.83±1.62 hours. The duration of anaesthesia in 45 patients was in a range initiating from 2 hours with maximum duration reported of 11.17 hours.

Non buffered solution

The table no.6 & graph no.5 represents the mean time for which the local anaesthesia showed its actions with buffering agent. The mean time regarding duration of local anaesthesia was 4.54±1.60 hours. The duration of anaesthesia in 45 patients was in a range initiating from 1.5 hours with maximum duration reported of 9.50 hours.

The bar diagram in graph no.5 represents the mean time for which the anaesthesia lasts in both buffered and non-buffered anaesthetic solutions. It can be observed that the buffered solution mean time duration was less than that of non-buffered solution.

Between the groups- When statistical test was applied to know the difference between the two groups it was found that a significant difference was observed between the duration of anaesthesia in patients anaesthetised with buffered solution than that of non-buffered solution.(Table no. 9) The patients anesthetised with buffered solution showed a statistically significant more time of duration as compared to the ones subjected to non- buffered solution. A mean difference of 1.29 hours was observed between the two groups with t-value of 3.79 and p=0.0001 was present which shows a highly significant difference between the groups. Graph no.6 represents a bar diagram regarding the mean difference in the duration of anaesthetic solutions of the two groups namely with and without buffering agent.

Overall, the results reveal that the buffered anaesthetic solution and non-buffered anaesthetic solutions are comparable in terms of pain felt by the patients during the time of administration. When it comes to onset of action and duration of local anaesthesia, the buffered anaesthetic solution was better over non-buffered solution. It initiated its action early as well as has a lasting effect over non-buffered solution for extraction of molar.

DISCUSSION

Discussion

Pain is defined as an unpleasant emotional experience usually initiated by anxious stimulus and transmitted over a specialized neural network to the central nervous system where it is interpreted as such.[69]

The local anesthesia which is utilized in pain control during dental extractions is itself related with torment pain during its administration. A large population dread the pain of local anesthesia and consequently are worried towards their visits to a dental specialist. This apprehension expands anxiety levels of the patients and may trigger crises such as syncope and hyperventilation. Such a situation calls for a modification in the administration of local anesthesia such as to reduce the uneasiness associated with it.[14, 70]

The inferior alveolar nerve block is the most widely recognized block given in the mandibular region for extraction of molars. The procedure of administration of nerve block can be explained in three steps. Firstly, the needle is inserted in the tissues. Secondly, after insertion of the needle it is slowly progressed into the tissue till it touches the bone at ramus area. Finally, the needle is withdrawn a little and the anesthetic agent is deposited at the site. Amongst the three steps, the final step is associated with maximum uneasiness because of the pressure created in the tissues while deposition. The pH of the solution along with the tension created at the site of injection together has a synergistic action of causing pain.

The spectrum of pain perception depends on multiple factors including the site of infiltration, the amount and volume of drug used, and the sensitivity of the area being anesthetized. For example, there is greater pain when a fresh open wound is infiltrated than normal uninjured tissue. Infiltration pain can sometimes be reduced by

administering the anesthetic very slowly, but this has the drawback of requiring a greater amount of time and, in some cases, only acts to prolong patient's discomfort.[71]

To overcome these issues literature reports various techniques which can be adopted by a dental health care professional during injecting local anesthesia to reduce pain to the patients. Few of them are about making necessary changes into the design of the syringe and needle; few are concentrating on the methodology by which it is administered while few are providing evidence about the changes into the anaesthetic solutions by adding a molecule to it. When it comes to the design of the syringe and needle the studies report that a sharp needle with a lager gauge tend to cause less discomfort to the patients. Another way is to change the bevel of the needle. The larger the bevel is angled the sharper will the needle be and thus the area of injury during the insertion process will be drastically reduced leading to minimized pain.[72,73]

Another technique uses Computer Controlled Local Anesthetic Delivery system wherein the amount of deposition of the anaesthesia and the speed of deposition of anesthesia is well regulated and under control. The slower the anaesthesia is introduced into the tissue the lesser would be the discomfort and pain to the patients. Ideally, 1 ml of the solution should be deposited in 1 minute. The device maintains a constant speed throughout the process and also takes into consideration the surrounding tissue type in which it is inserted.[74] Studies done by **Sumer et al** [75] and **Kammerer et al** [76] have reported of less pain to the patients when performing inferior alveolar nerve block. Another device works on Gate control theory, wherein the perception of vibrating stimulus is amplified thus blocking the pain perception through the spinal cord. In addition to this, the motor of the device also produces a 'hum' sound during the injection procedure which gives calm and soothing effect to

the patients. Such devices are attached to the syringe barrel via a clip bracket which can be autoclaved.[77,78]

Pain is also controlled by distraction techniques. This technique is based on the fact that the humans have a very limited capacity to concentrate in anything. Any experience can be felt only when the person concentrates on that issue. Thus, if the patients are not allowed to concentrate on the pain then they will not experience any pain and the syringe insertion and solution deposition can be done effectively. Now these distraction techniques which are used concentrate on the other sensations of body. Till date few of them which have been studied include listening some music, watching a video or playing a videogame which keeps the patient engaged and distracts his attention from the unpleasant sensation of pain.[79] A significantly lower pain experience was reported by the patients by using virtual reality games as reported by **Atzori B et al.**[80] Though all these procedures work toward improving patient's positive experience but they all come with various disadvantages like a device cost, portability of the devices, specification of the needle to be used etc.

One modality which can be effectively used for reducing pain upon administration of local anesthetic solution is bringing about change in the composition by adding a buffering agent. The major concern of the pain is also contributed to the acidic nature of the solution. This acidic nature of the local anaesthesia causes burning sensation, pain and irritation during administration. Thus if the pH is adjusted there is a drastic reduction in irritation and burning sensation. This issue is most commonly found with the commercially available solutions. Most local anesthetics, including lignocaine, are unstable in the uncharged form and are thus marketed at an acidic pH to enhance solubility and prolong shelf life.[2] Pain on infiltration of local anesthetics appears to be related, at least in part, to the acidity of the commercially available

solutions. Addition of adrenaline to lignocaine increases its anesthetic duration by reducing local absorption however the lower pH of the anesthetic solution renders its infiltration more painful.[81]

The local anaesthesia exists in acidic form is in water soluble state. The currently accepted mechanism of action of lignocaine by most but not all investigators postulates that two ionic forms of the LA exist in equilibrium within the anesthetic cartridge: RN (the uncharged, de-ionized, "active" free base form of the drug, which is lipid soluble) and RNH+ (the "charged" or ionized cationic form, which is not lipid soluble). Only the lipid-soluble de-ionized form can cross the nerve membrane. The equilibrium between the two is illustrated as follows:

RN + *H*+ --------→ RNH+

The relative amounts of de-ionized and ionized forms of LA are dependent on the pH of the solution, in accordance with the Henderson-Hasselbalch equation.[2]Once within the nerve, the RN picks up an H+ with the resultant RNH+ entering Na+ channel to block nerve conduction. Only after the body buffers the injected anesthetic solution to a pH closer to the physiologic range (7.35 to 7.45) will enough of the anesthetic enter into the nerve to effectively block nerve conduction. The time that this transformation requires is a key factor in anesthetic latency (e.g., 5 to 10 minute onset for most vasopressor-containing local anesthetic solutions). Thus, for commercially available preparations, the vast majority of lignocaine will be in the ionized state and not immediately capable of diffusing through the nerve sheath to affect anesthesia. The pain experienced during injection most likely results from a combination of the local irritative effects of the acidic solution and the time required for the above-mentioned dissociations to take place before anesthesia isachieved.[2, 20,81]

Based on knowledge of the mechanism of action of local anesthetics, studies were performed to determine whether a more rapidly acting local anesthetic could be developed simply by adjusting the pH of the injected solution upward (i.e., alkalinization) towards the pKa of the local anesthetic so that a greater percentage of the drug would be unionized and therefore immediately available to diffuse through the nerve membrane. Two strategies have been used to achieve this effect: addition of sodium bicarbonate to the anesthetic solution and the addition of carbon dioxide.[29, 82]

The most common method for buffering local anesthetics is by the addition of sodium bicarbonate. Sodium bicarbonate is a systemic alkalinizing agent. It increases the plasma bicarbonate concentration, buffers excess hydrogen ions, and raises the pH of the blood, thereby reversing clinical signs of acidosis. The addition of sodium bicarbonate to local anesthetics not only increases the pH of the solution but will also result in the production of some carbon dioxide.[83] Truly carbonated anesthetic solutions (hydro carbonate form) have been proposed to provide more effective anesthesia by trapping the anesthetic within the nerve, having a direct depressant action on nerves, and providing a synergistic relationship between carbon dioxide and local anesthetics.

