Comparative Evaluation of Effects of Additives to 2% Lignocaine for Surgical Extraction of Impacted Mandibular Third Molars: A Randomized Controlled Clinical Study

A Thesis Submitted

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY
IN
CLINICAL RESEARCH

By
Rinku Kalra
Admission No: 17SCRH301011

Clinical Research Division, Department of Biosciences
School Of Basic and Applied Sciences
Galgotias University, Greater Noida,
Uttar Pradesh- 226001

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Uttar Pradesh- 226001

2022

CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled "**Comparative Evaluation of Effects of Additives to 2% Lignocaine for Surgical Extraction of Impacted Mandibular Third Molars: A Randomized Controlled Clinical Study"** in fulfilment of the requirements for the award of degree of Doctor of Philosophy in Healthcare and Clinical Research and submitted to Galgotias University, Greater Noida, is an authentic record of my own work carried out during a period from Feb. 2017 to Dec 2021 under the supervision of Prof. Ranjana Patnaik

The matter embodied in this thesis has not been submitted by me for the award of any other degree of this or any other University/ Institute

(Dr Rinku Kalra)

This is to certify that the above statement made by the candidate is correct to the best of my knowledge.

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Sign of Supervisor Sign of External Examiner

STATEMENT OF THESIS PREPARATION

Comparative Evaluation of Effects of Additives to 2% Lignocaine for Surgical Extraction of Impacted Mandibular Third Molars: A Randomized Controlled Clinical Study

Submitted for the Degree of **Doctor of Philosophy In Healthcare And Clinical Research**

Under the guidance of **Prof. Ranjana Patnaik**

Specifications regarding thesis format have been closely followed
The contents of the thesis have been organized based on the guidelines
The thesis has been prepared without resorting to plagiarism
All sources used have been cited appropriately
The thesis has not been submitted elsewhere for a degree

Signature of the student:

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APPROVAL SHEET

This thesis, entitled '**Comparative Evaluation of Effects of Additives to 2% Lignocaine for Surgical Extraction of Impacted Mandibular Third Molars: A Randomized Controlled Clinical Study**' by **Dr. Rinku Kalra** is approved for the degree of **Doctor of Philosophy In Healthcare And Clinical Research**

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Date:

Place:

ABSTRACT

ABSTRACT

Adrenaline bitartrate is the most common vasoconstrictor used to counteract the vasodilatory properties of amide local anesthetics. Use of adrenaline has certain contraindications and disadvantages specially in patients with cardiovascular diseases. It is evident from the literature that there are conflicting opinions about usage of adrenaline with local anesthetics in dental procedures. Use of many drugs as additives to local anesthetics has been well documented for regional and spinal nerve blocks in the medical literature. However, there is dearth of such studies in dentistry and till date, Lignocaine hydrochloride with Adrenaline bitartrate is considered as the standard solution for local anesthesia for oro-facial procedures. Surgical extractions of impacted mandibular third molars, the most common surgical procedure in Oral and Maxillofacial surgery practice, have been used as a model for various comparative studies related to administration and evaluation of antibiotics, analgesics, steroids, use of surgical techniques, drains, suture materials etc

This double blind randomized controlled clinical study was thus designed to comparatively evaluate effectiveness of Clonidine hydrochloride, Potassium chloride, Dexamethasone sodium phosphate and Chlorpheniramine maleate Vs Adrenaline bitartrate, used as additives to 2% lignocaine hydrochloride for surgical extractions of impacted mandibular third molars in healthy young adults. The evaluation was based on onset, duration, depth of anesthesia, post-operative pain control, bleeding control and changes in hemodynamics.

A statistically significant difference was obtained for inter group comparison with Kruskall Wallis ANOVA for all variables used. Mann Whitney test using pair-wise comparison showed the effect of each drug pair. It was observed that number of injections used were maximum for CPM and plain Lig grp and least for Dexa and KCl grps. The onset was fastest with KCl and slowest for CPM grp. The duration of action was maximum for Dexa and least for plain Lig grp. Intra-operative pain control was best with Dexa and least with CPM grp, whereas, post-operative pain control was best with CPM and least with plain Lig grp. Bleeding control was best with Adr and least

with plain Lig grp. Hemodynamic stability was best seen in Dexa and Clonidine grps and least with Adr.

Thus, none of the drugs used as a substitute fo adrenaline has completely served the purpose, however, based on the statistical results, Dexamethasone and Clonidine are still comparable to Adr for most variables with an added advantage of better stability in hemodynamic variables. Further studies focusing on pH of the mixtures, shelf life of the solutions, comparison of drug plasma levels, usage in medically compromised pts, with other oro-facial block techniques, may be planned.

ACKNOWLEDGEMENTS

All my achievements, success, growth, good deeds, merits, in fact, my very existence are only due to blessings of the all merciful and ever loving GURUJI (ALMIGHTY), without whom, I would have been nothing! This feather in the hat is due to Him! I bow in gratitude to Him and dedicate this work to His Lotus Feet!

Parents are the greatest blessings and their support, encouragement and blessings have moulded me to what I am today. No word or deed can repay them. Their help in all possible ways made me complete this!

I am blessed with a mentor who entered my life as a God sent Angel. She is ever supportive, motivating, approachable and an extremely kind human. I am really indebted to Dr Ranjana Patnaik Madam for making me realise that I can complete this and Madam got me to this point which I had never imagined I would ever reach. My heartfelt gratitude to Madam!

I have no words to thank our co-ordinators Dr Gaurav Sir and Dr Charu Madam who have worked relentlessly for all the academic and administrative work which was required for easy facilitation of this program right from inception. They have been ever supportive with their ever-smiling faces! They helped in streamlining every single process which has finally led me to this day!

I am humbled by the approach of all the officials and senior faculty at the University, specially, Dr Preeti Bajaj Madam (Vice-Chancellor, Galgotias University), Dr Naresh Kumar Sir (Dean Research), Dr Arvind Jain Sir (Dean, SBAS) for every possible support and inputs to get this course to completion!

Absolutely instrumental in completion of this task, is my brother, Dr Dheeraj Kalra. From motivating me to appear for the entrance exam for PhD, getting me to do this project, completing the statistics, to putting this work on paper, he has been with me throughout. Equally important is the selfless help and support my sister-in-law Dr Pooja Kalra has extended.

My heartfelt gratitude to all my PhD colleagues, who have been a great support. I wish to specially acknowledge my colleagues, Satyajyoti and Kaptan, who have stood by me in all possible ways, helped in administrative tasks even in my absence at times, and made sure to drag me to the finish line!

I can never forget the selfless support extended by the management, my seniors, colleagues and post-graduate students at YMT Dental College and Hospital. Dr Kavita Pol Nalavade Madam (Director) and Dr Meghna Vandekar Madam (Dean) have always believed in my potential and endeavours and supported me throughout. This study would not have been completed without constant contribution from my Head of Dept. Dr Shreyas Gupte. He has always guided and brainstormed me to perfection, right from selection of study topic to its methodology, publications and creating this manuscript. I am absolutely thankful to all my colleagues at YMT Dental College who have supported me professionally and helped in managing my departmental roles and duties when I was engrossed in this endeavour. My students, Nidhi, Drishti and Nitin have worked for me tirelessly and helped me carry out all the clinical steps ethically and smoothly. I extend my heartfelt gratitude to the staff nurses and attendants in the dept. who had been extremely helpful in the conduct of this research. I also acknowledge the valuable inputs, expertise and guidance from Dr Mukund Nayak Sir (Asso. Prof, Anaesthesiology)

All the patients who consented to be a part of this experimental study have made this research possible and I am greatly indebted to all of them.

Last but not the least, I thank all my friends and well-wishers who have directly or indirectly contributed towards the success of my research.

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LIST OF ABBREVIATIONS

Abbreviation	Full form
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
RCT	Randomized Clinical Trial
ASA	American Society of Anaesthesiologists
pts	Patients
QOL	Quality of Life
CVD	Cardiovascular diseases
MI	Myocardial Infarction
HTN	Hypertension
Conc.	concentration
mg	Milligram
ml	Millilitre
Cc	Cubic centimetre
mm	Millimetre
Hg	Mercury
cm	Centimetre
kg	Kilogram
Inj	Injection
IV	Intravenous
IM	Intramuscular
SC	Subcutaneous
SM	Submucosal
IS	Intraspace (pterygomandibular space)
IO	Intraosseous
IP	Intra-pulpal
pdl	Periodontal
h	Hour
hr	Hour
min	Minutes
sec	Seconds
LITM	Lower impacted third molar
VAS	Visual Analog Scale
SD	Standard Deviation
ANOVA	Analysis Of Variance
Cap	Capsule
Tab	Tablet
tds	Thrice daily
Fig	Figure
F	Female
M	Male
Grp	Group

Pre-op	Preoperative
Post-op	Post-operative
B	Baseline
BP	Blood pressure
ECG	Electrocardiogram
CO	Cardiac output
SV	Stroke volume
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MABP	Mean arterial blood pressure
HR	Heart rate
Ptm	Pterygomandibular
LA	Local anaesthetic
GA	General anesthesia
Lig	Lignocaine hydrochloride
Lido	Lidocaine
Adr	Adrenaline bitartrate
Epi	Epinephrine
NE	Norepinephrine
Cloni	Clonidine hydrochloride
Dexa	Dexamethasone Sodium Phosphate
KCl	Potassium chloride
CPM	Chlorpheniramine maleate
PMN	Polymorphonuclear Neutrophils
HPLC	High Performance Liquid Chromatography
COMT	Catechol-O-Methyl Transferase

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2. Comparative evaluation of effectiveness of 2% lignocaine hydrochloride with 1.5% potassium chloride versus 2% lignocaine hydrochloride with adrenaline bitartrate versus 2% lignocaine hydrochloride as local anaesthetic for adult patients undergoing surgical extraction of impacted mandibular third molars: a randomized controlled clinical study Journal of Oral Med Oral Surg, 2021;27:55

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LIST OF PRESENTATIONS

1. Comparative evaluation of effectiveness of Dexamethasone and Adrenaline as additives to lignocaine for Pterygomandibular neve blocks in adult patients: a randomized controlled clinical study, presented at International e-conference on Forensic Science and criminology, Forensis Agora, 15th-16th May 2021.

2. Comparative evaluation of effectiveness of Clonidine and Adrenaline as additives to lignocaine for Pterygomandibular nerve blocks in adult patients: a randomized controlled clinical study, presented at International Conference on Advanced Materials for Next Generation Applications (AMNGA-2021), 29th-30th September,2021

Chapter 1

INTRODUCTION

INTRODUCTION

Local anesthetics (LA) are crucial asset in any clinician's armamentarium. LA are inseparable part of dentistry. They not only aid in carrying out various dental and minor surgical procedures, but also complement systemic analgesics in achieving optimum pain control.

Pain control in a setting of iatrogenic injury (eg dental extractions/ surgical procedures) is a responsibility of the treating clinician. Primary aim of any clinician is to achieve profound intra-operative anesthesia and adequate post-operative analgesia, thereby reducing patient discomfort and minimizing systemic intake of analgesics and their subsequent undesirable adverse effects. Various local anesthesia techniques and local anesthetics have been used and documented in dental literature.

The advent of local anesthetics dates back to 1859 when cocaine was isolated by Niemann. Following this, there were series of breakthrough events as summarized in **table 1**.[1] In order to extend the duration of action of cocaine, Heinrich Braun in 1903, suggested that epinephrine added to cocaine may serve as a "chemical" tourniquet by retaining cocaine molecules at the site and will thus aid in prolonging duration of action. Introduction of procaine in 1904 by Alfred Einhorn and synthesis of lidocaine in 1943 by Nils Lofgren were major turning points in history of local anesthetics. Other local anesthetics, mepivacaine (1960), prilocaine (1965), bupivacaine (1983) and articaine (2000) were subsequently reported. Adequate duration and efficacy, less toxicity and rare incidence of allergenicity made Lidocaine the 'Gold standard', against which other LAs are compared. [1]

Injectable Lignocaine for dental use in India, is available as a 2% solution of lignocaine hydrochloride with or without vasoconstrictor, most commonly Adrenaline (Adr). (**Fig 2 and 3).**

All LA molecules, except Cocaine have an inherent vasodilatory effect (**Table 2**)[2]. Due to this, a significant amount of drug enters systemic circulation within a short span of time, thereby causing, decreased duration and depth of anesthesia[3], lack of hemostasis, increased potential for systemic toxic reactions. Additionally, an inadequate depth of

Date	Individual / Company	Event
1859	Niemann	Isolation of cocaine
1884	Koller	Cocaine topical anesthesia
1884	Halstead	Cocaine regional anesthesia
1885	Corning	Tourniquet to retard absorption
1903	Braun	Epinephrine as a chemical tourniquet
1904	Einhorn	Synthesis of procaine
1905	Braun	Clinical use of procaine
1920	Cook Laboratories	Anesthetic syringe and cartridge
1943	Lofgren	Synthesis of lidocaine
1947	Novocol	Dental aspirating syringe
1948	Astra	Lidocaine for dentistry
1959	Cook-Waite	Sterile disposable needle

Table 1: Major events in history of dental anesthesia[1]

Local anesthetic	Vasodilating Activity
Articaine	1 (approximately)
Bupivacaine	2.5
Etidocaine	2.5
Lidocaine	1
Mepivacaine	0.8
Prilocaine	0.5
Tetracaine	NA

NA: not available

Table 2: Relative Vasodilating Values of Amide-Type Local Anesthetics[2]

anesthesia causes discomfort to the patient with a resultantly higher levels of endogenous catecholamine than that used in dental anesthesia[4]

The addition of vasoconstrictors, most commonly, Adr, improves duration and depth of anesthesia, aids in local hemostasis and delays systemic absorption of LA from the site of injection, thereby decreasing the possible risk of systemic toxicity due to LA[5].

However, use of Adr containing solutions is associated with an increase in Adr levels per se with significant[6] or non-significant[7] cardiovascular changes. In literature, opinions on using Adr with lignocaine are debatable. Goldstein et al[8] have reported that even a relatively small dosage of Adr (1:100,000) administered with 2% lignocaine for intraoral block anesthesia in healthy patients, was associated with increased circulating Adr levels and resultant cardiovascular changes.

According to the report of the 1964 working conference of the American Dental Association and the American Heart Association, use of usual conc. of vasoconstrictors in dental LA, if injected cautiously, slowly with aspiration, in pts with CVD, is not a contraindication. [9]

According to Malamed[2], Adr, although most frequently used, is not an ideal drug and its benefits and risks have to be given due considerations in any clinical situation. Just like LA, Adr also reaches systemic circulation the site of injection and. Since it has α and β effects, (**Table 3**)[2] it can lead to deleterious effects on heart. Even with administration of a single cartridge of lignocaine with Adrenaline (1:100,000), resting plasma Adr levels (39 pg/mL) are doubled[10]

Drug	α1	α2	β1	β2
Epinephrine	+++	+++	+++	+++
Norepinephrine	++	++	++	+
Levonordefrin	+	++	++	+

Table 3: Adrenergic Receptor Activity of Vasoconstrictors[2]

Elevation of plasma levels of Adr is linearly dose dependent and lasts from few minutes to 30 minutes after administration[11]. It was previously accepted that usual doses of Adr administered with LA for intraoral anesthesia did not lead to cardiovascular response. It was believed that endogenously released Adr made the patient more prone to an untoward adverse event compared to that from an exogenously administered Adr[12] Evidence now suggests that plasma Adr levels after intra-oral injections are equivalent to those resulting from moderate to heavy exercise[5] and are there by associated with moderate increase in cardiac output (CO) and stroke volume (SV), with minimal change in BP and HR[13]. Even with usual precautions, (e.g., aspiration, slow injection) in cardiac patients, absorbed Adr can lead to 'Epinephrine reaction'[14].

However, Niwa et al[15] state that low dose of Adr as in dental anesthesia, does not lead to serious effects in cardiac patients. This view was supported by Cintron et al[16] (who studied Adr related BP and HR changes in pts with recent MI and Blinder et al.[17]

The existing literature is thus highly controversial. Well planned clinical trials are required to reach to a definitive conclusion. Considering that most of the literature has brought out the question of adverse events and hemodynamic derangements, use of Adr safely in a patient with cardiovascular disease and comorbidities is questionable and the need of the hour is to find an alternative drug which will be medically safe, chemically stable, readily available, synergistic and/ or additive to LA similar to Adr and cost effective but carries no systemic risks as adrenaline. In medical anesthesia, various drugs have been reported as additives with LA for different nerve blocks. With that background, this study was thus planned to comparatively evaluate the quality of anaesthesia, pain control, vasoconstriction effects and hemodynamic stability in patients undergoing surgical extraction of impacted mandibular third molars under pterygomandibular nerve blocks (Fig.7) with 2% lignocaine and clonidine, 2% lignocaine and potassium chloride, 2% lignocaine and dexamethasone and 2% lignocaine and chlorpheniramine with standard 2% lignocaine and 2% lignocaine with Adrenaline 1:80000.