When sodium bicarbonate ($NaHCO_3$) solution is admixed with local anesthetic solution, it interacts with the hydrochloric acid in the local anesthesia to create water and carbon dioxide (CO_2). The CO_2 begins to diffuse out of solution immediately and continues to do so even after the solution has been injected. **Catchlove** concluded that CO_2 in combination with lignocaine HCl potentiates the action of lignocaine HCl by (1) providing a direct depressant effect of CO_2 on the axon, (2) concentrating the local anesthetic inside the nerve trunk through ion trapping, and (3)changing the charge of the local anesthetic inside the nerve axon. **Condouris and Shakalis** demonstrated that

CO_2 possesses an independent anesthetic effect and caused a seven fold potentiation in anesthetic action.[24, 83, 85] The technique of buffering the solution provides increase in the alkalinity of the solution and thus the body does not activate the acid sensing channels further nociceptors and cause any pain.[25, 26, 84]

This "sedative buffering" process brings about a clinically favourable outcomes such as reduced pain on administration of local anesthetic agent, rapid onset of anesthesia and reduced tissue damage.Buffering is well known and accepted in medical field where injections of local anesthetic into the skin are considerably more uncomfortable. Buffering is used frequently in ophthalmology, ear nose and throat, dermatology. In several procedures like before peripheral Intravenous cannula insertion, open carpal tunnel decompression, laceration repair, arterial puncture for blood gas analysis, periocular surgery, blepharoplasty etc. In dentistry its importance is illustrated in endodontic surgery, pediatric trauma and infection.

Certain dento alveolar procedures such as extractions are lengthy wherein the nerve block needs to be repeated because of fading of effect of anesthesia. The additional pricks could be a cause of concern. It may be pointed out here that the local anaesthetic agents which are short acting require multiple administrations after a particular period of time. So, a long acting anesthetic agent would serve the purpose in such conditions with an additional advantage of post operative pain control.

In the present study a combination of 2% Lignocaine with epinephrine and 0.5% Bupivacaine was used. Lignocaine has a quick onset but a moderate duration of action whereas bupivacaine has a slower onset but a longer duration of action. So, the mixture of these two provides a quick onset with a longer duration of anesthesia. In cases of molar extractions where extraction time may tend to be long, a second prick needs to be done to again anaesthetise the working area in oral cavity. The effect of

bupivacaine lasts for around 5 to 9 hours. In the other group buffering of the above mixture of local anesthetic solution was done.

The pain intensity at the time of administration of LA was assessed with Visual analog scale and the comparision was done between the buffered solution and the non-buffered solution. The mean score of pain intensity during administration in the buffered solution group was 3.67±1.21. The intensity was in the range with minimum of score 1 on VAS and maximum score of 8 in the buffered solution group. In the non-buffered solution the mean score of pain intensity was 3.69±1.02. The intensity with this solution was in the range with minimum of score 2 on visual analog scale and maximum score of 7. On comparing the pain intensity in the present study it was observed that a mean difference of 0.02 was present between them and no significant difference was present in pain intensity between the group administered with buffered anaesthetic solution and the group administered with non-buffered anaesthetic solution for molar extraction. A similar result was found with the study conducted by **Primosch RF and Robinson L** [30] wherein a 2%lidocaine solution was injected palatally for the extraction of maxillary canines. A lidocaine solution with epinephrine and sodium bicarbonate was administered in 20 patients. The pain intensity in patients administered with buffered solution and conventional solution was comparable.[30]

Hobeich P et al, [86] **Balasco M et al**,[87] **Whitcomb M et al** [31] and **Chaney M A et al** [85] concluded that there was no significant reduction in pain on injection while using buffered lignocaine. Though these studies used 2% lignocaine with epinephrine and 8.4% sodium bicarbonate in intervention group and in the present study instead of 8.4%, 7.5% sodium bicarbonate was used along with an additional Bupivacaine yet the results were comparable to the present study.

Contrasting results were found in a meta-analysis assessing the difference between buffered and non-buffered solution in inferior alveolar nerve block. Chopra R et al in 2016,[88] **Comerci AW et al** in 2014,[89] **Phero JA et al** in 2016 [57] and **Tavaka SP** in 2013[90] too showed no significant difference between the buffered and non-buffered solution for pain intensity. But when a meta-analysis was performed by including one more study **Warren VT et al** [91] favouring buffered solution it was found that a significant difference was present in pain intensity with buffered solution anaesthetised patients showed less score on VAS scale (0-100) while non-buffered showed scores at a higher level. Studies by **Al Sultan FA**,[91] **Kashyap VMet al,**[92] **Malamed S F et al** [20] and **Gupta S et al** [62] concluded that pain of injection was reduced by a statistically significant amount when using buffered local anesthetics versus conventional solutions.

The onset of time of action in the present study was assessed in seconds. The mean time taken for the onset of anaesthesia was 99.20±31.22 seconds with a minimum time taken of 56 seconds and maximum of 220 seconds in buffered solution groups whereas in non-buffered solution group the mean time taken for the onset was 168.76±54.56 seconds with minimum of 80 seconds and maximum of 316 seconds. The present study reported a significant difference in the onset time between the groups with buffered solution having quick onset while non-buffered taken significantly more time. A meta-analysis conducted by **Guo J et** al[66] in 2018 showed similar results as that of present study with the buffered solution having faster onset over non-buffered. Though the inference was similar but the difference in the time of onset was 48 seconds while the present study it was 69.56 seconds which is higher than the previous study. This can be because of the difference in the anaesthetic solution contents. The studies included in meta-analysis has lignocaine, epinephrine

and sodium bicarbonate as intervention while in the present study adding to these even bupivacaine was present leading to a greater difference between the two groups. Another study by **Kashyap et al** [93] gave a similar result to that of present study with buffered group showing rapid onset than control. A study done for the pulpal anaesthesia again concluded the same result as that of present study.

Contrasting results were portrayed by **Chopra** [98] in 2016 which conducted a study in 12 year old patients in whom lidocaine and epinephrine was administered in first visit and adding of buffering agent in the second visit. In this sense the same patients in intervention served their own controls. The study concluded that both the groups showed similar onset of action of local anaesthesia. **Hobeich P et al** [86] tried to assess the difference of non-buffered solution with two buffered solutions with different sodium bicarbonate percentages. One intervention was with 5% sodium bicarbonate while other with 10% bicarbonate. The mean onset time in buffered groups was found to be 16-121 seconds while in non-buffered it was 119 seconds indicating no significant difference between the groups.

In the present study the mean time regarding duration of local anaesthesia was 5.83±1.62 hours. The duration of anaesthesia was in a range initiating from 2 hours with maximum duration reported of 11.17 hours patients administered with buffered solution while in the non-buffered group duration of local anaesthesia was 4.54±1.60 hours. The duration of anaesthesia was in a range initiating from 1.5 hours with maximum duration reported of 9.50 hours. A mean difference of 1.29 hours was observed between the two groups indicating a significant difference between the two groups. Very few studies have been reported in the literature on duration of anaesthesia and most of them are regarding pulpal anaesthesia rather than soft tissue anaesthesia. **Kurien RS et al** [94] conducted a split mouth study wherein inferior

alveolar nerve bock was given in one group with warm local anaesthesia with buffering agent and other group was administered with conventional local anaesthesia. Similar to the present study this study too reported a significantly greater duration of action for buffered solution which was around 5.5 hours while 2.9 hours for non-buffered solutions. When the same solutions were assessed in warm condition similar results were obtained indicating that buffering the solution with sodium bicarbonate improved the action for a longer time.

While LA intents a pain free treatment, yet is related with some amount of pain upon its administration. The method used in this study is a basic alteration of a normally polished strategy and doesn't require acquiring of new abilities by the dentist. This investigation has endeavoured to make the experience of local anesthesia having a combination of lignocaine, bupivacaine, epinephrine and sodium bicarbonate infusion easy and increasingly agreeable to the patient with quicker onset of anesthesia bringing about diminished working time and expanding the term of anesthesia consequently decreasing the need of extra administration and thus pricking the mucosa.

SUMMARY AND CONCLUSION

Summary and Conclusion

Summary

Local anaesthesia is used for controlling pain universally during dental extractions. Though used as a pain controller it itself may cause pain during its administration. It also increases the anxiety of the patient coming in the way of an effective treatment since anxiety is the biggest barrier to dental procedures.

Inferior alveolar nerve block is the most widely employed mandibular nerve block for dentoalveolar procedures.. The acidic nature of the anaesthesia is usually responsible for burning and stinging sensation at the injection site. Moreover, lower pH traumatizes the tissues post injection. Few measures such as needle gauge, injecting pressure and speed are undertaken to reduce the pain but still the issue remains unresolved. The newer techniques being experimented are the use of buffering agent in the local anaesthesia in addition to vasoconstrictors to reduce pain and discomfort during and also post the procedure.

To evaluate the anaesthetic effectiveness of mixture of 2% Lignocaine with 1:200,000 epinephrine, 0.5% Bupivacaine and 7.5 % Sodium Bicarbonate for mandibular molar extractions under Inferior alveolar nerve block through a randomized controlled trial was conducted.

A total of 90 patients requiring mandibular molar extraction were recruited in the study. The patients were then randomly allotted to either Group A wherein patients were injected with buffered anaesthetic solution of Group B wherein patients were injected with non-buffered anaesthetic solution. Keeping the speed of injection same

for every patient, local aesthetic mixture was administered. Following this the surgical site was checked for the subjective and objective signs of anaesthesia after achievement of which the surgical procedure was initiated. All the patients were operated by a single operator. Visual Analog Scale was used to assess the pain on injection in both the groups. Other parameters which was assessed was the time of onset of local anaesthesia using a stop watch from the time of retrieval of needle to up to first sign of anesthesia. The time of duration of anaesthesia was also recorded in the patients by calling the patient next day over a telephonic call to note the duration of anesthesia.

Overall, the results revealed that the buffered anaesthetic solution and non-buffered anaesthetic solutions were comparable in terms of pain felt by the patients during the time of administration. The buffered solution stood better in terms of onset of action and duration of local anaesthesia. The buffered solution initiated its action early as well as had a lasting effect over non-buffered solution for extraction of molars.

Local anesthesia having a combination of lignocaine, bupivacaine and sodium bicarbonate has proved to be easy in administration and increasingly agreeable to the patient with quicker onset of anesthesia thus enhancing the properties of local anesthetic agent. The addition of buffering agent does not reduce the pain intensity and discomfort in the patients but since the duration of the buffered anaesthesia is longer, it minimizes the repeated pricking of the needle to administer new dose after fading off of previous dose.

Conclusion

Within the limitations of the study it can be concluded that an improvement in time of onset and duration of anesthesia was observed whereas pain on administration of solution will need further evaluation. The longer duration of action render no haste in the operator and also provides a good measure of post operative pain control.

Limitation of the study

Pain perception is a subjective parameter. The perception may vary from person to person, despite using a standard VAS tool. A larger sample size is required to further validate the results of the study.

Future recommendation

Studies with change in temperature of the anaesthetic solution with the same contents can be done.

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TABLES

Tables

Table No. 1: Randomization

Subject	Group Assigned	Subject	Group Assigned	Subject	Group Assigned
1	Group B	31	Group A	61	Group B
2	Group B	32	Group B	62	Group A
3	Group B	33	Group A	63	Group A
4	Group A	34	Group B	64	Group B
5	Group A	35	Group B	65	Group A
6	Group B	36	Group A	66	Group B
7	Group B	37	Group B	67	Group A
8	Group A	38	Group B	68	Group A
9	Group A	39	Group A	69	Group B
10	Group B	40	Group B	70	Group B
11	Group A	41	Group B	71	Group A
12	Group A	42	Group B	72	Group A
13	Group B	43	Group B	73	Group B
14	Group B	44	Group A	74	Group A
15	Group A	45	Group A	75	Group A
16	Group B	46	Group A	76	Group B
17	Group A	47	Group A	77	Group A
18	Group B	48	Group A	78	Group B
19	Group B	49	Group A	79	Group B
20	Group B	50	Group A	80	Group B
21	Group B	51	Group A	81	Group A
22	Group B	52	Group A	82	Group B
23	Group A	53	Group B	83	Group A
24	Group B	54	Group A	84	Group A
25	Group A	55	Group B	85	Group A
26	Group B	56	Group A	86	Group A
27	Group B	57	Group A	87	Group B
28	Group A	58	Group A	88	Group B
29	Group B	59	Group B	89	Group A
30	Group B	60	Group B	90	Group A

Table No. 2: Demographic details related to age in buffered and non-buffered group

Age group(years)	Buffered solution group	Non-Buffered solution group
16-20	0	1
21-25	12	10
26-30	11	8
31-35	8	4
36-40	7	6
41-45	3	8
46-50	1	0
51-55	3	3
56-60	0	4
61-65	0	1

Table No. 3: Gender distribution among the two groups

Groups	Males	Females
Buffered solution	17	28
Non-buffered solution	20	25

Table No. 4: Descriptive data of Mean Visual Analog Score for pain perception on administration of local anesthesia in buffered and non-buffered groups

Groups	N	Minimum	Maximum	Mean	Std. Deviation
Buffered solution	45	1	8	3.67	1.21
Non-buffered solution	45	2	7	3.69	1.02

Table No. 5: Descriptive data regarding mean time required for the duration of onset of buffered and non-buffered anaesthetic solutions

Groups	N	Minimum	Maximum	Mean	Std. Deviation
Buffered solution	45	56	220	99.20	31.22
Non-buffered solution	45	80	316	168.76	54.56

Table No. 6: Descriptive data of mean hours of duration of anaesthesia in buffered and non-buffered groups

Groups	N	Minimum	Maximum	Mean	Std. Deviation
Buffered solution	45	2.00	11.17	5.83	1.62
Non-buffered solution	45	1.50	9.50	4.54	1.60

Table No. 7: Difference between the buffered and non-buffered anaesthetic solution with respect to pain

Groups	N	Mean	t-value	Significance (p)
Buffered Solution	45	3.67	0.094	0.92
Non-Buffered Solution	45	3.69		

Significance at $p<0.05$

No significant difference was observed for pain perception in patients anesthetised with buffered solution and those anaesthetised with non-buffered solution

Table No. 8: Difference between the buffered and non-buffered anaesthetic solution with respect to duration of onset

Groups	N	Mean	t- value	Significance (p)
Buffered Solution	45	99.20	7.42	**0.000***
Non-Buffered Solution	45	168.76		

Significance at p<0.05

A significant difference was observed between the duration of onset in patients anaesthetised with buffered solution than that of non-buffered solution. The patients anesthetised with buffered solution showed a statistically significant less time to initiate the action of local anaesthesia as compared to the ones subjected to non-buffered solution.

Table No. 9: Difference between the buffered and non-buffered anaesthetic solution with respect to duration of action

Groups	N	Mean	t-value	Significance (p)
Buffered Solution	45	5.83	3.79	**0.000***
Non-Buffered Solution	45	4.54		