(The rationale for selecting these molecules has been discussed later). Thus, the need for this study was,

To search for an alternative additive in place of Adrenaline, which should be able to:

a) Provide optimal onset of action

b) provide optimum post-operative analgesia after adequate intra-operative anaesthesia so as to prevent traumatic lip/cheek bite

c) increase depth of anaesthesia without reduction in potency of Lignocaine

d) prevent systemic adverse effects due to Lignocaine and should not itself cause any serious adverse systemic reaction

e) Minimize the dose of Lignocaine required

f) Minimize the need for post-operative analgesics

g) Minimize blood loss by counteracting vasodilatory effect of lignocaine, without causing any residual tissue damaging and systemic adverse effects

Research Question: Is there any difference in quality of anaesthesia, pain control, vasoconstrictive actions, hemodynamics with 2% lignocaine hydrochloride with Adrenaline compared with 2% lignocaine hydrochloride with additives used for pterygomandibular nerve blocks for surgical extraction of impacted mandibular third molars in adult patients?

Null Hypothesis (H0)

There is no difference in quality of anaesthesia, pain control, vasoconstrictive actions, hemodynamics with 2% lignocaine hydrochloride with Adrenaline compared with 2% lignocaine hydrochloride with additives used for pterygomandibular nerve blocks for surgical extraction of impacted mandibular third molars in adult patients.

Research hypothesis: There is a difference in quality of anaesthesia, pain control, vasoconstrictive actions, hemodynamics with 2% lignocaine hydrochloride with Adrenaline compared with 2% lignocaine hydrochloride with additives used for pterygomandibular nerve blocks for surgical extraction of impacted mandibular third molars in adult patients

Chapter 2

REVIEW OF LITERATURE

REVIEW OF LITERATURE

In 1955, **New York Heart Association** recommended that, for dental pts with history of cardiac diseases, the amount of epinephrine should not be exceeded than 0.2 mg (<11 cartridges of 1:100,000 epinephrine) per session.[18] **Vernale** (1960) used 1:1,00,000 epinephrine with 2% lidocaine in both, normotensive and hypertensive individuals and reported that SBP increased more in hypertensive subjects There was however no significant difference in the amount of BP changes between 2 groups.[19]

Keesling and Hinds (1963) used Epinephrine in various concentrations with lidocaine to study duration and depth of anesthesia and concluded that concentrations of 1: 250,000 to 1:300,000 were as equally effective as 1:50,000 epinephrine to prolong duration of action of lidocaine.[20]

In 1964, **Working Conference of the American Dental Association and the American Heart Association** concluded that, using dental LA solutions with usual conc. of vasoconstrictors, injected cautiously, slowly with aspiration, in pts with CVD, is not a contraindication.[9]

Cowan (1964) reported that the duration of anesthesia was more prolonged with use of epinephrine in concentration of 1: 1,00,000 as compared to that with 1: 200,000. It was suggested that for practical vasoconstriction in dental surgical procedures, the ideal level of epinephrine is 1/80-100,000. However, levels beyond these, may lead to deleterious effects. In procedures where haemostasis is not a major concern, the usage of epinephrine in concentration of 1/3,00,000 may be considered.[21] **Kennedy et al** (1966) studied effects of 1:2,00,000 Epi on cardiovascular parameters with LA for epidural, brachial plexus and subarachnoid blocks and reported statistically significant changes for epidural and brachial plexus blocks. It was also concluded that as the concentration of epinephrine is increased above 1: 2,00,000, duration of block remains unchanged.[22] **Gangarosa and Halik** (1967) studied the effects of concentration of epinephrine on anesthesia with lidocaine and concluded that 1: 300,000 epinephrine was comparable with 1: 1,00,000 epinephrine in terms of degree of hemostasis, duration and depth of anesthesia.[23]

Barkin et al (1978) reported their findings in 225 patients undergoing oral surgical procedures using electrocardiogram (ECG). Preoperative or intraoperative dysrhythmias were detected in 36pts when 1: 100,000 epinephrine was used with 2% lidocaine. Discrimination between pre-existing dysrhythmia and resultant post-injection dysrhythmia could not be inferred, hence, it was suggested that this incidence should serve as evidence on the basis of which, it was strongly recommended to have routine pre-operative ECG monitoring or precordial stethoscope for all patients receiving local anesthetics.[24]

Goebel et al (1980) used maxillary supra-periosteal infiltration with 1.8 mL of 2% lidocaine with 1: 100,000 epinephrine and 1.8 mL of 2% lidocaine without epinephrine and compared peak plasma concentrations of lidocaine. It was noted that peak plasma concentration of lidocaine was not significantly different with usage of 1: 100,000 epinephrine.[25] **Tolas et al** (1982) reported that 5min after injecting 1.8 mL of 2% lidocaine with 1: 100,000 epinephrine (18 ug of epinephrine) intraorally, plasma epinephrine concentration was 240 $\pm$ 69 pg/ml, whereas, the baseline level was 98 + 38 pg/ml. However, levels did not alter when plain lidocaine was injected. It was also shown that, mean arterial pressure, heart rate and rate pressure product, in healthy subjects, remained unchanged after epinephrine injection.[10]

Kabambe (1982) compared amount of analgesia in 162 patients with 2 % Lig with and without Adr for dental extractions and minor oral surgery. It was shown that plain lignocaine did not provide satisfactory analgesia in more than 50% pts.[3]

Goldstein et al (1982) showed a significant rise in HR, SBP and CO in 21 subjects undergoing third molar surgeries. There was no significant change in DBP. Plasma NE levels showed a rise of 60% intra-operatively in non- diazepam subjects.[8]

Smith and Pashley (1983) used pistol-grip syringe for IV, IO, IP, SC, Pdl, IM, and SM injections in dogs and compared normal saline, 2% lidocaine with and without 1:100,000 Epi, 3% Mepivacaine and 1:100,000 Epi alone and reported no significant changes in BP and HR with all the routes.[26] In the same year, **Holroyd** (1983) stated that the amount of injected Epi is much lower than the endogenously released catecholamines in response to stressful situation like dental extraction.[12] **Chernow et al** (1983) used epinephrine in local anesthetic for inferior alveolar nerve block and showed that for 2 min there was a transient rise in heart rate and plasma epinephrine concentration rose to 3.5 times the pre-injection levels after 8 min, without any significant changes in hemodynamic variables.[7] However, **Dionne RA et al** (1984)

reported an approximate rise of 5 times in plasma epinephrine titres in 5 min while using 2% lidocaine with 1: 100,000 epinephrine unilaterally for extractions of maxillary and mandibular third molars. There was significant rise in heart rate and systolic BP. The same parameters showed no significant increase with contralateral use of plain 2% lidocaine for third molar extractions.[27]

Fellows et al (1985) reported that IV infusions of Epi in 7 healthy young males resulted in 30% rise in HR, which remained elevated even after 30 minutes after infusion was stopped, although the plasma Epi conc. returned back to baseline 15min later. There was an increase in metabolic rate and SBP. The DBP showed a decrease. There was vasodilation in calf muscles due to the infusion.[28] In the same year, **Yagiela et al** (1985) studied interactions between LA with and without epinephrine, norepinephrine and levonordefrin and phenelzine, chlorpromazine and desipramine, in dogs and noted significant changes in vasoconstrictor effects with desipramine, specifically with levonordefrin and norepinephrine.[29] **Cioffi et al** (1985) reported an increase in plasma epinephrine from 28 $\pm$ 8 pg/mL to 105 $\pm$ 28 pg/mL after 5 min using 1.8 mL of 2% lidocaine with 1: 100,000. Mean arterial pressure remained unchanged. However, heart rate increased along with plasma epinephrine concentration.[30]

Stratton et al (1985) reported 58% and 74% increases in CO with IV infusion of 50 and 100 ng/kg/min of Epi, respectively using isotopic ventriculography. A 20% to 30% rise in cardiac rhythm was reported in dose- dependent manner.[31]

Cintron et al (1986) reported his results involving 40 pts with recent history of acute MI, injected with 2% lido and 1:100 000 Epi. BP, HR, ECG and other cardiac symptoms showed no significant changes to anesthesia and dental procedures including tooth extraction, indicating that limited dental procedures could be safely carried out in pts with recent uncomplicated MI.[16] In the same year, **Freyschuss et al** (1986) studied the metabolic and cardiovascular effects of IV infusion of Adr in 11 healthy subjects. Significant changes in CO and vascular resistance were observed with invasive methods of measurements whereas, non-invasive methods depicted only moderate changes with the same.[32] When **Meyer** (1986) compared cardiovascular response of normotensive and hypertensive subjects using plain lidocaine, lidocaine with 1:100,000 epinephrine and lidocaine with 1:20,000 Nor epinephrine during extractions, he stated that, differences in heart rate and blood pressure were comparable in plain lidocaine and lidocaine with epinephrine groups. A significant rise in blood pressure and a fall in heart rate were noted with lidocaine with NE.[33]

Again, **Meyer** (1987) carried out dental extractions in normotensive and hypertensive subjects with 2% Lido, Lido with Epi and Lido with NE. It was observed that BP and HR changes in the 2 groups were similar, whereas. Use of NE produced a significant increase in BP and decrease in HR and concluded that NE should not be used in hypertensive subjects for dental extractions.[4] **Troullos et al** (1987) studied cardiovascular effects and plasma levels of catecholamine with administration of LA with Epi. It was reported that the level of Epi, 1 minute post injection, was 27.5 times the baseline level along with significant increase in SBP, HR and rate-pressure product. It was concluded that Epi should be used with due precautions in CVD pts.[6]

Sung et al (1988) assessed cardiovascular effects of infused Epi in patients with coronary artery disease. Even with lowest infusion rates, significant changes in SBP, HR, rate-pressure product, CO and SV were recorded, even with similar dose response curves to Epi in healthy subjects and CAD pts. At the lowest infusion rate, increase in Epi conc. was equivalent to conc achieved with 1.8 to 5.4 ml of LA with Epi 1: 100,000.[34] In the same year, **Abraham-Inpijn et al** (1988) also evaluated cardiovascular changes in forty patients pre, intra and post-operatively for tooth extraction under local anesthesia with epinephrine. Changes in HR, BP and ECG were studied for forty normotensive and hypertensive subjects. A statistically significant rise in blood pressure was obtained in all subjects, with greater raise in hypertensive pts.[85]

Kiyomitsu et al (1989) stated that anesthesia with 1: 80,000 epinephrine added to 2% lidocaine led to increase in HR, CO, and SV and decreased afterload and MABP. The severity of these responses was more evident in elderly pts.[86] Then, **Kaneko et al** (1989) studied relationship between plasma Epi levels and circulatory changes in 11pts undergoing orthognathic surgery under general anesthesia. There was a direct relationship between the amount of Epi injected intra-orally and plasma levels. All the cardiac parameters like CO, SV, BP, rate pressure product increased in dose dependent manner.[13]

Yagiela (1991) mentioned about 6 clinical studies on blood levels of Epi and has provided a comprehensive figure collating data from those studies. It has been shown with regression analysis that a single dental cartridge of 2% lido with 1:100,000 Epi doubles the baseline levels.[5] Also, **Knoll-Kohler et al** (1991) conducted a randomized study and concluded that the serum epinephrine concentration is determined by the amount of its absorption from the site of injection and that the risk of inducing a cardiovascular adverse event during oral surgical procedure is directly related to the

extent of surgery and indirectly related to the epinephrine dose in the anesthetic solution.[37] In the same year, **Niwa et al (1991**) showed that left ventricular diastolic function was activated with epinephrine and inactivated with NE when healthy human subjects were infiltrated with lidocaine with epinephrine or NE.[38]

Renald Perusse et al (1992) reviewed contraindications to use of vasoconstrictors in patients with cardiovascular problems. They have discussed use and adverse effects of these in specific cardiac conditions and mentioned absolute contraindications for clinical practice.[39]

Brown RS (1994) documented that LA without vasoconstrictors when used for dental procedures, do not provide adequate control of pain, thereby increasing the levels of endogenously secreted catecholamines, particularly, NE, in response to the stressful situation.[40] On similar lines, **Jastak et al** (1995) stated that Epi injected with dental LA significantly raises plasma levels. However, elevated levels of plasma Epi does not necessarily increase sympathetic tone. When released during sympathetic nervous system stimulation, the primary role of Epi is to bring about vasodilation in skeletal muscles. Intravascular injections of 15 to 20 ug of Epi can significantly raise HR, hence, aspiration before injection should be practised specially in cardiac pts.[11]

Meechan (1997) reported no significant change in BP in hypertensive dental pts undergoing surgical procedure with 2% lidocaine with 1:80,000 epinephrine.[41]

Pallasch (1998) stated that the changes in hemodynamics as a result of increased conc, of plasma Epi are evident only for short time duration due to short plasma half-life of Epi, ie less than 1 minute. Exogenously administered Epi undergoes metabolism with the help of catechol-O-methyl transferase (COMT) in the blood, lungs, liver and other body tissues and is eliminated in approximately 10 minutes. It was stated that although Epi causes rise in HR, SV, SBP, cardiac automaticity and myocardial oxygen consumption, it decreases DBP.[42] When **Blinder et al** (1998) studied ECG changes in 40 pts with history of cardiac disease, undergoing dental extractions under LA using Holter monitor for 24 hours, it was noted that 15 pts out of which 8 were on digoxin, showed ECG changes within 1st 2 hrs after LA. It was concluded that pts on digoxin were more prone to have ECG changes with LA than other CVD pts. HR increased more when vasoconstrictor was added to LA.[17]

In 2000, **Niwa et al** suggested that 3.6 mL 1:80,000 epinephrine and lidocaine can be safely injected in pts with exercise capacity of more than 4 metabolic equivalents.[43]

Again, **Niwa et al** (2001) evaluated hemodynamic responses to 1.8 mL 2% lidocaine with 1:80,000 epinephrine in 27 patients with cardiovascular disease with impedance cardiology. lidocaine- epinephrine was concluded to be safe since it showed no significant hemodynamic changes in patients with CVD.[15] In the same year, **Meechan et al** (2001) studied effects of LA with and without Epi in pts who had undergone cardiac transplants. It was observed that such pts had a significant rise in HR, 10 min post injection of LA with Epi for dental procedures. No significant change in HR and BP was reported with plain LA solution.[44] **Bader et al** (2001) reviewed literature on effects of Adr with LA in hypertensive subjects and reported that adverse effects in dental pts with history of HTN are uncommon. It was recommended to have a prospective long-term protocol that documents pre-existing cardiovascular diseases along with ongoing medications must be used to evaluate effects in dental procedures in further studies.[45]

Faraco (2003) published their results involving restorative management on maxillary molars in 19 normotensive adults using Lig with Epi 1:1,00,000 as infiltration, with and without diazepam. It was concluded that during such clinical procedures, there were no clinically and statistically significant changes in the parameters. During anesthesia, significant differences in DBP were observed between groups.[46]

Meral et al (2005) conducted a study on 17 healthy patients to study adverse hemodynamic effects of Adr with lignocaine used for impacted third molar surgeries. HR, MABP, peripheral oxygen saturation range, electrocardiography and blood levels of Adr were measured. It was concluded that Adr -lignocaine combination was effective and did not lead to any adverse consequences in all the 17 subjects. However, it was recommended that close monitoring of high-risk pts is essential when Epi is administered and even in healthy subjects, intravascular injection must be prevented.[47]

Again, **Faraco et al** (2007) presented their results from dental implant surgeries in 11 normotensive adults under LA with 2% lido with Epi 1:80 000. Maximum changes in SBP were observed before anesthesia and during incision placement. DBP decreased during osteotomy and increased 10 min post procedure. Maximum changes in HR were observed post-procedure. However, the changes were not statistically significant.[48]

Neves et al (2009) studied ECG and BP in 62 patients with coronary artery disease undergoing restorative procedures under LA with and without Epi without any change in their systemic cardiac medications. No notable changes were observed in BP and HR. No episodes of ischemia and arrhythmias in either group were noted, thus

concluding that administration of vasoconstrictor is safe within the recommended range.[49]

In 2012, **Figallo et al** reviewed RCTs published in the preceding decade on cardiovascular effects of LA in pts with cardiopathies and concluded that in controlled hypertensives and CVD pts after the stipulated time period when dental treatment may be contraindicated, vasoconstrictors may be used cautiously with a dose limited to 1.8- and 3.6-ml. However, studies on severe hypertensives and advanced cardiac problems were recommended.[50] In the same year, **Ketabi et al** (2012) showed clinically and numerically insignificant but statistically significant rise in BP and HR 10 min after injection of lido and Epi 1:80000 when compared with baseline for both, infiltrations and inferior alveolar nerve blocks.[51]