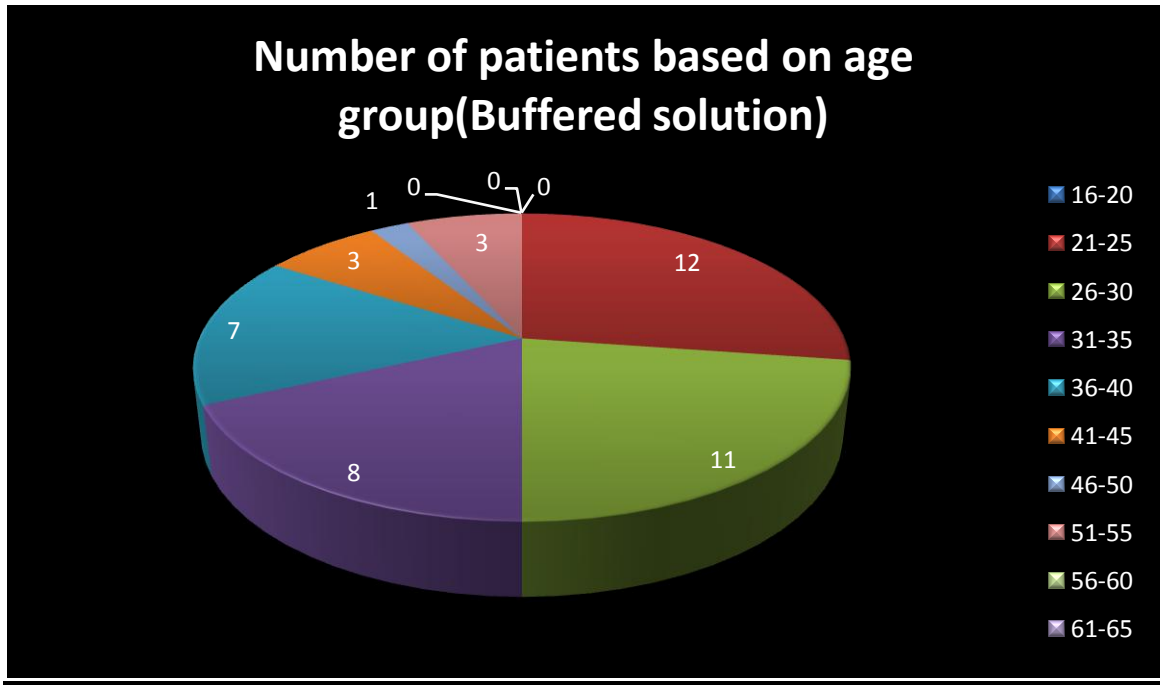
Significance at p<0.05

A significant difference was observed between the duration of action in patients anaesthetised with buffered solution than that of non-buffered solution. The patients anesthetised with buffered solution showed a statistically significant more time of action of local anaesthesia as compared to the ones subjected to non- buffered solution.

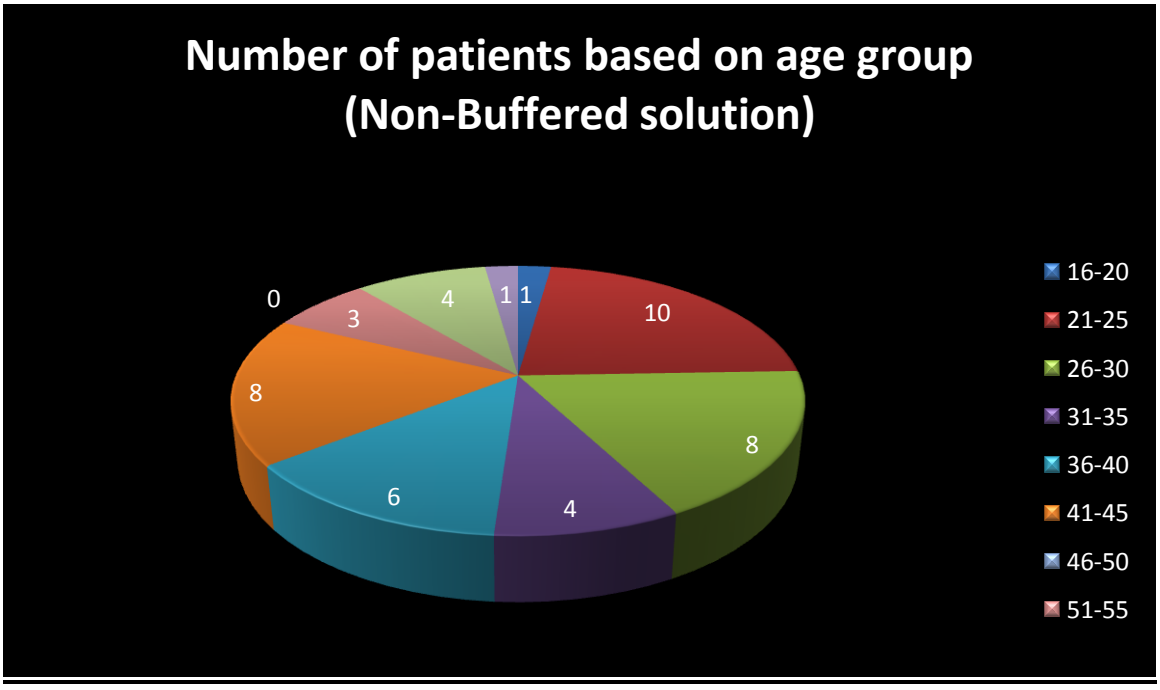
GRAPHS

Graphs

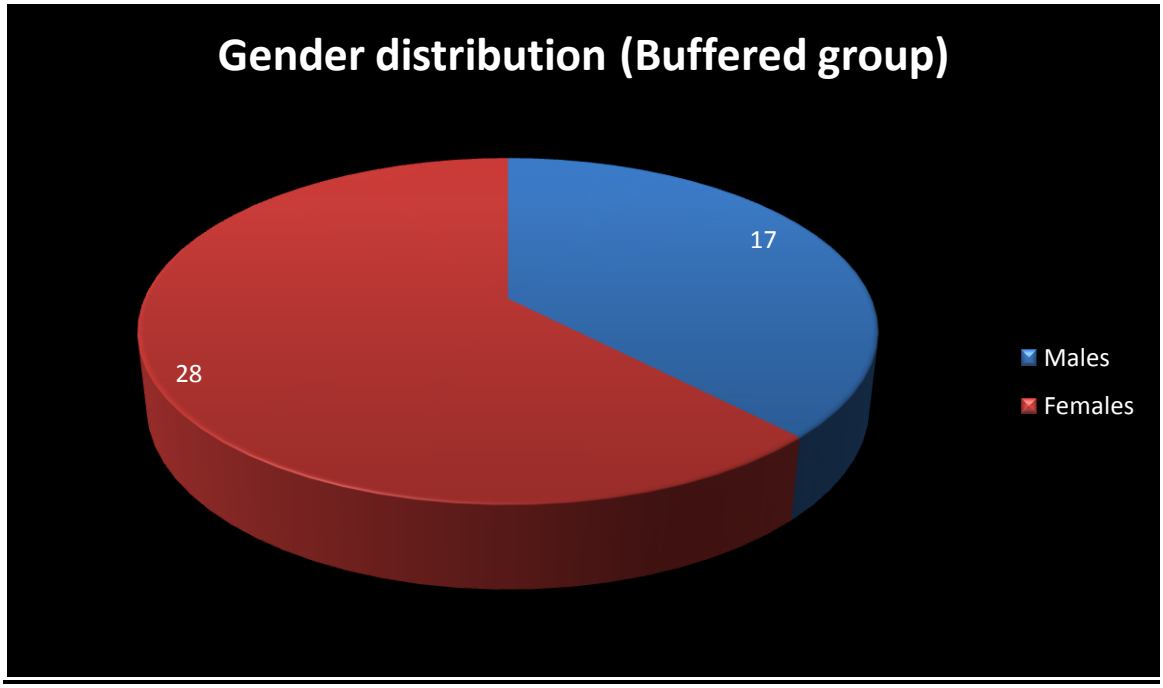
Graph No.1a: Pie chart representing age groups in Group A



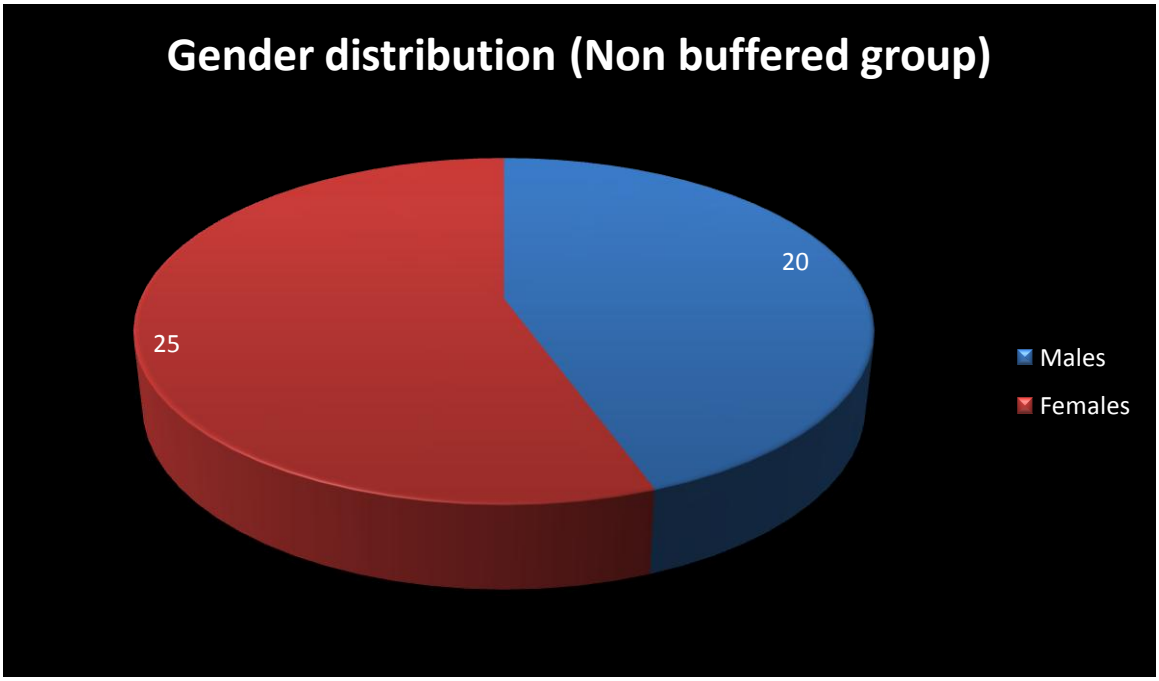
Graph No.1b: Pie chart representing age groups in Group B



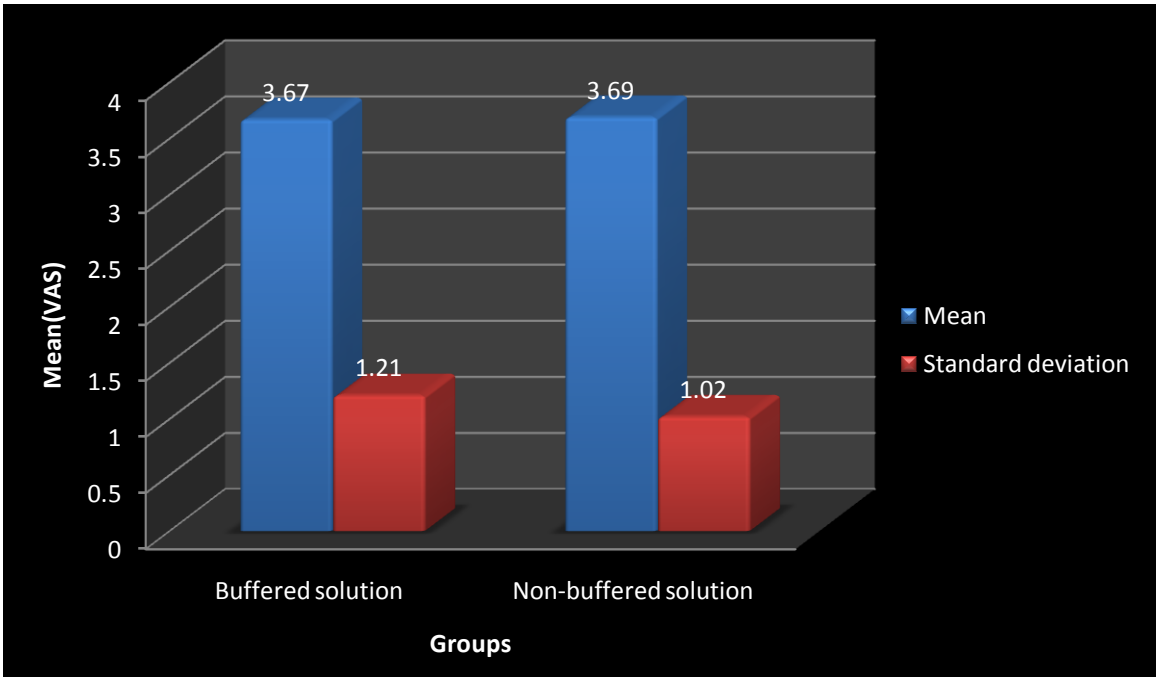
Graph No. 2a: Gender distribution in buffered solution group (Group A)



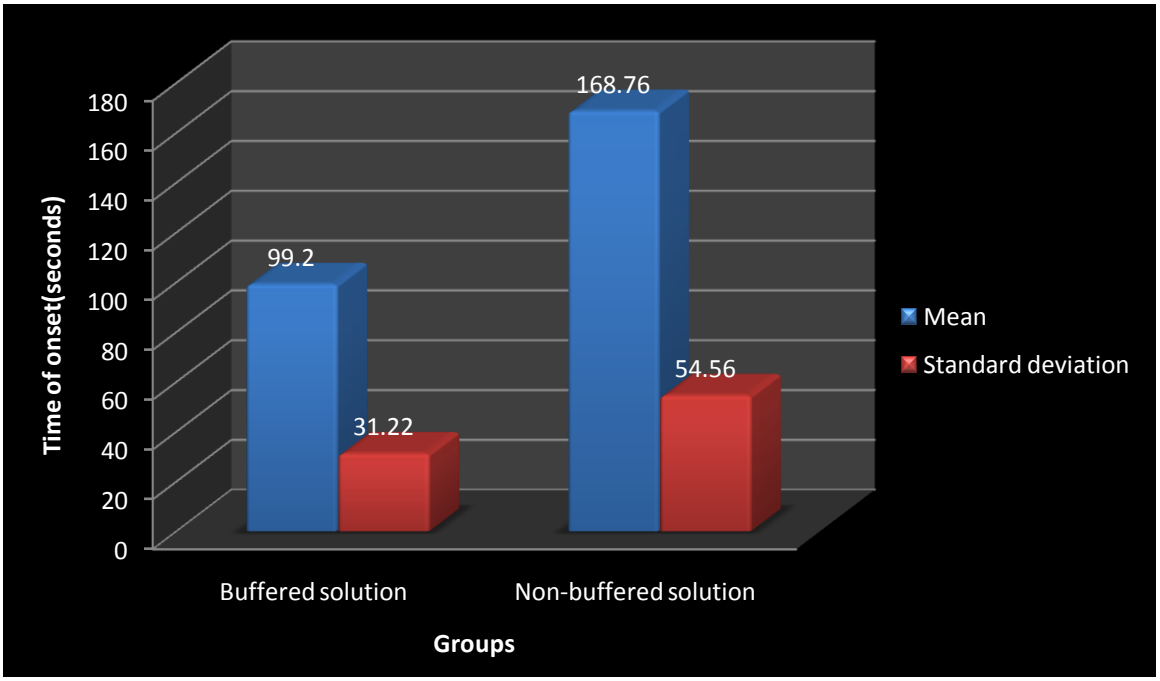
Graph No. 2b: Gender distribution in non-buffered solution group (Group B)



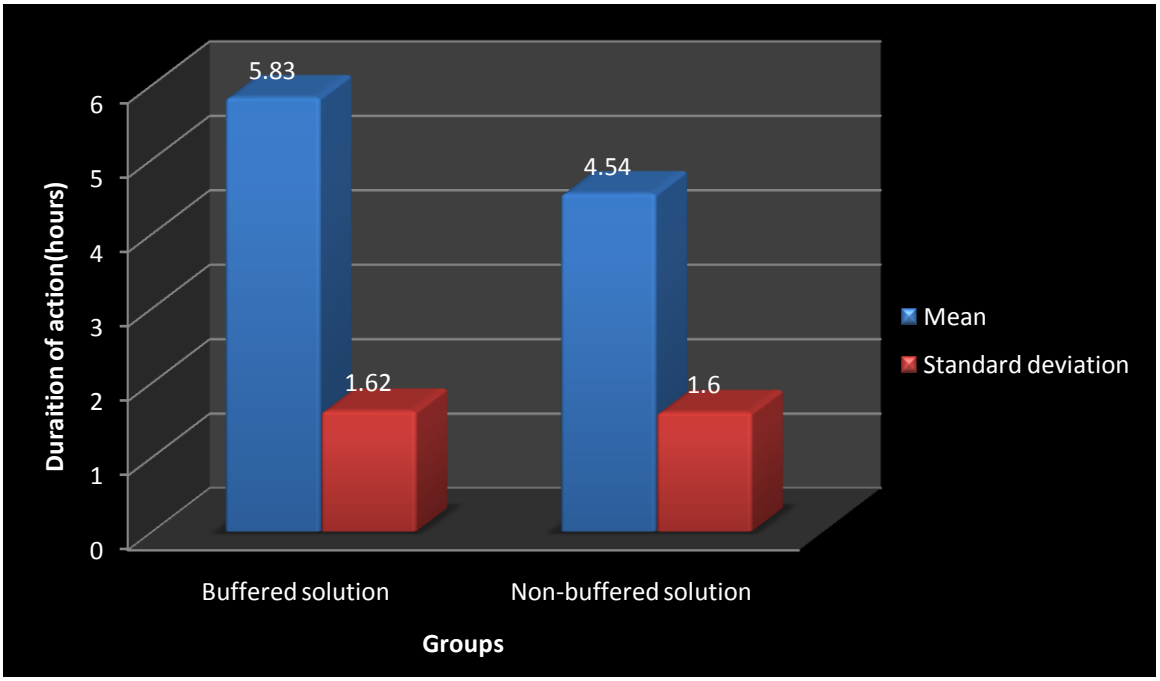
Graph No. 3: Bar diagram representing mean VAS scores in both the groups