In 2015, **Managutti et al** (2015) reported their results on bilateral mandibular extractions with 2% lig and 1:80000 Adr and 2% lig and 1:200000 Adr. It was shown that efficacy and duration was the same with both the conc. SBP and HR were more elevated with Adr 1:80000, hence 2% lignocaine with 1:200000 Adr was recommended in cardiac and aged pts.[52] In the same year, **James et al** (2015) conducted single tooth extraction in 325 healthy adults with Lig with and without Adr. It was shown that there were no significant differences in hemodynamics between the groups for simple extraction.[53]

Fernandez (2017) published their study on SBP, DBP and HR assessed pre and 5 min post infiltration in 120 pts with 3 % mepivacaine and 3% mepivacaine with 1:100 000 Epi. There was no significant change in SBP and HR. However, DBP was significantly raised in Epi grp.[54]

Yadav et al (2020) studied changes in HR, BP and oxygen saturation in 70 normal pts pre and 10 min post injection with 1:80,000 Adr in 1.8 ml of 2% Lidocaine and compared with 2% lidocaine without Adr. They concluded that 1.8 ml of Lignocaine with 1:80000 Adr gave statistically significant rise of parameters. However, the study subjects were normotensive and medically fit, hence, the rise was not clinically significant.[55] In the same year, **Decloux D et al** (2020) reviewed pharmacology, techniques and advances in dental LA. It has been recommended that LA containing vasoconstrictors should be cautiously used for hypertensives or cardiovascular diseases for the risk of rise in BP or cardiac dysrhythmias.[56]

Guimaraes et al (2021) reviewed 10 RCTs to evaluate safety of vasoconstrictors with LA in CVD pts. Meta-analysis showed that SBP decreased when vasoconstrictor was

used in LA. no statistical difference was noted for other parameters. Most of the included studies had high risk of bias and poor quality of evidence as per GRADE profile. It was however concluded that Epi when used in low doses is safe in certain CVD pts. But the authors recommended more studies in future to reach to the results.[57]

Chapter 3

RATIONALES

3.1 RATIONALE FOR USE OF CLONIDINE HYDROCHLORIDE

Clonidine is chemically an imidazole compound with α-adrenergic agonistic activity, selectively for α-2 receptors.[58] In Humans, it was first used in epidural anesthesia in 1984.[59] Since then, it has been reported to have been safely used for various regional and spinal nerve blocks.[60, 61] Clonidine is known to have effects like hypnosis, sedation, analgesia and reduces need for post-op opioids.[60]

The α-2 agonists exert analgesic actions via receptors in brain, spinal and peripheral regions. In peripheral nerves, Clonidine facilitates action of LAs acting on C and Aδ fibers by increasing conductance of trans-membrane K^+, thereby decreasing nerve conduction and also by α-1 mediated vasoconstriction which retains LA molecules at the site of injection.[62-64]. A secondary mechanism of action may be explained by inhibition of calcium voltage-dependent channels.[65]

Activation of α-2 receptors causes bradycardia and decreases BP by decreasing sympathetic tone by inhibiting release of NE at synaptic junctions.[66] Due to these effects, Clonidine is also used as an anti-hypertensive.

Brkovic et al (2005) studied Cloni vs Adr with Ligno for time of onset, duration, depth of anaesthesia, postop analgesia, SBP, DBP, MAP, HR, ST segment depression, and incidence of cardiac arrhythmias in 40 healthy pts undergoing mandibular 3rd molar surgeries. There was significantly lower onset and need for post-op analgesics in Cloni grp. Duration and depth of anesthesia were comparable in 2 grps. DBP was significantly reduced in Cloni grp. However, there was no significant difference in SBP, DBP and MAP between groups. HR was significantly increased in the Epi grp 5 min post injection and intra-operatively. It was concluded that Cloni may be used as a replacement for Epi for dental block techniques.[67] **Brkovic et al** (2008) also studied Cloni vs Adr with Ligno for maxillary infiltration for third molar surgeries in 40 healthy pts. There was significant decrease in HR and SBP in Cloni grp 10 min post-surgery. All the other hemodynamic and anesthetic parameters were comparable in the 2 grps. Clonidine was shown to have vasoconstrictive effects on isolated human infraorbital arteries.[68]

Patil et al (2012) conducted a double-blind study on 50 subjects with moderate hypertension which was poorly controlled and required extraction of upper third molars. Hemodynamic variables, onset, duration, and depth of anesthesia, postoperative analgesia was compared between Cloni and Adr grps. Control of hemodynamics and post-op pain was better with Clonidine as compared to Adr. The other variables showed no significant difference. It was concluded that Cloni may be a better alternative to Adr in Hypertensive and ASA-II pts.[69]

In 2017, **Sivaramakrishnan** conducted a systematic review on Cloni used with Ligno in 5 published RCTs on extraction of maxillary as well as mandibular impacted and erupted molars and for endodontic treatment in cases of irreversible pulpitis in mandibular molars. It was noted that Cloni significantly reduced onset of LA when evaluated subjectively, however, duration of effect and post-op analgesia were comparable with Adr. Cloni did not alter hemodynamic stability and hence was proposed as an alternative to Adr in pts with contra-indications to use of Adr.[70]

Fernandes (2018) also reviewed use of clonidine and concluded that its systemic use peri-operatively in GA pts, reduces severity of pain and decreases need for post-op analgesics. Since it causes bradycardia and hypotension, it should be used with caution systemically. When used perineurally, it enhances sensory and motor nerve blocks with prolonged duration of action and delays the need for post-op rescue analgesic.[71]

Alam et al (2019) compared Clonidine and Adr added to lignocaine for surgical extraction of mandibular third molars in 30 healthy pts. SBP, DBP, MAP were observed to decrease both intra-op and post-op in Cloni grp in contrast to Adr grp. There was a statistically significant difference seen in VAS scores, but no significant difference on onset and duration of anesthesia in the 2 grps. It was concluded that Clonidine is as effective as Adr and has better hemodynamic stability, thus may be used in place of Adr in 3rd molar surgical procedures.[72]

Based upon the above evidences and characteristics of Clonidine, it was noted to have effectiveness equivalent to Adr with better control of hemodynamic variables. Not many studies in the literature have been published on its use in cases of impacted mandibular third molars and none of these studies evaluated comparative vasoconstrictive effects with Adr. Thus, it was included in this study.

3.2 RATIONALE FOR USE OF POTASSIUM CHLORIDE

Potassium chloride is a physiologic salt, normally present in human body. Potassium (K^+) is primarily present (98%) intracellularly with a conc. of 140-150 mmol/l, and (2%) extracellularly, at conc. of 3.5 and 5 mmol/l. A balance between intracellular-extracellular levels determines membrane voltage gradient in excitable nerves. It is inert, stable and compatible with lignocaine.

Mathison (1911) studied the effect of KCl on iv inj, intra-arterial injection on heart, blood vessels, blood pressure, skeletal and plain muscles. Vasoconstrictive effect of KCl was described.[73] **Tainter et al** (1940) stated that potassium salts are quite potent as procaine in local anesthetic action. It was also added that the quantity of LA required for the optimum level of anesthesia is decreased with addition of potassium salts, hence LA toxicity is also minimized.[74] **Chamberlain** (1966) stated that use of vasoconstrictors in pts with CVD when contraindicated, KCl may be used with lidocaine for its effective anesthetic properties.[75]

Bromage et al (1966) reported prolonged duration of action with lidocaine-KC1 used in epidural blocks in comparison to lidocaine alone**.**[76] **Aldrete** (1967) anesthetized 40 patients satisfactorily for bronchoscopies by transcricoid injection for bilateral superior laryngeal nerve block using lidocaine plus KC1and observed significant alteration in serum potassium levels. It was suggested that extracellular potassium balance is not affected by small amount of KC1as used with LA.[77] Again, **Aldrete et al** (1969) showed that KCl added to lidocaine provided a prolonged effect in rabbit ulnar nerve blocks and topical anesthesia. In digital and ulnar nerve blocks in volunteers the effect lasted 1.5 to 1.8 times longer with KCl added, as compared to plain lidocaine, without causing any gross local tissue reactions. It was stated that the exogenously administered KCl increased concentration of potassium ions outside nerve membrane and blockade produced by lidocaine is thereby reinforced and prolonged due to delay in repolarization.[78] In the same year, **Sidon et al** (1969) stated that addition of KCI to lidocaine affords a longer duration of action than lidocaine alone, but not as long as lidocaine with epinephrine. The results were statistically significant for mandibular blocks and not to supra-periosteal infiltration. It was concluded that KCl-Lig does not

have any harmful additive, are physiologically compatible and achieve satisfactory and effective anesthesia, hence can be studied further.[79]

Kircha et al (1983) studied infraorbital nerve blockade in the rat with physiological concentration of potassium added to isotonic solution of lignocaine and observed additive effect without any adverse effects.[80]

P. Macke Consigny (1991) discussed pathways and chemical modulation of contraction and relaxation of smooth muscles and mentioned KCl as a vasoconstrictor.[81]

Shobhana et al (2016) studied the efficacy of KCl in comparison with Sodium Bicarbonate added to Bupivacaine for Supraclavicular brachial plexus blocks and showed that the addition of KCl reduces time of onset for both sensory and motor blocks, whereas the addition of sodium bicarbonate extends the duration of action.[82]

Ramaiah et al (2020) evaluated and compared efficacy of 0.2 mmol KCl added to 0.5% ropivacaine with plain ropivacaine 0.5% in supraclavicular brachial plexus block and inferred that KCl added to Ropivacaine was advantageous with regards onset, duration, quality of sensory and motor blocks and post-operative analgesia.[83]

With the above review it is clear that KCl added to LA leads to better and effective anesthesia in epidural, ulnar, brachial plexus blocks etc. It also has vasoconstrictive properties. Its use in dentistry has not been reported for the variables used in this study, hence, evaluation and comparison of KCl added to Lig was undertaken in this study.

3.3 RATIONALE FOR USE OF DEXAMETHASONE SODIUM PHOSPHATE

Dexamethasone, 1-dehydro-16alpha-methyl-9alphafluorohydrocortisone,
is a synthetic glucocorticoid with 20–30 times more potency when compared to cortisol and is commonly used in surgical procedures, not only for its anti-inflammatory effects, but also as an adjunct to loco-regional anesthesia for better and prolonged post-operative analgesia.

Coates TD et al (1983) explained that Dexamethasone, via membrane-bound calcium release, blocks superoxide production and lysosomal enzyme release in PMNs thereby inhibiting degranulation.[84] **Tiwana et al** (2005) studied effects of IV corticosteroids on third molar surgical wound healing and concluded that clinical recovery was not hampered.[85] **Grossi et al** (2007), in their prospective study on surgical extractions of third molars, tested submucosal dexamethasone for reduction of postoperative discomfort and presented encouraging results. Comparison between 4mg Vs 8 mg Dexa showed no statistically significant difference between the 2 grps.[86]

Thorén H et al (2009) studied effects of glucocorticosteroids (administered perioperatively) on wound healing post-surgery and stated that with doses of 30 mg or less of Dexamethasone, there is no interference in healing of bony wounds.[87] **Ata-Ali** (2011) described anti-inflammatory mechanism of Dexa by facilitating synthesis of certain protein endogenously, to block activation of phospholipase A2, there by inhibiting release of arachidonic acid from cell membranes, thus, interfering with synthesis of thromboxane, prostaglandins and leucotrienes.[88]

Wang *et al* (2011) reported that topical corticosteroids have to be used cautiously in nerve proximity since large doses may affect neural conduction adversely, in a dose-dependent manner.[89]

Bhargava et al (2013) conducted a pilot study to evaluate effects of addition of 1 ml of 4mg/ml of Dexa to 1.8 ml 2 % Ligno with 1:200,000 Epi (TWIN MIX) on onset, duration and post-operative quality of life, when administered in pterygo-mandibular space (Intra-space/ IS route) for surgical extractions of 20 bilateral impacted mandibular third molars using a split mouth study design. pH of the solutions tested

with pH meter showed that pH of Lig-Adr was 4.5 whereas Dexa had an alkaline pH of 8.5. The pH of Twin Mix was 6. This proved to be beneficial in causing less pain on injection. It was also observed that there was a considerable reduction in the onset and prolonged duration of effect with Twin Mix. Pain, swelling and trismus were better controlled with Twin Mix. Hence, IS use of Dexa being highly recommended.[90]

Herrera-Briones (2013) reviewed use of Corticosteroids in 3rd molar surgeries. It has been stated that anti-inflammatory actions of steroids are exerted in multimodal manner via inhibition of vasodilation, reduction of transudation and thereby reducing edema, reducing cellular exudates, and decreasing deposition of fibrin at the surgical site. Other mechanisms include inhibition of chemotaxis of leukocytes, inhibition of function of fibroblasts and endothelial cells, and suppression and/ or inhibition of production of various mediators of inflammation.[91]

Again, **Bhargava et al** (2014) compared Dexa administered IS as Twin Mix with submucosal, intramuscular, intravenous and per-oral routes. All routes were found to be comparable with regards control of post-op pain, swelling and trismus. However, IS administration held added advantages like single needle prick, less pain on injection, reduced onset, increased duration of anaesthesia, better post-op QOL and no additional injection skill required as for other parenteral routes.[92]

Williams et al (2014) cautioned against use of 8 mg or more of dexamethasone perineurally since the clinical benefits obtained will be equivalent to those obtained with lower doses.[93] **Choi et al** (2014) reviewed RCTs on use of dexamethasone as adjuvant to LA. It was concluded that adding Dexamethasone to LA was the safest way for increasing duration of post-op analgesia. It was shown to be superior to clonidine, epinephrine and midazolam. However, since there is no commercially available formulation, perineural use must be exercised with caution.[94] **Noss et al** (2014) through their review, reported that perineural use of Dexa has been mentioned in literature, although its use perineurally has not been approved. However, no complication or neurotoxic effect has been reported with this route in humans.[95]

De Oliveira et al (2014) stated that post-operative analgesia is better when dexamethasone is administered perineurally as LA adjunct without any clinical evidence of alteration of neural function or causing neural damage.[96]

Bhargava et al (2015) used double beam UV-visible spectrophotometery to assess stability of individual components of 'Twin Mix'. It was found to be a chemically stable mixture with no change in the individual pharmacologically active compounds. This

study reinforced the advantages of Intra-space administration of Dexa as Twin Mix in third molar surgeries.[97] **Bhargava et al** (2016) also assessed and compared intravenous plasma levels of Dexa 30 min and 60 min following administration of Dexa as a Twin Mix IS Vs same quantity as IM injection high performance liquid chromatography (HPLC). It was reported that plasma levels with the 2 routes were comparable, with better post-op QOL with IS Dexamethasone.[98]

The existing literature points out that Dexamethasone is stable with commonly used anesthetics, possesses anti-inflammatory, analgesic and vasoconstrictive actions and its use with regional anesthesia improves post-operative quality of life, decreases onset and prolongs action. Intra-space administration has been shown to be equivalent to other routes of administration, causes no perineural adverse effects and offers other advantages as mentioned. However, instead of using it as an already reported 'Twin Mix', in this study, it was used as an additive to plain 2% lignocaine. Hemodynamic variables and vasoconstrictive properties were additionally studied, since they have never been reported in the literature.