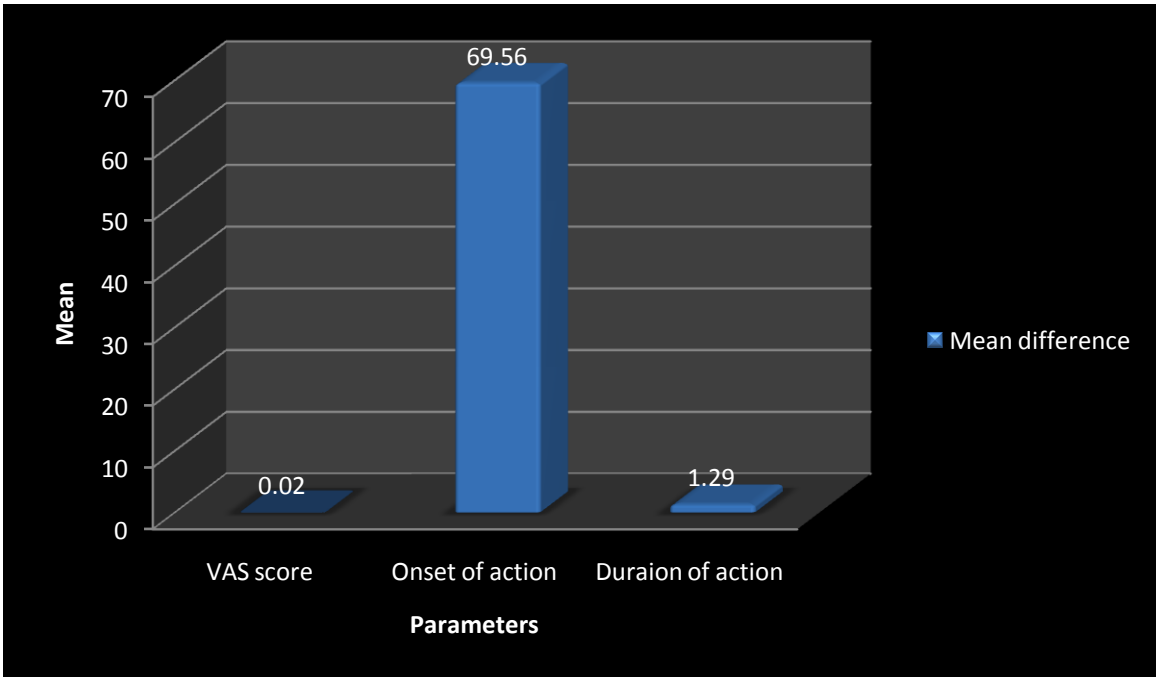
Graph No. 4: Bar diagram representing mean seconds required for the onset of action in both the groups



Graph No. 5: Bar diagram representing mean hours of duration of action of anaesthetics solution in both the groups



Graph No. 6: Difference between the groups for VAS, onset of action and duration of action between the two groups