3.4 RATIONALE FOR USE OF CHLORPHENIRAMINE MALEATE

Chlorpheniramine, a tertiary amino compound, is a Class 1 H1-receptor antagonist, with antipruritic, anti-allergic, antidepressant and serotonin uptake inhibitor actions. It is chiefly used in allergic reactions, urticaria, asthma, hay fever and rhinitis. It causes less drowsiness and sedation than promethazine.[99]

Rosenthal et al (1939) demonstrated the anesthetic action of the antihistaminic drugs for the first time using intracutaneous and local thymoxyethyldiethylamine (929 F), which produced local anesthesia similar to and more prolonged as compared to procaine hydrochloride.[100] **Halpern** (1942) stated that all antihistamines have local anesthetic properties.[101] **Halpern et al** (1947) published their results from experiments on rabbit cornea and further stated that anesthetic activity of the antihistamines is entirely independent of their antihistaminic power.[102] **Graham** (1947) used Neo-Antergan (mepyramine) intracutaneously in guinea pigs and showed that it was 3.3 times more potent as procaine.[103] **Moseley** (1948) reported first successful use of 1% tripelennamine solution in 30 patients for topical anesthesia prior to gastroscopy.[104]

Reuse (1948) studied anesthetic effect of four antihistaminic drugs on lumbar plexus of frog and inferred that the local anesthetic action was not related to their antihistaminic actions.[105] **Code et al** (1950) compared the ability of flare reduction of various antihistamines with their degree of LA effects on human skin and reported an inverse relation between the two.[106] **Reynolds et al** (1950) reported use of topical solutions of diphenhydramine, pyrilamine, and tripelennamine prior to gastroscopy in 42 patients with excellent results and no untoward effects.[107]

Landau et al (1951) used Antistine, Phenergan, Pyribenzamine, Histadyl, Neo-Antergan, Benadryl and Dramamine on guinea pig and human skin and concluded that these antihistamines are 2 to 4 times more potent than procaine.[108]

Steffan et al (1956) used 0.5% diphenhydramine, 1% diphenhydramine or 2% procaine as local anesthetic in 50 cases while performing minor skin surgery. It was concluded that the action of 1% solution of diphenhydramine was better than 0.5% solution and equivalent to 2% procaine.[109] **Steffen et al** (1957) also evaluated local anesthetic properties of tripelennamine, diphenhydramine hydrochloride, pyrilamine maleate and

chloroprophenpyridamine maleate for surgical procedures and concluded that these drugs as 1% solutions were satisfactory and safe substitutes for procaine in known cases of procaine allergy or anesthesia failure.[110]

Smith (1961) successfully carried out extraction of maxillary teeth with infiltration of 15 mg. of diphenhydramine HCl locally. No tissue irritation or sloughing was reported post-operatively.[111] **Rosanov et al** (1963) conducted a series of 200 cases of minor surgical procedures on skin using 1% solution of diphenhydramine HCI as local anesthetic and observed that these compounds have negligible toxicity, rare allergenicity, rapid onset of action and potent local anesthetic property.[112]

Abramson et al (1963) concluded that when CPM is used parenterally, it exerts vasoconstrictive effect lasting beyond 30 min. It was observed that CPM caused a marked reduction in flow of blood locally without any untoward systemic vascular response, and the local action was mostly observed in the cutaneous arterial tree, particularly in the distal portions of the limbs.[113]

Campolattaro (1964), successfully carried out extraction of malposed maxillary third molars using l.5ml of 10 mg/ml sterile solution of diphenhydramine hydrochloride as local anesthetic in a patient with allergy history to both procaine and lidocaine. Profound anesthesia was noted 5 min after injection and approximate duration of action was 50 min. No untoward local/ systemic adverse effects were noted.[114] **Welborn** (1964) reported first series of mandibular blocks with 1% diphenhydramine and 1:100,000 epinephrine. It was reported that the average onset of anesthesia was quite longer than lidocaine-epinephrine, and a larger volume of diphenhydramine-epinephrine had to be injected for adequate anesthesia. no tissue swelling or sloughing post-operatively was noted.[115]

Altura et al (1965) studied the effects of antihistamines on rat mesocecal microcirculation using diphenhydramine hydrochloride, chlorpheniramine maleate, promethazine hydrochloride and pyrilamine maleate in 0.01 M concentration and stated that these blocked the local action of dilator histamine, by their vasoconstrictor actions similar to epinephrine.[116]

Malamed (1973) used "diphenhydramine HC1 10mg/ml with epinephrine 1: 100,000" for dental treatment in 25 pts. 1-1.5ml of the solution was used for maxillary infiltration and 2-3ml for inferior alveolar nerve blocks. The effect was profound within 5 min and lasted for 30-40min for maxillary arch. For mandibular anesthesia, onset was reported to be 30 min, duration of action lasted from 15min-75min.[117]

Yeh (1986) reported antinociceptive effect of chlorpheniramine in rats.[118] Similarly, **Raffa (2001)** in their review showed the role of histamine as a mediator of pain. And concluded that antihistamines with anti-nociceptive effects act on all the three known histamine receptor subtypes (H1, H2 and H3) in brain and spinal cord. It was also suggested that the analgesic property may be due to some unknown pharmacologic property, still unidentified.[119] Following this, **Galeotti** (2002) explained that the antinociception induced by H1 receptor antagonists underlies the activation of a signal transduction mechanism operated by Gi proteins.[120]

Orhan et al (2007) evaluated and compared the effects of intradermal CPM, midazolam, lidocaine and saline for pain during injection and degree of LA effect in humans and concluded that chlorpheniramine produced local anesthesia better than midazolam, however the duration of action was shorter than lidocaine.[121]

Hung et al (2010) stated that antihistamines also exhibit sodium channel blockade. Chlorpheniramine and Pyrilamine were used on Rat Sciatic Nerve to check if antihistamines are potential adjuvant or an alternative agent for clinical local anesthetics, It was observed that Chlorpheniramine was more potent than lidocaine and pyrilamine. Duration of anesthesia was prolonged with addition of lidocaine to these drugs, implying that drug combinations were better than individual drugs.[122]

Khaji (2014) successfully used pheniramine maleate and Diphenhydramine hydrochloride as local anesthetic agents for dental procedures in two pts with known allergy to lidocaine and concluded that antihistamines can be used as alternatives in such patients for minor dental procedures in routine dental practice.[123]

Tzeng et al (2015) have shown that CPM produces spinal sensory and motor nerve blocks in rats.[124] **Lirk** (2018) documented that there is no similarity in the molecular structure of CPM and common local anesthetics.[125] **CC Chiu (**2019) assessed and compared cutaneous analgesic effect of chlorpheniramine with bupivacaine in dorsal skin of rats and concluded that both the drugs dose-dependently provoked cutaneous analgesia. Chlorpheniramine worked for longer duration but was less potent than bupivacaine.[126]

The use of antihistamines as local anesthetics has not been thoroughly explored as evident from the above review of literature. Their use in dentistry was considered only when patients with known allergies to amides as well as ester anesthetics reported to

the respective authors. The usage of these agents did not yield any untoward local or systemic reaction as per the above reports. Their anesthetic, analgesic, anti-allergic, vasoconstrictive properties are well documented. These drugs have been shown to be more potent than procaine and give an optimum onset and satisfactory duration of anesthesia. Chlorpheniramine has not been evaluated for it effects like diphenhydramine and tripelennamine. Hence, it was considered as one of the additives to lignocaine in this study.

Chapter 4

AIM AND OBJECTIVES

AIM AND OBJECTIVES

AIM:

To evaluate and compare effectiveness of 2% Lignocaine with adrenaline versus 2% Lignocaine with other additives for pterygomandibular nerve block for adult patients undergoing surgical extraction of impacted mandibular third molars

OBJECTIVES:

1. To evaluate and compare onset, duration, depth of 2% Lignocaine with Adrenaline and 2% Lignocaine with other additives.

2. To evaluate and compare Heart rate, systolic, diastolic, mean arterial blood pressure with 2% Lignocaine with Adrenaline and 2% Lignocaine with other additives.

3. To evaluate and compare amount of blood loss with 2% Lignocaine with Adrenaline and 2% Lignocaine with other additives.

4. To evaluate and compare post-operative pain control with 2% Lignocaine with Adrenaline and 2% Lignocaine with other additives.

5. To check for signs and symptoms of any systemic/ local complication associated with the use of any of these drugs

Chapter 5

MATERIALS AND METHODS

MATERIALS AND METHODS

5.1 STUDY DESIGN:

Triple blinded Randomized Controlled Clinical study where in, the operator, subject and the observer were blinded.

5.2 LOCATION AND SETTINGS:

Dept. of Oral & Maxillofacial Surgery of a recognized dental college and hospital (YMT Dental College and Hospital, Kharghar, Navi Mumbai)

5.3 STUDY POPULATION:

18-45-year-old pts reporting to the Dept. of Oral & Maxillofacial Surgery, for surgical extraction of impacted mandibular third molars were randomly selected. **Ethical clearance** was obtained from the Institutional Ethics Committee (**Appendix 1**). Required permissions were taken from the Institutional Review Board, concerned authorities at Galgotias University and Y.M.T. Dental College and Hospital and a written consent was obtained from all subjects prior to the beginning of the study (**Appendix 4**).

5.4 SAMPLE SIZE CALCULATION:

Sample size was determined using the estimates of mean and standard deviation values from literature using the formula[127]

$$n = \frac{2 (Z_\alpha + Z_\beta)^2 \ [s]^2}{d^2}$$

where Z_α is the z variate of alpha error i.e. a constant with value 1.96, Z_β is the z variate of beta error i.e. a constant with value 0.84

Approximate estimates:

1. 80% power
2. Type I error to be 5%
3. Type II error to be 20%

4. True difference of at least 1.2 units between the groups for primary outcome variable
5. Pooled standard deviation of 1.89

Substituting the values,

$$n = \frac{2\,(2.8)^2\,[\,1.89\,]^2}{(1.2)^2}$$

n = 38.89

40 subjects per group were taken to complete the trial.

5.5 SAMPLING TECHNIQUE:

Simple random sampling using computer generated numbers

5.6 SELECTION OF STUDY SUBJECTS

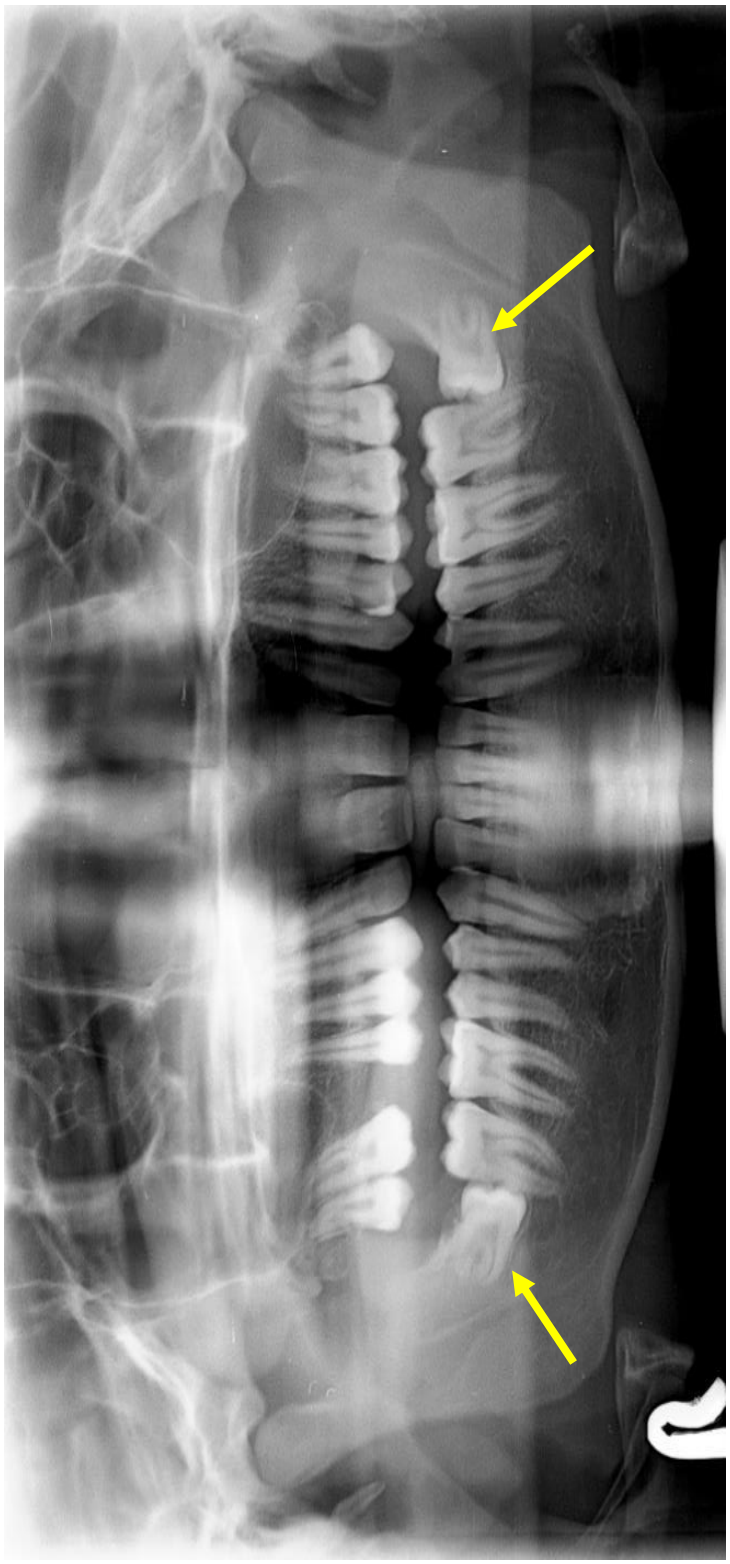
Inclusion criteria:

- Patients requiring surgical extraction of impacted mandibular third molars (Pederson's difficulty index[128] 5-7, **Fig 1)** under pterygomandibular nerve blocks
- Age group of 18-45 years.
- Physically and mentally fit patients without any systemic contraindications for surgical extraction (ASA-I).
- Patients consenting for the study
- no history of allergy to the drugs used in this research
- not been on any medications preoperatively (1 week)

Exclusion criteria:

- Patients with uncontrolled systemic illness. (ASA-II, ASA-III, ASA-IV)
- Pregnant and lactating mothers.
- Apprehensive patients
- Patients with active Oro-facial or systemic infections
- Patients in which any of the drug to be used is contraindicated.
- History of concurrent or chronic use of any medication.
- Patients who refuse to give consent, or not willing to comply for follow-ups.

Fig.1 OPG showing impacted mandibular third molars with moderate Pederson's Difficulty index



Withdrawal criteria:

- Patients who consented for study but did not report for surgery.
- Patients who did not comply with postoperative follow ups.

5.7 STUDY GROUPS:

Randomly selected subjects, requiring surgical extraction of mandibular third molars, fulfilling the above criteria and consenting for the study were then randomly allocated (using computer generated numbers) to one of the following study groups.

STUDY GROUPS	**Drugs used for pterygomandibular nerve block (Fig. 2-7)**
I	2% Lignocaine hydrochloride with 1:80,000 Adrenaline
II	2% Lignocaine hydrochloride
III	2% Lignocaine hydrochloride with Clonidine hydrochloride
IV	2% Lignocaine hydrochloride with Potassium chloride
V	2% Lignocaine hydrochloride with Dexamethasone sodium phosphate
VI	2% Lignocaine hydrochloride with Chlorpheniramine maleate

Fig. 2 Injection 2% Lignocaine hydrochloride with Adrenaline bitartrate

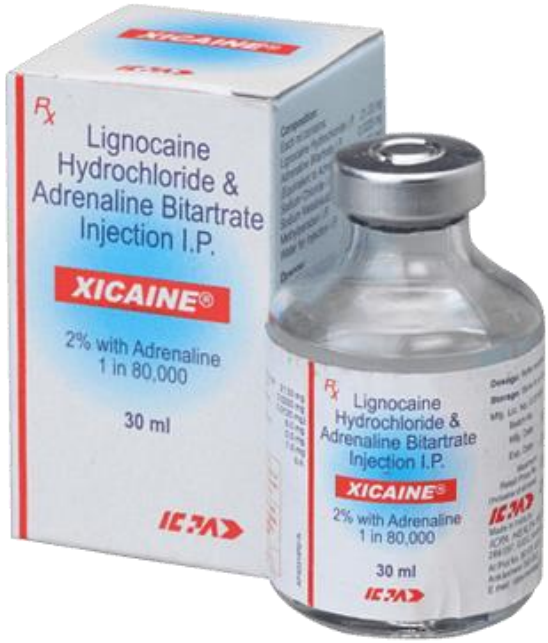


Fig.3 Injection 2% Lignocaine hydrochloride

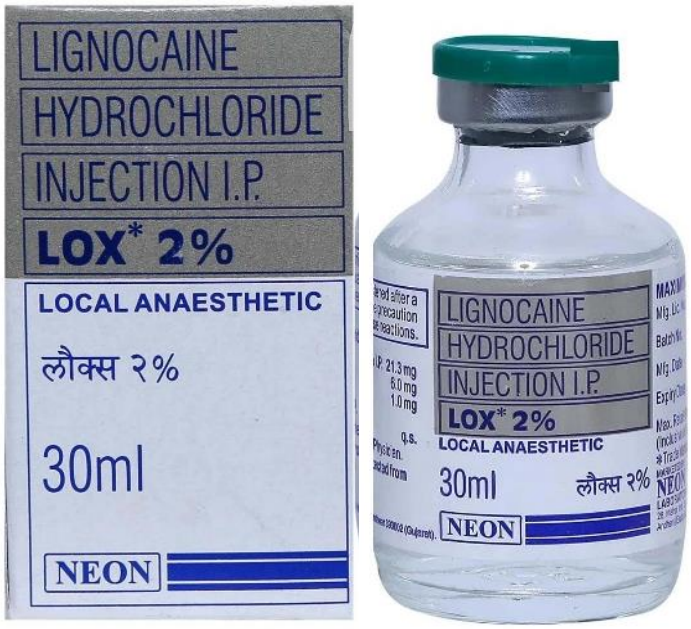


Fig.4 Injection Clonidine hydrochloride

Fig.5 Injection Potassium Chloride

Fig.6 Injection Dexamethasone sodium phosphate

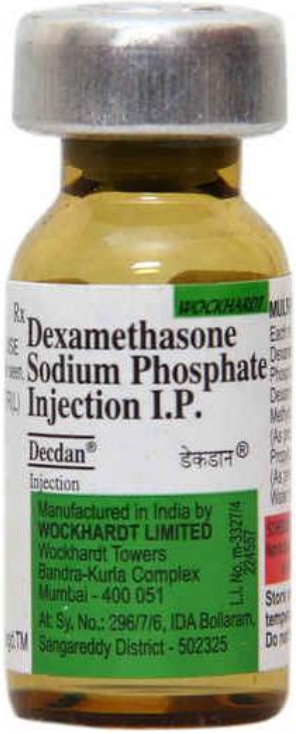


Fig.7 Injection Chlorpheniramine maleate

5.8 INJECTION MIXTURES USED IN THE SIX GR0UPS FOR LOCAL ANESTHESIA:

1. 3ml of Inj. **XICAINE**- consisting of 2 % Lignocaine hydrochloride (21.33mg/ml) with 1:80,000 Adrenaline bitartrate (0.0125mg/ml) (ICPA Laboratories),
2. 3ml of **LOX 2 %** consisting of Lignocaine hydrochloride (21.33mg/ml) (Neon Laboratories)
3. Freshly prepared solution of 2 ml of 2 % Lignocaine hydrochloride (**LOX 2 %**, Neon Laboratories) mixed with 1 ml of 150µg/ml of Clonidine hydrochloride (inj. **CLONEON**, Neon Laboratories)
4. Freshly prepared solution of 2 ml of 2 % Lignocaine hydrochloride (**LOX 2 %**, Neon Laboratories) mixed with 1 ml of 1.5% Potassium chloride solution, which was obtained by diluting 1ml of 150 mg/ml inj. **POTCL** (i e 15%, Neon laboratories) in 9 ml of sterile normal saline.
5. Freshly prepared solution of 2 ml of 2 % Lignocaine hydrochloride (**LOX 2 %**, Neon Laboratories) mixed with 1 ml of Dexamethasone sodium phosphate inj. **DECDAN** (4mg/ml, Wockhardt limited)
6. Freshly prepared solution of 2 ml of 2 % Lignocaine hydrochloride (**LOX 2 %,** Neon Laboratories) mixed with 1.5 ml of 10mg/ml solution of Chlorpheniramine maleate (Lordcent and Torcent Healthcare pvt ltd)