FIGURES

Figures

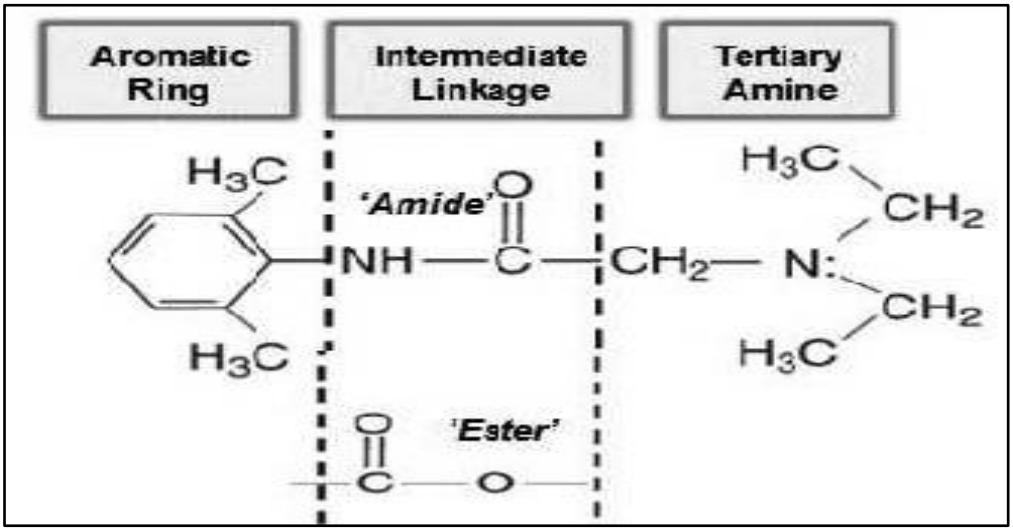


Fig.1 Structural difference between amide and ester

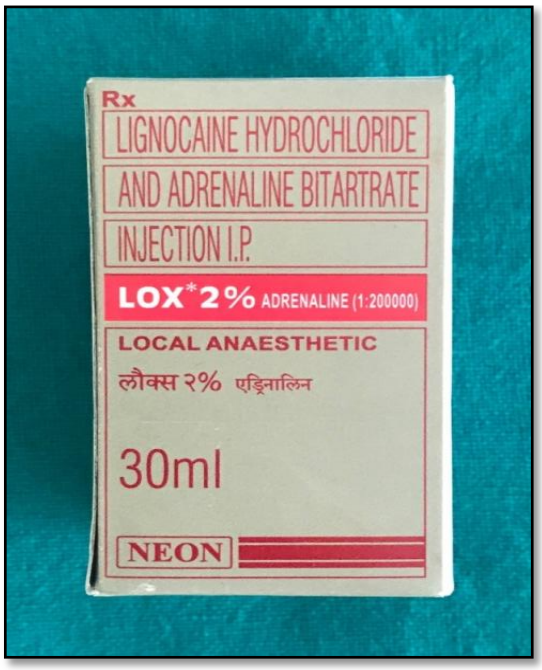


Fig.2 2%Lignocaine with 1:200,000 Epinephrine

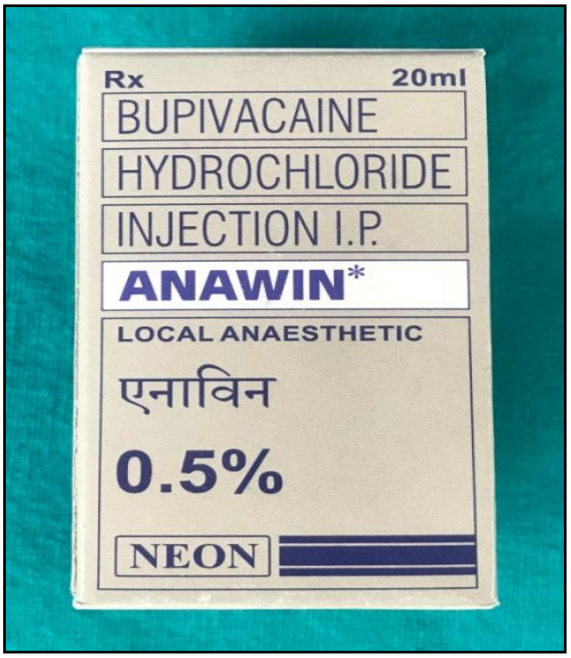


Fig.3 0.5% Bupivacaine

Fig.4 7.5% Sodium Bicarbonate

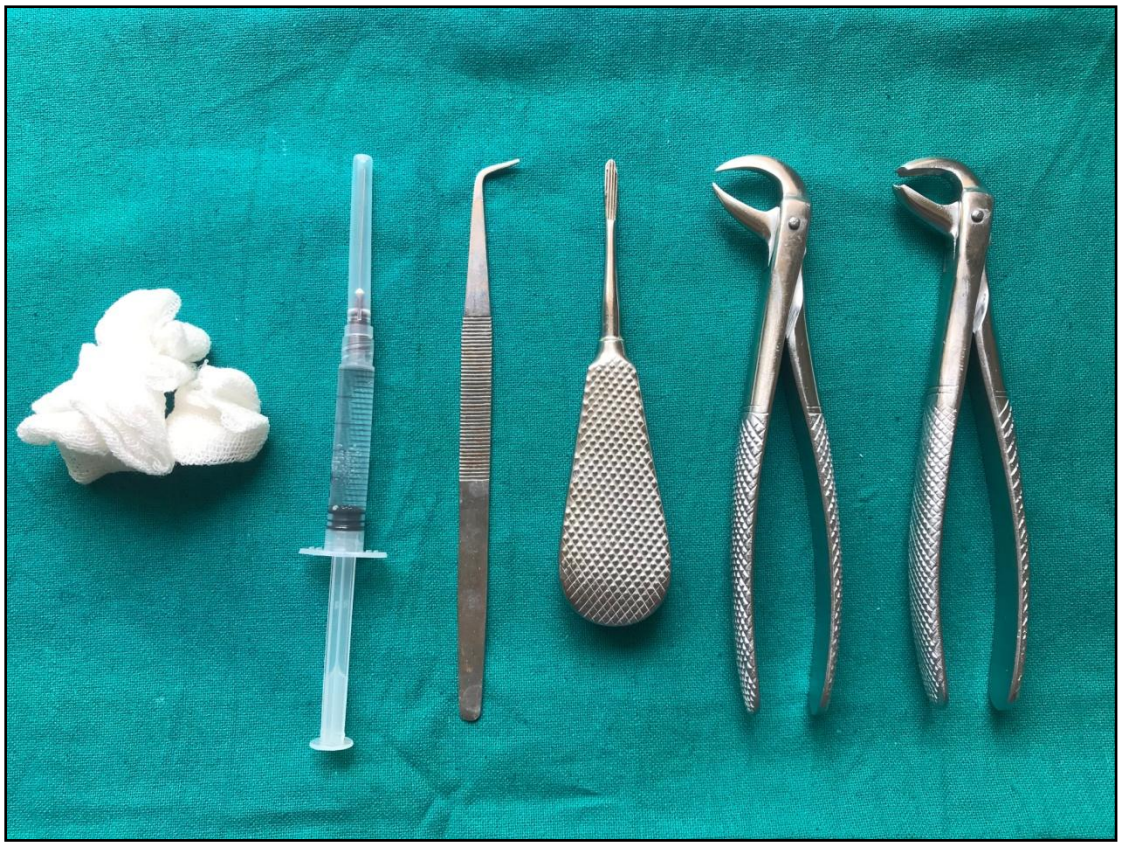


Fig.5 Armamentarium for mandibular molar extraction

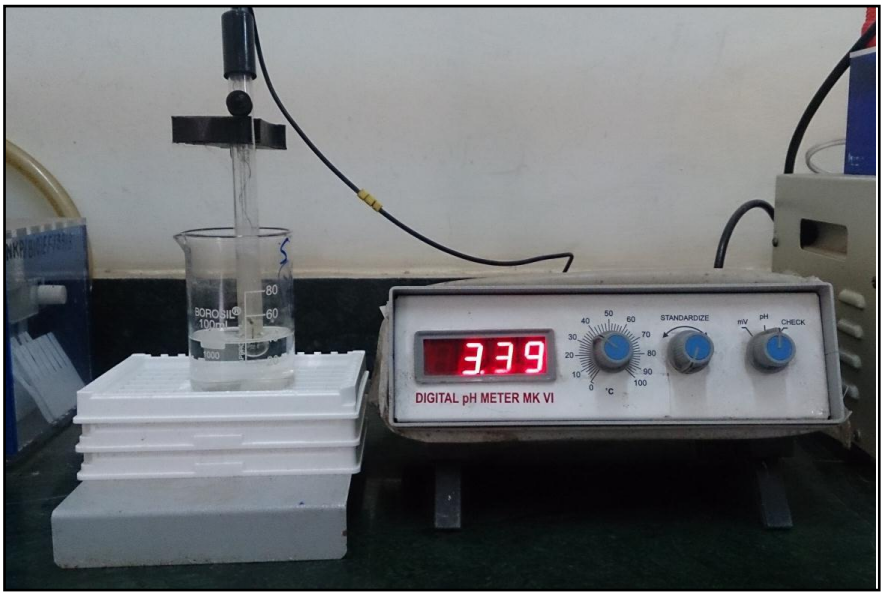


Fig.6 Pre buffering pH

Fig.7 Post buffering pH

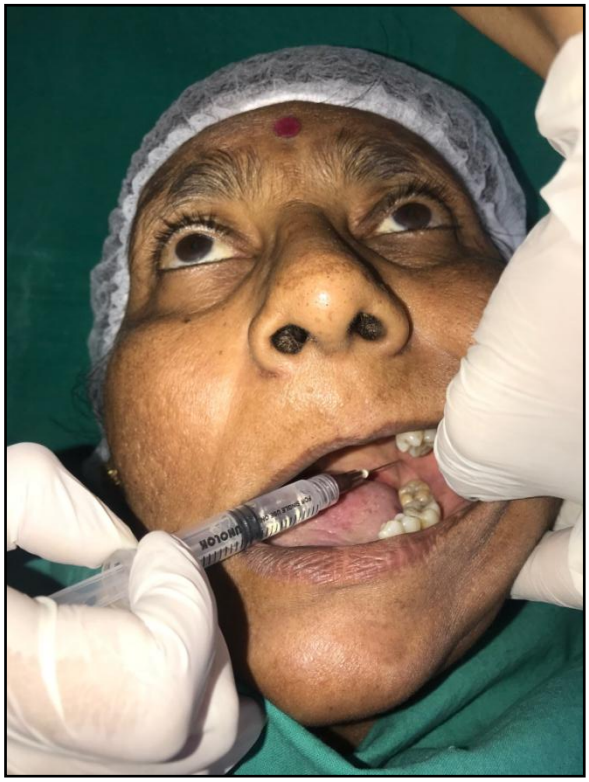


Fig.8 Inferior alveolar nerve block

ANNEXURE

ANNEXURE

ANNEXURE- I

CASE HISTORY PROFORMA

Case number-
Date-
Name-
Age/Sex-
Registration No-
Address-
Education-
Occupation-
Chief Complaint-
History of present illness –

Cause of tooth extraction-

- Caries
- Periodontitis
- Orthodontic extraction
- Fractured tooth

(Graded as "1", "2" ,"3" and "4" respectively.)
Past Medical History-
Past Dental History-
Drug Allergy History-
Family History

Personal History-

- Diet
- Oral habits
- Sleep
- Oral hygiene

Examination-

Extra-oral examination:

- Facial Symmetry
- TMJ
- Lymph nodes

Intra-oral Examination:

- Teeth present
- Missing teeth

- Root piece
- Occlusion
- Caries/attrition/abrasion/erosion/abfraction
- Mobility
- Others

Diagnosis-

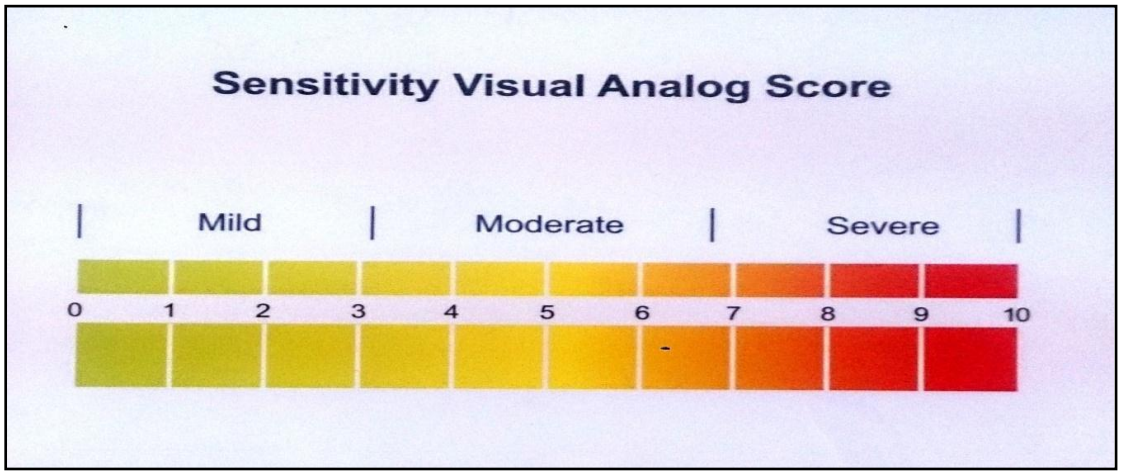
Radiographic investigations: IOPA, OPG,

Other investigations:

Advice:

ANNEXURE - II

ASSESSMENT FORM



ANNEXURE-III

INFORMED CONSENT FORM
(Confidential)

"To evaluate the anesthetic effectiveness of mixture of 2% Lignocaine with 1:200,000 epinephrine, 0.5% Bupivacaine and 7.5 % Sodium Bicarbonate for patients undergoing mandibular molar extractions using Inferior alveolar nerve block-

A randomized controlled trial"

वैयक्तीक माहिती

रूग्णाचे नाव :
वय/लिंग :
पत्ता :

दिनांक :

मोबाईल नंबर :

मी कबूल करतो की डॉक्टरांनी मला या संशोधन प्रकल्पाबद्दल समाधानकारक माहिती दिली आहे. मी माझ्या एक्स-रे, छायाचित्रे, इंप्रेशन आणि आवश्यकतेनुसार अन्य तपासण्या करण्यास सहमत आहे. मी या प्रकल्पात भाग घेण्यास सहमती देतो आणि या चाचणीच्या कालावधीत कोणतेही अन्य प्रकल्प एकत्रित करणार नाही. मला डेन्टल हॉस्पिटल किंवा इतर ठिकाणी दिलेल्या भेटीची तारीख आणि वेळ सांगितली आहे. मी डॉक्टर आणि पॅरामेडिकल कर्मचा-यांना सर्व बाबतीत सहकार्य करेल. या अभ्यासात मी माझ्या सहभागाचे निकाल प्रकाशित करण्यास परवानगी देतो. मला कोणतीही नुकसान भरपाई दिली जाणार नाही. असे करण्यासाठी कोणतेही कारण न देता मला कोणत्याही वेळी या संशोधन प्रकल्पातून बाहेर पडण्याचा अधिकार मिळालेला आहे. मी या अन्वये केलेल्या चाचणीत सहभागासाठी माझी संमती नोंदवित आहे.

१) रूग्णाचे नाव	स्वाक्षरी	तारीख	वेळ
२) साक्षीदाराचे नाव	स्वाक्षरी	तारीख	वेळ
३) डॉक्टरचे नाव	स्वाक्षरी	तारीख	वेळ

Master Sheet

S No.	Data Set	Age	Sex	VAS	DOO	DOA
1	Group B	29	M	2	90sec	6hrs 45mins
2	Group B	17	F	3	80sec	5hrs 5mins
3	Group B	42	F	2	86sec	3hrs 30 mins
4	Group A	35	F	3	90 secs	5hrs 10mins
5	Group A	54	M	3	80secs	6hrs 20mins
6	Group B	22	F	3	195sec	2hrs
7	Group B	30	F	4	240sec	4hrs 22mins
8	Group A	23	F	4	120secs	7hrs 10mins
9	Group A	42	M	3	85secs	7hrs 20mins
10	Group B	27	F	3	147sec	5hrs 30mins
11	Group A	24	F	4	60secs	6hrs 20mins
12	Group A	38	F	6	98secs	8hrs
13	Group B	23	F	4	116sec	3hrs 30 mins
14	Group B	21	F	5	104sec	7hrs 1mins
15	Group A	32	F	4	180secs	5hrs 25mins
16	Group B	32	F	3	180sec	5hrs
17	Group A	38	F	2	82secs	4hrs
18	Group B	25	F	4	145sec	5hrs 55mins
19	Group B	22	F	3	90sec	4hrs 30 mins
20	Group B	26	F	2	156sec	5hrs
21	Group B	22	F	3	140sec	5 hrs
22	Group B	38	F	4	316sec	3hrs
23	Group A	27	M	3	93secs	6hrs
24	Group B	39	M	3	180sec	6hrs 18mins
25	Group A	53	M	2	78secs	4hrs 20mins
26	Group B	35	F	4	185sec	4hrs 48mins
27	Group B	62	M	4	180sec	7hrs 25mins
28	Group A	36	F	4	100secs	4hrs 50mins
29	Group B	36	M	4	185sec	2hrs 10mins
30	Group B	22	M	3	95sec	6hrs 10mins
31	Group A	35	M	5	88secs	6hrs 5mins
32	Group B	42	F	4	108sec	4hrs 17mins
33	Group A	24	M	8	120secs	6hrs 15mins
34	Group B	44	M	3	130sec	3hrs 35mins
35	Group B	23	M	4	155sec	3hrs 30 mins
36	Group A	27	F	4	111secs	5hrs 50mins
37	Group B	39	F	4	130sec	4 hrs 22mins
38	Group B	55	M	4	158sec	4hrs 10mins
39	Group A	29	F	3	96secs	3hrs 10mins
40	Group B	28	M	5	285sec	3hrs 55mins
41	Group B	45	M	6	202sec	2hrs 35mins
42	Group B	43	F	4	158sec	2hrs 50mins
43	Group B	59	M	7	124sec	3hrs 30mins
44	Group A	32	F	5	85secs	5hrs 30mins
45	Group A	23	F	5	72secs	6hrs 15mins

S No.	Data Set	Age	Sex	VAS	DOO	DOA
46	Group A	43	F	4	75secs	7hrs 10mins
47	Group A	27	F	4	92secs	2hrs 50mins
48	Group A	35	M	4	100secs	11hrs10mins
49	Group A	41	F	4	102secs	5hrs 45mins
50	Group A	37	F	4	90secs	6hrs 25mins
51	Group A	28	F	3	93secs	8hrs 15mins
52	Group A	24	F	4	92secs	4hrs 30mins
53	Group B	38	F	3	194sec	2hrs 35mins
54	Group A	36	M	3	110secs	9hrs
55	Group B	58	M	4	190sec	4hrs 20mins
56	Group A	33	M	3	56secs	6hrs 20mins
57	Group A	31	M	3	63secs	2hrs
58	Group A	49	F	1	87sesc	5hrs 35mins
59	Group B	23	M	6	210sec	5hrs 15mins
60	Group B	30	F	5	138sec	9hrs 30mins
61	Group B	42	F	3	198sec	3hrs 50mins
62	Group A	25	M	1	98secs	6hrs 5mins
63	Group A	30	M	6	100secs	5hrs 40mins
64	Group B	29	M	4	151sec	7hrs 10mins
65	Group A	26	F	4	100secs	7hrs 15mins
66	Group B	32	F	3	225sec	1hr 30mins
67	Group A	24	M	4	76secs	4hrs 20mins
68	Group A	31	F	4	87secs	6hrs 10mins
69	Group B	56	F	4	153sec	5hrs 55mins
70	Group B	60	M	3	215sec	3hrs 30mins
71	Group A	24	F	4	99secs	7hrs
72	Group A	27	M	4	104sces	5hrs 5mins
73	Group B	55	M	4	134sec	3hrs
74	Group A	51	F	4	99secs	5hrs 20mins
75	Group A	30	M	4	93secs	4hrs
76	Group B	45	M	4	201sec	5hrs 10mins
77	Group A	39	F	4	102secs	5hrs 10mins
78	Group B	23	F	4	135sec	4hrs 45mins
79	Group B	28	F	3	165sec	5 hrs
80	Group B	32	M	3	190sec	3hrs50min
81	Group A	25	F	3	78secs	4hrs 50mins
82	Group B	43	M	3	300sec	2hrs50mins
83	Group A	25	M	3	220secs	5hrs 45mins
84	Group A	38	F	3	96secs	3hrs 20mins
85	Group A	27	F	3	130secs	5hrs 50mins
86	Group A	24	F	3	94secs	6hrs 15mins
87	Group B	37	F	3	240sec	4hrs 20mins
88	Group B	55	M	3	195sec	6hrs
89	Group A	32	M	3	200secs	6hrs 10mins
90	Group A	25	F	3	90secs	7hrs 5mins