The solutions were prepared for injection by a trained nursing staff who was not involved in the administration of anesthesia or the evaluation of the results

5.9 DEFINED VARIABLES MEASURED IN THIS STUDY WERE:

1. Number of injections used
2. Onset of anesthesia (sec)
3. Duration of analgesia (min)
4. Depth of anesthesia (intra-operative VAS score)
5. Total blood lost (gauze pieces+ suction jar)
6. Number of analgesics taken in 3 days

7. Systolic, Diastolic, Mean Arterial blood pressure and heart rate measured pre-operatively, 5,10,15,30 and 45 min post-injection.

5.10 METHODS OF MEASUREMENTS

1. **Onset of action**, was measured as time elapsed in sec from the time of injection to the onset of first tingling sensation on the lower lip was considered as onset of action of LA. It was evaluated using a stop watch
2. **Duration of analgesia** was measured in min from the onset of first tingling sensation on the lower lip to the first recue analgesic taken by the subject. It was noted when the subject notified the observer about the 1st analgesic taken.
3. **Depth of anesthesia** was assessed as the intra-operative pain experience using 0-10 Visual Analog Scale. **(Fig 8)** The Scale ranges from '0' representing one pain extreme (i.e. “no pain”) to '10' representing the other pain extreme (e.g. “pain as bad as you can imagine” or “worst pain imaginable”). Subjects were asked to indicate the numeric value on the segmented scale that best described their pain intensity. VAS pain scores were collected on the day of surgery.
4. **Total Blood lost:** This indicated the vasoconstriction property of the additive used. It was measured indirectly as follows:

   For every surgical case,

   A. Gauze piece method: **(Fig 9)**
      i. Weight of dry, unused, sterile gauze pieces taken on the trolley was measured pre-operatively.
      ii. Weights of blood-soaked gauze pieces were measured.
      iii. Mathematical difference between the above 2 was computed.

   B. Suction jar Method: **(Fig 10)**
      i. The total volume of fluid collected in the suction jar was measured post-operatively.
      ii. The amount of Normal saline used for the procedure was noted
      iii. The difference between the above 2, was estimated volume of blood loss.

      The sum of A(iii) +B(iii) was considered as total loss of blood.

5. The total no. of analgesics consumed by the subject: This was telephonically asked to the subject at the end of 3 post-op days. This evaluated the amount of post-op analgesia.
6. SBP, DBP, HR- Phillips Intellivue MP30 Multiparameter Cuff and sensor with probe were connected to the monitor **(Fig 11)** and the subject for 1st reading 5 min pre-op followed by 5min, 10 min, 15min, 30min and 45 min post-injection. MABP was computed using the formula

$$MABP = DBP + \frac{(SBP - DBP)}{3}$$

To evaluate relationship between pressure, systemic resistance and flow of blood, MABP is more reliable than SBP and DBP.

Other than the above measured variables which formed the primary objective, any untoward local and /or systemic events/findings were noted in the case record sheet (**Appendix 2**)

Fig. 8 VAS scale

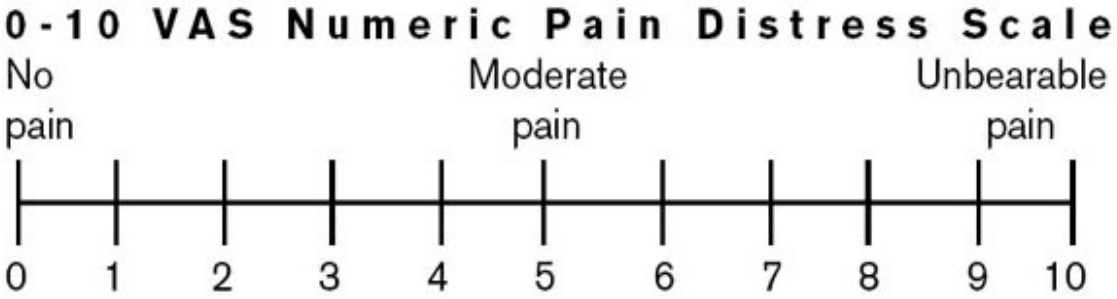
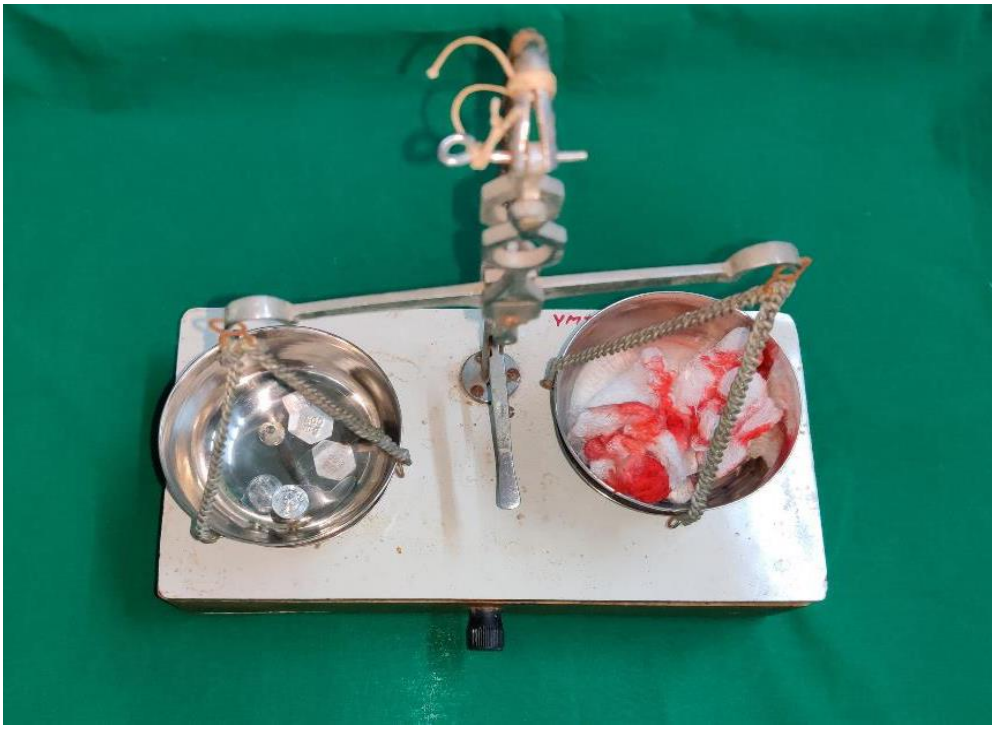


Fig.9 Measurement of gauze using weighing scale



ig.10 Measurement of volume of blood using suction jar method

Fig.11 Phillips Multiparameter Monitor

5.11 ADDITIONAL POINTS FOR RCT:

1. **Randomization Method:**

Total of 240 randomly selected patients, who met the above inclusion criteria, were randomly allocated to the six groups using computer generated numbers (40 patients in each group) by a trained staff nurse.

2. **Allocation Concealment**:

Allocation concealment was done by the same staff nurse who was aware of the allocated group of the subject, but not involved in observation and results. She freshly prepared and handed over the respective solution mixture to the blinded primary investigator at the time of the surgical procedure, who was unaware of the allocated group and study drug being used.

3. **Blinding**: The primary investigator/ operator, observer and all subjects were blinded.
4. **Standardization**: To avoid bias, same operator (primary investigator) administered local anesthesia and performed all surgical procedures under all aseptic precautions. A single trained staff nurse was involved in allocation of subjects and preparation and handling of solution mixtures. Same standards of observations were used by a single observer in all cases.

5.12 ARMAMENTARIUM (Fig. 12)

DIAGNOSTIC INSTRUMENTS:

a) Mouth mirror
b) Tweezer
c) Probe

SCRUBBING AND DRAPPING:

a) Swab holder
b) Gauze pieces
c) Stainless steel bowls
d) Kidney tray
e) Betadine scrub and solution
f) Drapes
g) Towel clips

LOCAL ANESTHESIA:

a) 2% lignocaine hydrochloride with or without additive
b) Disposable syringe 2cc
c) Disposable syringe 5cc for irrigation
d) 26 gauge 1" or 1.5" needle
e) Drug to be used as additive

INSTRUMENTS FOR EXTRACTION:

b) Moons probe
c) Periosteal elevator
d) BP handle No 3
e) Surgical blade No 15
f) Suction tube and suction machine
g) Micro-motor with straight handpiece and burs
h) Cheek retractors
i) Extraction forceps and elevators
j) Luxators
k) Periotome
l) Artery forceps big and small
m) Bone file, Bone Ronguers
n) Curettes
o) Needle holder
p) Adson's tissue holding forceps
q) 3-0 Black braided silk suture material with cutting edge needle
r) Scissors

Fig.12 Armamentarium

5.13 SURGICAL PROCEDURE

A detailed case history was obtained. The details of the procedure were explained to the subject & relatives and the subject was advised routine radiographs and blood investigations. After ascertaining that the subject met all the inclusion criteria, a well- informed written consent was obtained for the procedure.

All subjects were operated under similar conditions by same operating surgeon using standard aseptic surgical protocols. All Surgical extractions were carried out under local anaesthesia using pterygomandibular nerve blocks and long buccal nerve blocks in all cases, however, based on allotment of the subject to a specific group, the additive added was different. The additive was freshly added by the same staff nurse who had been trained about dosing of the mixtures. The operator was handed over the LA mixture to be injected and was kept unaware about its content. The observer who was also unaware about the contents of the syringe, recorded the required variables at the time intervals as specified.

Steps involved in the surgical procedure:

Pre-operative SBP, DBP, HR were recorded.

The subject was scrubbed and draped as per standard aseptic protocol.

Pterygomandibular nerve block and long buccal nerve block were administered using the allocated LA mixture.

After ascertaining the appearance of subjective symptoms of LA, standard Ward's incision was taken with Blade no 15 on Bard Parker handle no 3. Full thickness muco-periosteal flap was reflected to expose the impacted molar. Ostectomy was performed on distal and buccal aspects using bur no. 702 with straight handpiece and micromotor under thorough irrigation. Appropriate tooth sectioning was carried out. Tooth was elevated and extracted. The socket was thoroughly curetted and irrigated. Hemostasis was achieved, flap was replaced back and sutured with 3-0 black silk interrupted sutures and gauze pack was placed (the weight of this gauze pack was excluded from the measurement of the ones used during the procedure)

Weights of used gauze pieces were taken and volume of the fluid collected in the suction jar was measured.

At the completion of the procedure, standard post-operative instructions and prescription consisting of Cap Amoxicillin 500 mg tds, Tab Diclofenac 50mg sos

were explained to the subject by the operator. The subject was additionally instructed to use Tab. Diclofenac only as a rescue analgesic and record the number of tablets consumed in 3 days.

Subjects were asked to follow-up on the next day and subsequently in the event of any other sequelae. Sutures were removed on the 7^{th} post-operative day.

Fig.13 Patient, scrubbed and draped with monitor attached

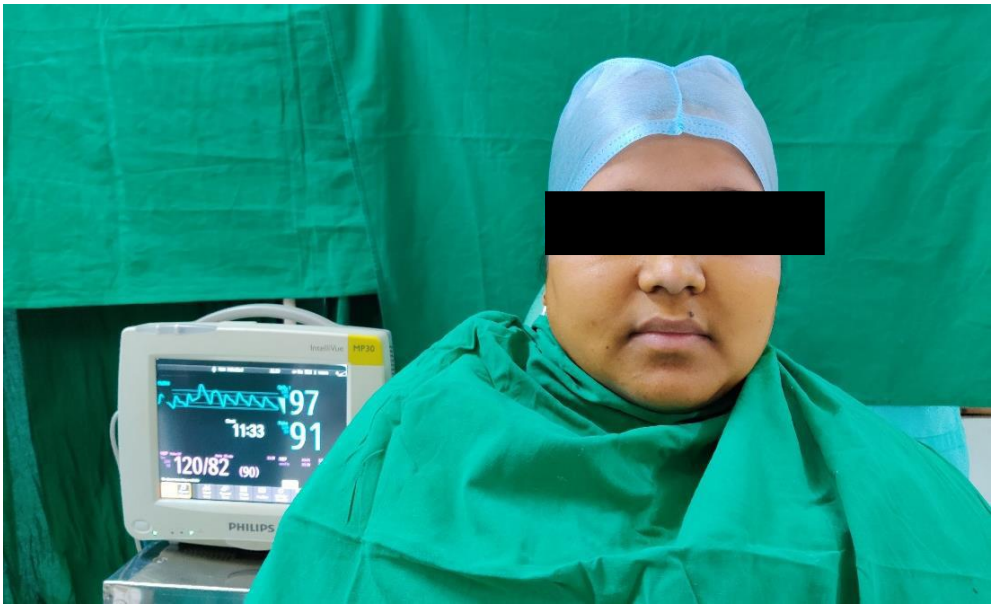


Fig.14 Pterygomandibular nerve block

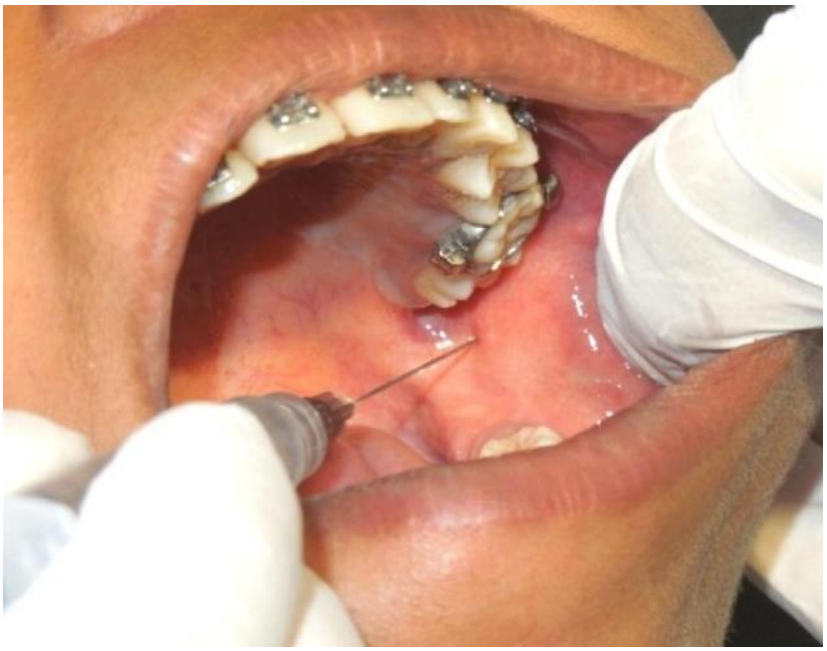
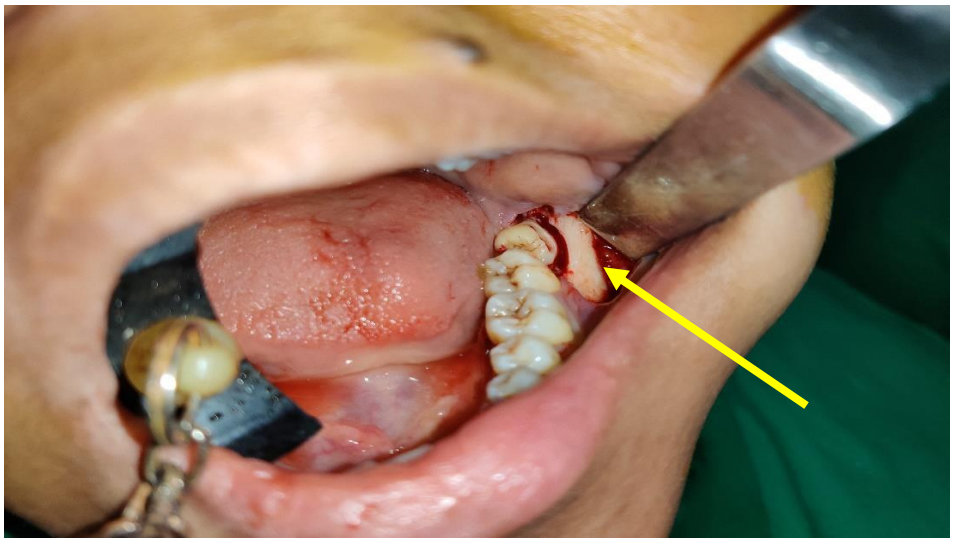


Fig.15 Surgical exposure of impacted third molar



5.14 STATISTICAL PROCEDURE

All data were entered into a computer by giving coding system, proofed for entry errors

· Data obtained was compiled on a MS Office Excel Sheet (v 2019, Microsoft Redmond Campus, Redmond, Washington, United States).

· Data was subjected to statistical analysis using Statistical package for social sciences (SPSS v 26.0, IBM).

· Descriptive statistics like frequencies and percentage for categorical data, Mean & SD for numerical data has been depicted.

Inter group comparison for mean age and other demographic numerical data, independent variables (>2 groups) were done using one way ANOVA followed by pair wise comparison using post hoc test.

Comparison of frequencies of categories of variables with groups was done using chi square test.

Normality of numerical data was checked using Shapiro-Wilk test & was found that the data did not follow a normal curve; hence **non-parametric tests** have been used for comparisons.

Inter group comparison (>2 groups) was done using Kruskall Wallis ANOVA followed by pair wise comparison using Mann Whitney U test.

Intra group comparison was done using Friedman's (for >2 observations) followed by pair wise comparison using Wilcoxon Signed rank test.

For all the statistical tests, $p<0.05$ was considered to be statistically significant, keeping α error at 5% and β error at 20%, thus giving a power to the study as 80%.

Chapter 6

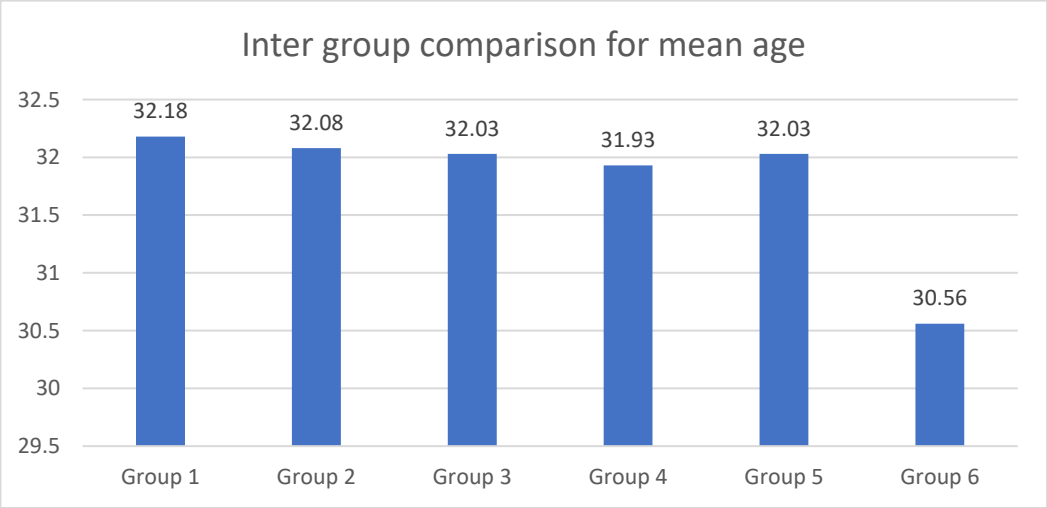
RESULTS

RESULTS

The mean **age** of all the subjects in this study was 31.82± 4.694. Inter-group comparison with one way ANOVA (**Table 4)** showed a statistically non- significant difference ($p>0.05$) between the groups as regards age of the subjects. **(Graph 1)**

This study comprised of 99 females (41.9%) and 137 males (58.1%). There was a statistically non-significant difference seen for the frequencies between the groups ($p>0.05$) as regards **gender (Table 5), (Graph 2)**

Graph 1:



Graph 2:

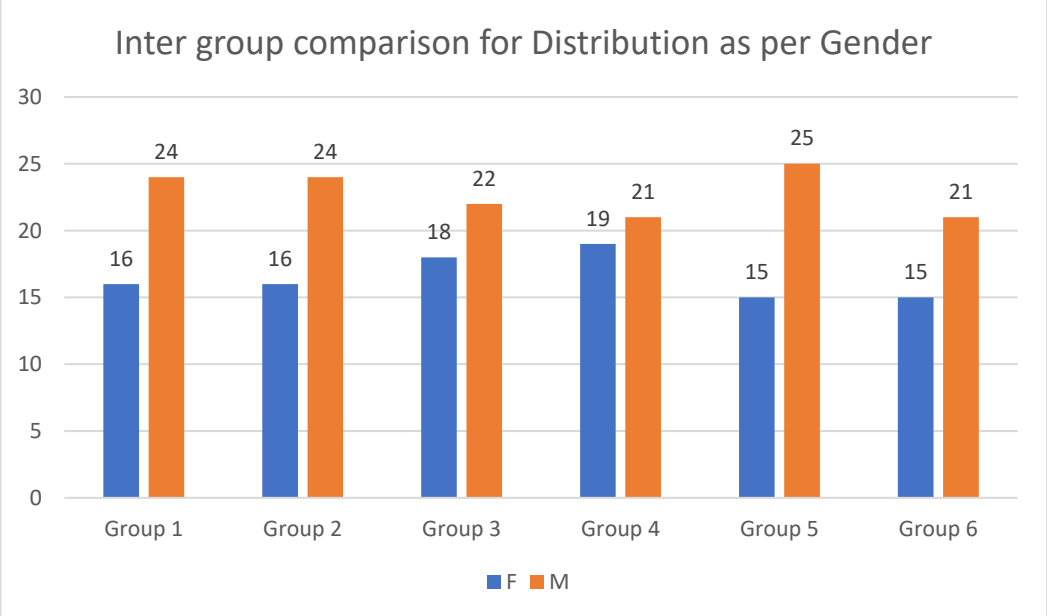


Table 4: Inter group comparison for mean age

Groups					95% Confidence Interval for Mean					
	N	Mean	Std. Deviation	Std. Error	Lower Bound	Upper Bound	Minimum	Maximum	F value	P value of one- way ANOVA
1	40	32.18	4.272	.675	30.81	33.54	23	42		
2	40	32.08	5.045	.798	30.46	33.69	23	42		
3	40	32.03	3.786	.599	30.81	33.24	23	37	.621	.684#
4	40	31.93	4.346	.687	30.53	33.32	24	42		
5	40	32.03	5.046	.798	30.41	33.64	23	42		
6	36	30.56	5.644	.941	28.65	32.47	20	42		
Total	236	31.82	4.694	.306	31.22	32.42	20	42		

There was a statistically non-significant difference seen for the values between the groups ($p>0.05$) for mean age

#= non-significant

Table 5: Inter group comparison for Distribution as per gender

		Sex				
		F	M	Total	Chi-Square value	p value of Chi-Square test
Group	1	16	24	40		
	2	16	24	40		
	3	18	22	40	1.110	0.953#
	4	19	21	40		
	5	15	25	40		
	6	15	21	36		
	Total	99	137	236		

There was a statistically non-significant difference seen for the frequencies between the groups ($p>0.05$)

#= non-significant

Number of injections used in the six groups showed a statistically highly significant difference between the groups ($p<0.01$) (**Table 6),** with maximum numbers in plain lignocaine group (1.40± 0.496) followed by CPM grp (1.39±0.494) and least numbers in KCl (1.03±0.158) and Dexa (1.03±0.158) groups (**Graph 3)**

A statistically highly significant difference between the groups ($p<0.01$) (**Table 6),** for the **onset of action** is noted. In this study, time elapsed in sec from the time of injection to the onset of first tingling sensation on the lower lip was considered as onset of action of LA. The order of onset noted was, KCl (44.20±5.450sec) < Dexa (78.10±4.012sec) < Cloni (95.60±4.056sec) < Adr(102.60±9.803sec) < plain Lig (143.68±4.875sec) < CPM (224.75±10.608sec). (**Graph 4)**

In this study**, duration of analgesia** was measured in min from the onset of first tingling sensation on the lower lip to the first recue analgesic taken by the subject. A statistically highly significant difference ($p<0.01$) (**Table 6)** was obtained between the groups ($p<0.01$), the order being, plain Lig grp (74.50±5.966min) < Adr (136.95±9.403min) < CPM (147.78±30.809min) < Cloni (183.75±13.291min) < KCl (205.20±28.399min) <Dexa grp (206.10±18.854min). (**Graph 5)**

There was a statistically highly significant difference between all the grps ($p<0.01$) (**Table 6)** for **depth of anesthesia**. (**Graph 6)** The mean VAS scores were CPM 4.28±1.059> plain Lig 3.35±.533> Adr 1.85±.700> Cloni 1.83±.747> KCl 1.80±.758> Dexa 1.65± .736.

For **total amount of blood lost**, there was a statistically highly significant difference in the total amount of blood lost in all grps ($p<0.01$) (**Table 6)** in the order, plain Lig 70.25±7.270ml> KCl 66.45±6.656ml> Dexa 59.38±6.376ml> CPM 57.89±5.942ml> Cloni 57.53±4.750ml> Adr 55.80 ±6.653ml. (**Graph 7)**

Post-operative pain control was indirectly assessed by the total number of analgesics consumed by the subjects in three post-operative days. There was a statistically highly significant difference in all grps ($p<0.01$) (**Table 6)** in the order CPM (4.03±.878) < Dexa (5.50±.555) < Cloni (6.50±.641) < KCl (6.88±1.042) < Adr (7.93±.764) < plain Lig (8.20±.758). (**Graph 8)**

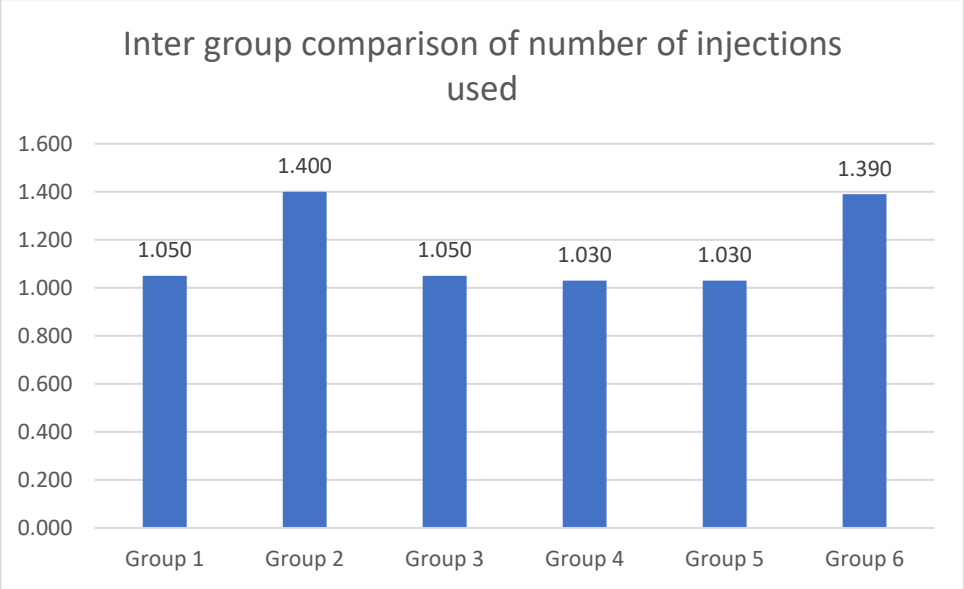
Table 6: Inter group comparison of mean of non-cardiac variables (Kruskall-Wallis test)

	Group	Mean	Std. Deviation	Std. Error	Mean rank	Median	Chi square value	p value of Kruskal-Wallis Test
number of injections used	1	1.05	.221	.035	106.40	1		
	2	1.40	.496	.078	147.70	1		
	3	1.05	.221	.035	106.40	1		
	4	1.03	.158	.025	103.45	1		
	5	1.03	.158	.025	103.45	1		
	6	1.39	.494	.082	146.39	1	50.861	0.000**
Onset in sec	1	102.60	9.803	1.550	129.83	103		
	2	143.68	4.875	.771	180.50	143.5		
	3	95.60	4.056	.641	110.53	95		
	4	44.20	5.450	.862	20.50	45		
	5	78.10	4.012	.634	61.15	79		
	6	224.75	10.608	1.768	218.50	221	222.568	0.000**
Rescue analgesic taken after (min)	1	136.95	9.403	1.487	77.68	138	184.614	0.000**
	2	74.50	5.966	.943	20.50	73		
	3	183.75	13.291	2.102	146.65	180		
	4	205.20	28.399	4.490	180.55	199.5		
	5	206.10	18.854	2.981	189.25	198		
	6	147.78	30.809	5.135	93.92	140		
VAS score	1	1.85	.700	.111	88.93	2	136.921	0.000**
	2	3.35	.533	.084	178.29	3		
	3	1.83	.747	.118	87.18	2		
	4	1.80	.758	.120	85.50	2		

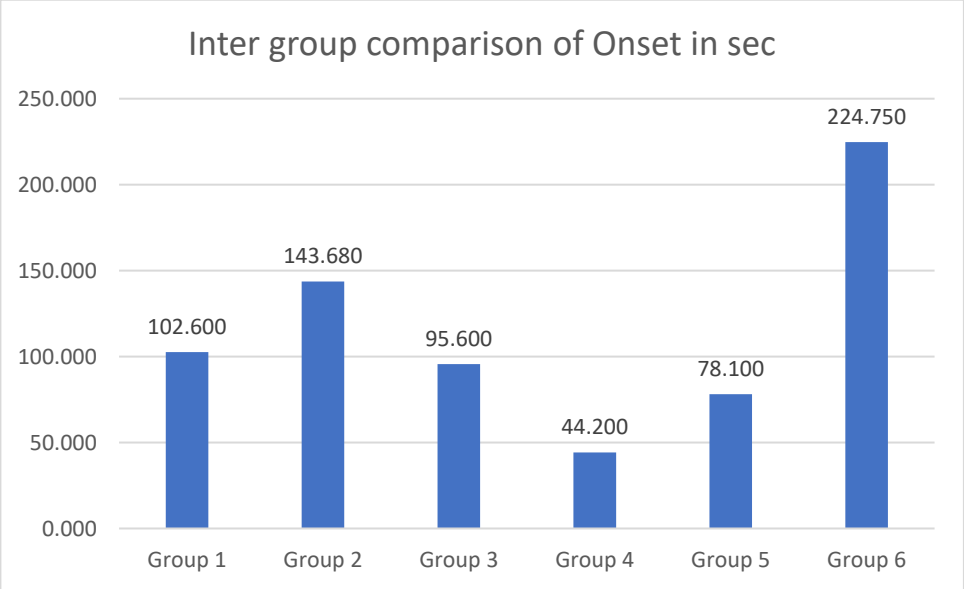
	5	1.65	.736	.116	75.60	1.5		
	6	4.28	1.059	.176	204.07	4		
total blood lost (a+b)	1	55.80	6.653	1.052	66.73	57	100.037	0.000**
	2	70.25	7.270	1.150	185.24	70		
	3	57.53	4.750	.751	73.85	58		
	4	66.45	6.656	1.052	159.44	68		
	5	59.38	6.376	1.008	93.74	60		
	6	63.89	5.942	.990	133.51	64		
no. of analgesics in 3days	1	7.93	.764	.121	179.48	8	178.263	0.000**
	2	8.20	.758	.120	190.90	8		
	3	6.50	.641	.101	112.13	6		
	4	6.88	1.042	.165	130.35	7		
	5	5.50	.555	.088	64.70	5		
	6	4.03	.878	.146	24.00	4		

**** = highly significant**

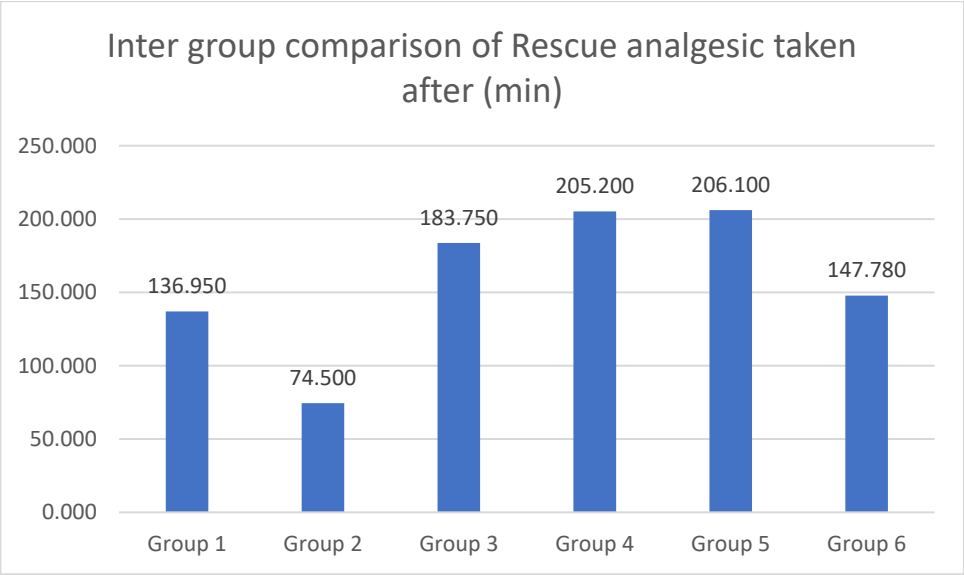
Graph 3:



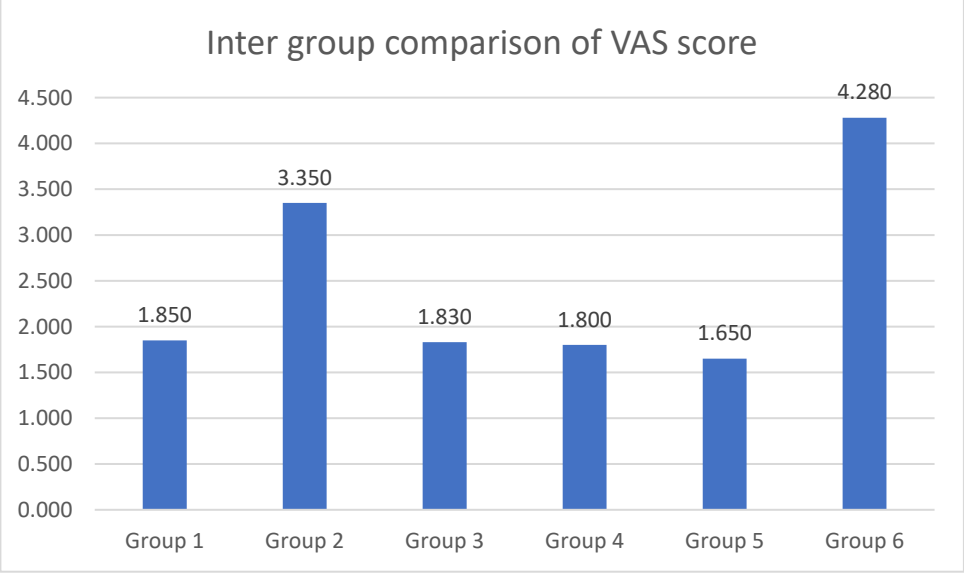
Graph 4:



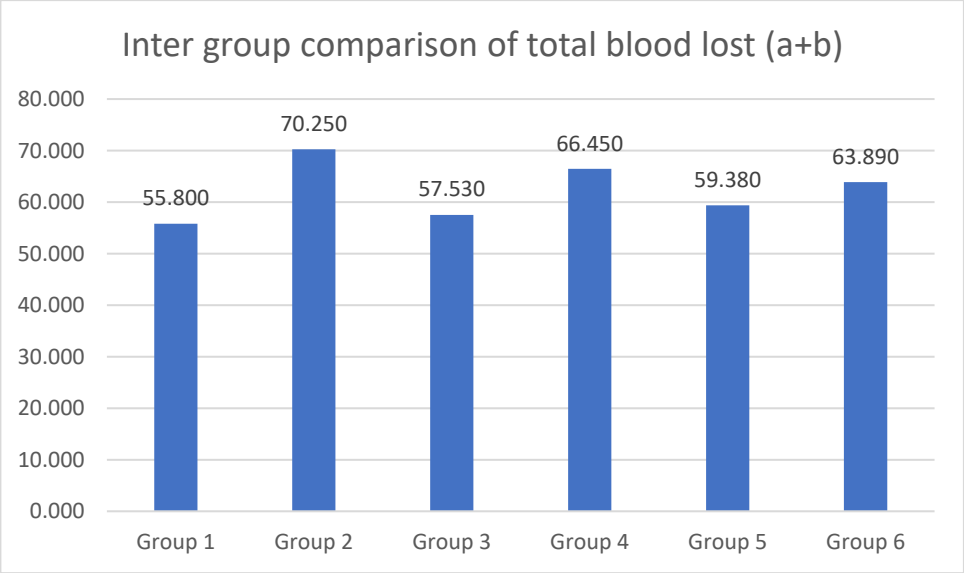
Graph 5:



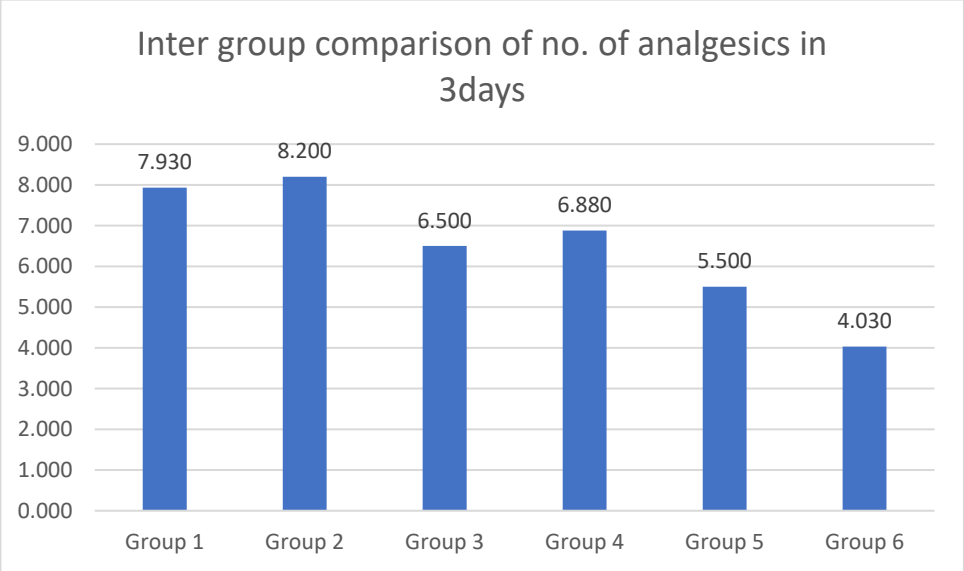
Graph 6:



Graph 7:



Graph 8:



Using Kruskal-Wallis test for **Inter group comparison** for **Cardiovascular variables**, there was no significant difference for pre-op SBP, DBP, MABP and HR, indicating that the groups were similar pre-operatively. There was a statistically highly significant difference for all these variables at all time intervals, ie. 5min, 10min,15min, 30min and 45min. (**Table 7),** (**Graph 9, 10, 11, 12)**

Table 7 Inter group comparison of mean of cardiovascular variables (Kruskall-Wallis test)

						95% Confidence Interval for Mean						
		N	Mean	Std. Deviation	Std. Error	Lower Bound	Upper Bound	Minimum	Maximum	Median	Chi square value	p value of Kruskal-Wallis Test
SBP pre-op	1	40	120.50	3.672	.581	119.33	121.67	112	128			
	2	40	120.20	1.964	.311	119.57	120.83	116	124			
	3	40	120.10	2.262	.358	119.38	120.82	116	124			
	4	40	119.50	2.253	.356	118.78	120.22	114	122			
	5	40	119.75	3.176	.502	118.73	120.77	112	124			
	6	36	120.33	2.217	.369	119.58	121.08	116	124			
	Total	236	120.06	2.664	.173	119.72	120.40	112	128		2.954	0.707#
SBP 5min	1	40	123.95	3.987	.630	122.67	125.23	116	132			
	2	40	120.70	1.951	.308	120.08	121.32	116	124			
	3	40	119.80	2.633	.416	118.96	120.64	112	124			
	4	40	119.80	2.255	.357	119.08	120.52	114	124			
	5	40	119.85	2.327	.368	119.11	120.59	114	124			
	6	36	120.17	1.935	.322	119.51	120.82	116	124			
	Total	236	120.72	2.993	.195	120.34	121.10	112	132		39.980	0.000**
SBP 10 min	1	40	128.05	3.374	.533	126.97	129.13	122	136			
	2	40	120.95	1.867	.295	120.35	121.55	116	124			
	3	40	119.70	3.314	.524	118.64	120.76	110	124			
	4	40	120.00	1.695	.268	119.46	120.54	116	122			
	5	40	119.90	1.751	.277	119.34	120.46	116	122		117.395	0.000**

	6	36	118.00	2.484	.414	117.16	118.84	114	122			
	Total	236	121.15	4.083	.266	120.63	121.68	110	136			
SBP 15 min	1	40	127.90	3.388	.536	126.82	128.98	118	134			
	2	40	120.70	2.003	.317	120.06	121.34	116	124			
	3	40	119.70	2.244	.355	118.98	120.42	114	124			
	4	40	119.80	1.911	.302	119.19	120.41	116	124			
	5	40	119.95	2.050	.324	119.29	120.61	116	124			
	6	36	118.33	2.268	.378	117.57	119.10	112	122			
	Total	236	121.11	3.923	.255	120.61	121.61	112	134		105.330	0.000**
SBP 30 min	1	40	126.90	3.448	.545	125.80	128.00	120	134			
	2	40	120.10	1.865	.295	119.50	120.70	116	124			
	3	40	119.80	1.682	.266	119.26	120.34	116	122			
	4	40	119.60	1.878	.297	119.00	120.20	116	124			
	5	40	119.95	2.417	.382	119.18	120.72	116	124			
	6	36	118.72	17.456	2.909	112.82	124.63	18	126			
	Total	236	120.88	7.587	.494	119.91	121.85	18	134		98.627	0.000**
SBP 45 min	1	40	121.80	2.857	.452	120.89	122.71	116	126			
	2	40	120.10	1.972	.312	119.47	120.73	116	124			
	3	40	119.75	2.687	.425	118.89	120.61	110	124			
	4	40	119.50	2.112	.334	118.82	120.18	114	124			
	5	40	119.90	1.972	.312	119.27	120.53	116	124			
	6	36	120.17	2.360	.393	119.37	120.97	114	124			
	Total	236	120.20	2.446	.159	119.89	120.52	110	126		20.793	0.001**
DBP pre-op	1	40	80.00	1.812	.286	79.42	80.58	76	84			
	2	40	80.10	2.307	.365	79.36	80.84	74	84			
	3	40	79.90	2.122	.336	79.22	80.58	76	84			
	4	40	79.95	1.894	.299	79.34	80.56	76	84			
	5	40	80.15	1.594	.252	79.64	80.66	78	82			
	6	36	80.22	1.899	.317	79.58	80.86	76	84		1.145	0.950#

	Total	236	80.05	1.934	.126	79.80	80.30	74	84			
DBP 5 min	1	40	81.85	1.777	.281	81.28	82.42	78	84			
	2	40	80.50	1.854	.293	79.91	81.09	78	88			
	3	40	79.80	2.431	.384	79.02	80.58	74	84			
	4	40	80.05	1.467	.232	79.58	80.52	78	84			
	5	40	80.10	1.865	.295	79.50	80.70	76	82			
	6	36	79.22	1.987	.331	78.55	79.89	76	82			
	Total	236	80.27	2.061	.134	80.01	80.54	74	88		35.483	0.000**
DBP 10 min	1	40	83.55	1.395	.221	83.10	84.00	82	86			
	2	40	80.60	1.128	.178	80.24	80.96	78	82			
	3	40	79.70	2.053	.325	79.04	80.36	74	84			
	4	40	80.10	1.751	.277	79.54	80.66	76	84			
	5	40	80.15	1.942	.307	79.53	80.77	76	84			
	6	36	79.00	2.318	.386	78.22	79.78	76	82			
	Total	236	80.54	2.292	.149	80.25	80.84	74	86		88.555	0.000**
DBP 15 min	1	40	83.45	1.358	.215	83.02	83.88	80	86			
	2	40	80.65	1.994	.315	80.01	81.29	78	88			
	3	40	79.70	2.003	.317	79.06	80.34	76	82			
	4	40	80.10	2.023	.320	79.45	80.75	74	84			
	5	40	80.10	2.170	.343	79.41	80.79	76	84			
	6	36	79.44	1.827	.305	78.83	80.06	76	82			
	Total	236	80.59	2.324	.151	80.30	80.89	74	88		80.890	0.000**
DBP 30 min	1	40	82.30	1.786	.282	81.73	82.87	78	86			
	2	40	80.50	2.112	.334	79.82	81.18	76	88			
	3	40	79.75	1.932	.305	79.13	80.37	76	82			
	4	40	80.25	1.984	.314	79.62	80.88	74	84			
	5	40	80.05	2.148	.340	79.36	80.74	76	84			
	6	36	79.56	1.978	.330	78.89	80.22	76	82			
	Total	236	80.42	2.171	.141	80.14	80.69	74	88		40.210	0.000**

DBP 45 min	1	40	80.90	1.566	.248	80.40	81.40	78	84			
	2	40	80.20	1.800	.285	79.62	80.78	76	84			
	3	40	79.75	1.645	.260	79.22	80.28	76	84			
	4	40	79.90	1.809	.286	79.32	80.48	74	84			
	5	40	80.05	1.535	.243	79.56	80.54	78	82			
	6	36	80.00	1.586	.264	79.46	80.54	76	82			
	Total	236	80.14	1.686	.110	79.92	80.35	74	84		12.635	0.027*
MABP pre-op	1	40	93.50000	2.035301	.321809	92.84908	94.15092	89.333	98.000			
	2	40	93.46667	1.599145	.252847	92.95524	93.97810	89.333	96.667			
	3	40	93.30000	1.439769	.227647	92.83954	93.76046	89.333	96.000			
	4	40	93.13333	1.368760	.216420	92.69558	93.57108	89.333	96.667			
	5	40	93.35000	1.412097	.223272	92.89839	93.80161	89.333	96.000			
	6	36	93.59259	1.436732	.239455	93.10647	94.07871	89.333	96.000			
	Total	236	93.38701	1.558001	.101417	93.18720	93.58681	89.333	98.000		3.181	0.672#
MABP 5 min	1	40	95.88333	1.996507	.315675	95.24482	96.52185	90.667	99.333			
	2	40	93.90000	1.436599	.227146	93.44055	94.35945	91.333	99.333			
	3	40	93.13333	1.812901	.286645	92.55354	93.71313	89.333	96.667			
	4	40	93.30000	1.178632	.186358	92.92306	93.67694	91.333	96.000			
	5	40	93.35000	1.193405	.188694	92.96833	93.73167	91.333	95.333			
	6	36	92.87037	1.423784	.237297	92.38863	93.35211	90.667	95.333			
	Total	236	93.75424	1.828034	.118995	93.51980	93.98867	89.333	99.333		55.983	0.000**
MABP 10 min	1	40	98.38333	1.508853	.238571	97.90078	98.86589	95.333	101.333			
	2	40	94.05000	1.028234	.162578	93.72115	94.37885	92.000	96.000			
	3	40	93.03333	2.069725	.327252	92.37140	93.69526	88.000	96.667			
	4	40	93.40000	1.430637	.226204	92.94246	93.85754	89.333	96.000			
	5	40	93.40000	1.177181	.186129	93.02352	93.77648	90.667	96.000			
	6	36	92.00000	1.520234	.253372	91.48563	92.51437	88.667	94.667			
	Total	236	94.07910	2.517336	.163865	93.75626	94.40193	88.000	101.333		120.806	0.000**
	1	40	98.26667	1.390239	.219816	97.82205	98.71129	94.667	101.333		110.713	0.000**

MABP 15 min	2	40	94.00000	1.539601	.243432	93.50761	94.49239	91.333	99.333			
	3	40	93.03333	1.546617	.244542	92.53870	93.52797	89.333	96.000			
	4	40	93.33333	1.667521	.263658	92.80003	93.86663	88.000	96.667			
	5	40	93.38333	1.527618	.241538	92.89478	93.87189	90.000	96.000			
	6	36	92.40741	1.354853	.225809	91.94899	92.86582	89.333	94.667			
	Total	236	94.09887	2.451539	.159582	93.78448	94.41326	88.000	101.333			
MABP 30 min	1	40	97.16667	1.574367	.248929	96.66316	97.67017	92.667	100.667			
	2	40	93.70000	1.660330	.262521	93.16900	94.23100	91.333	99.333			
	3	40	93.10000	1.277016	.201914	92.69159	93.50841	91.333	95.333			
	4	40	93.36667	1.625649	.257038	92.84676	93.88657	88.667	96.000			
	5	40	93.35000	1.684435	.266333	92.81129	93.88871	89.333	96.000			
	6	36	92.61111	5.677860	.946310	90.69000	94.53222	60.667	96.667			
	Total	236	93.90395	3.022720	.196762	93.51631	94.29160	60.667	100.667		85.637	0.000**
MABP 45 min	1	40	94.53333	1.409775	.222905	94.08247	94.98420	91.333	96.667			
	2	40	93.50000	1.348208	.213170	93.06882	93.93118	90.667	96.667			
	3	40	93.08333	1.389316	.219670	92.63901	93.52766	88.667	96.000			
	4	40	93.10000	1.420645	.224624	92.64566	93.55434	90.000	96.667			
	5	40	93.33333	1.159625	.183353	92.96247	93.70420	91.333	95.333			
	6	36	93.38889	1.238278	.206380	92.96992	93.80786	90.667	95.333			
	Total	236	93.49153	1.408325	.091674	93.31092	93.67213	88.667	96.667		25.373	0.000**
HR pre-op	1	40	77.08	2.223	.352	76.36	77.79	70	82			
	2	40	75.78	3.246	.513	74.74	76.81	70	82			
	3	40	77.00	3.523	.557	75.87	78.13	70	83			
	4	40	75.95	3.637	.575	74.79	77.11	70	83			
	5	40	76.33	2.654	.420	75.48	77.17	68	82			
	6	36	75.83	2.783	.464	74.89	76.77	71	82			
	Total	236	76.33	3.071	.200	75.94	76.73	68	83		8.410	0.135#
HR 5min	1	40	83.10	2.872	.454	82.18	84.02	76	89			
	2	40	76.43	3.876	.613	75.19	77.66	69	85		78.306	0.000**

	3	40	77.88	3.383	.535	76.79	78.96	72	85			
	4	40	76.08	3.415	.540	74.98	77.17	69	85			
	5	40	76.75	2.539	.402	75.94	77.56	71	81			
	6	36	75.86	2.949	.491	74.86	76.86	69	83			
	Total	236	77.71	4.053	.264	77.19	78.23	69	89			
HR 10 min	1	40	83.00	3.351	.530	81.93	84.07	75	88			
	2	40	76.45	4.006	.633	75.17	77.73	69	87			
	3	40	77.95	3.202	.506	76.93	78.97	73	83			
	4	40	76.15	3.606	.570	75.00	77.30	69	87			
	5	40	76.70	3.314	.524	75.64	77.76	70	84			
	6	36	75.89	2.755	.459	74.96	76.82	69	82			
	Total	236	77.72	4.181	.272	77.18	78.26	69	88		71.077	0.000**
HR 15 min	1	40	81.65	2.931	.463	80.71	82.59	76	86			
	2	40	76.55	3.170	.501	75.54	77.56	72	82			
	3	40	77.83	2.986	.472	76.87	78.78	73	83			
	4	40	76.10	3.350	.530	75.03	77.17	70	83			
	5	40	76.35	3.613	.571	75.19	77.51	71	88			
	6	36	75.92	4.108	.685	74.53	77.31	70	87			
	Total	236	77.42	3.893	.253	76.92	77.92	70	88		60.643	0.000**
HR 30 min	1	40	79.93	2.859	.452	79.01	80.84	74	84			
	2	40	76.53	3.366	.532	75.45	77.60	71	83			
	3	40	77.73	2.918	.461	76.79	78.66	72	84			
	4	40	75.98	3.977	.629	74.70	77.25	71	83			
	5	40	76.30	3.123	.494	75.30	77.30	71	83			
	6	36	75.81	4.302	.717	74.35	77.26	71	86			
	Total	236	77.06	3.703	.241	76.59	77.54	71	86		37.523	0.000**
HR 45 min	1	40	78.78	3.634	.575	77.61	79.94	73	89			
	2	40	75.88	3.784	.598	74.66	77.09	70	82			
	3	40	77.68	3.832	.606	76.45	78.90	71	84		18.939	0.002**

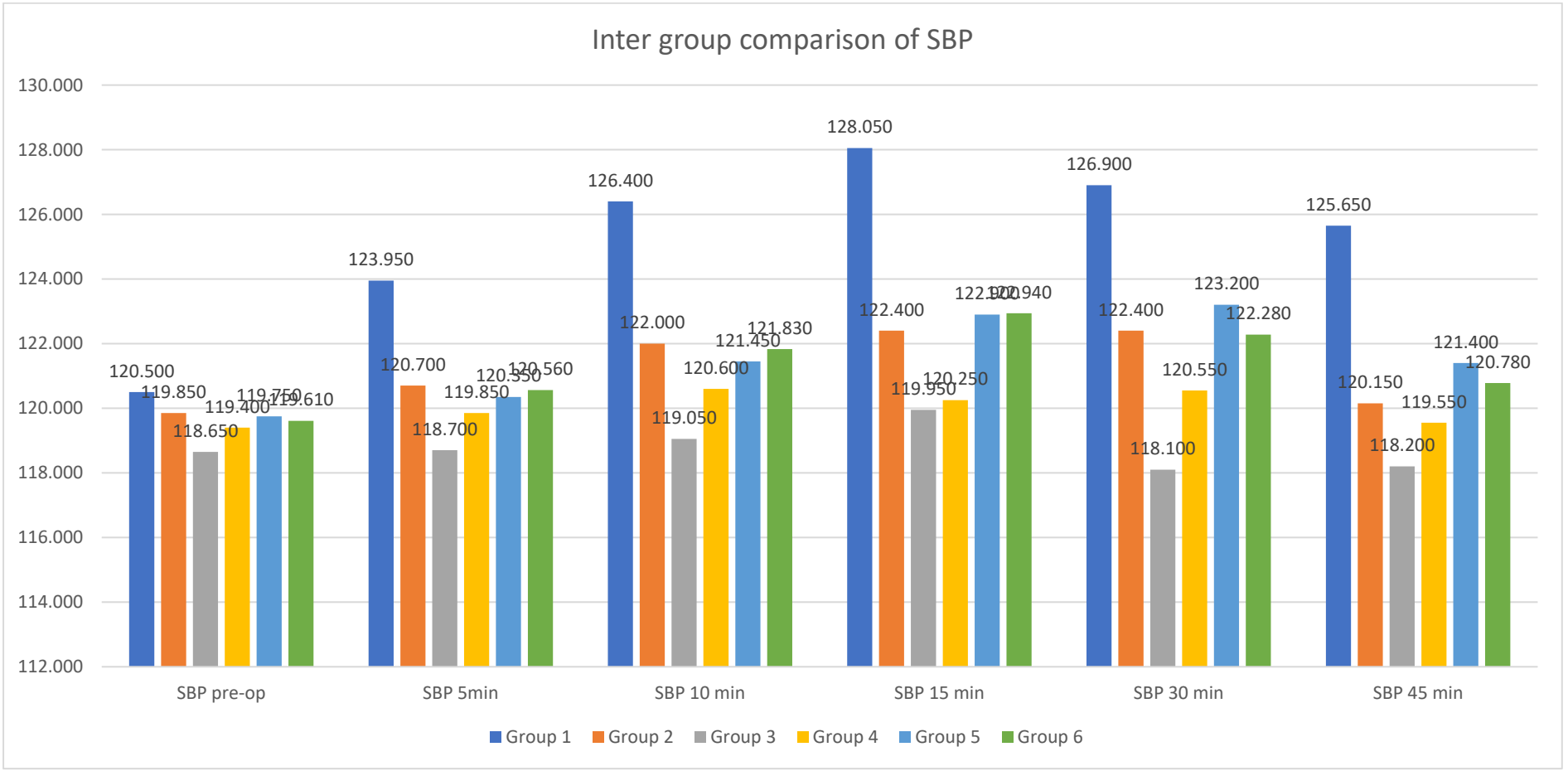
	4	40	75.93	3.526	.557	74.80	77.05	70	82			
	5	40	76.20	3.884	.614	74.96	77.44	70	84			
	6	36	75.67	4.309	.718	74.21	77.12	70	85			
	Total	236	76.70	3.957	.258	76.20	77.21	70	89			

 # = non-significant

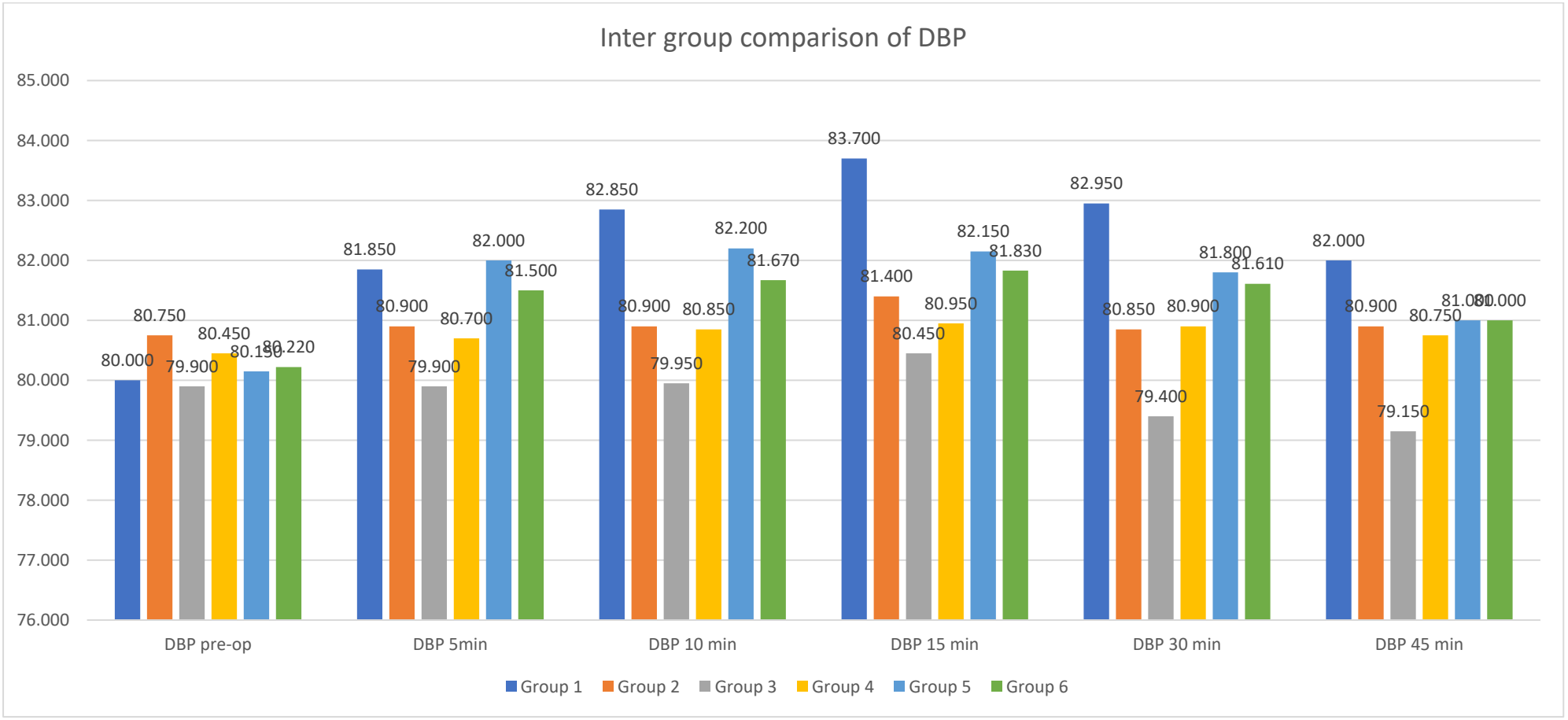
***= significant**

****= highly significant**

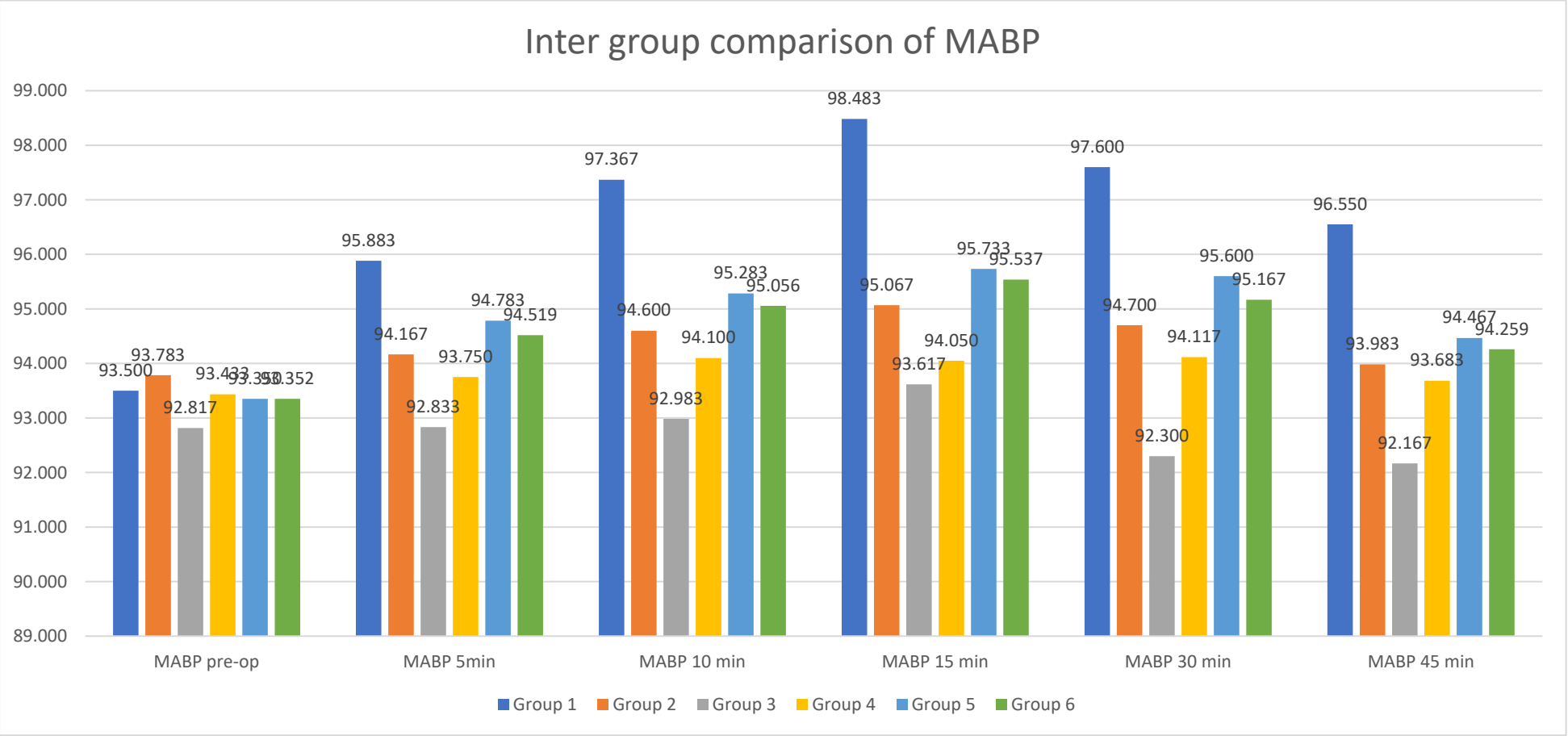
Graph 9:


Inter group comparison of SBP
130.000
128.000
126.000
124.000
122.000
120.000
118.000
116.000
114.000
112.000
120.500
119.850
118.650
119.400
119.750
119.610
123.950
120.700
118.700
119.850
120.350
120.560
126.400
122.000
119.050
120.600
121.450
121.830
128.050
122.400
119.950
120.250
122.940
126.900
122.400
118.100
120.550
123.200
122.280
125.650
120.150
118.200
119.550
121.400
120.780
SBP pre-op
SBP 5min
SBP 10 min
SBP 15 min
SBP 30 min
SBP 45 min
Group 1
Group 2
Group 3
Group 4
Group 5
Group 6

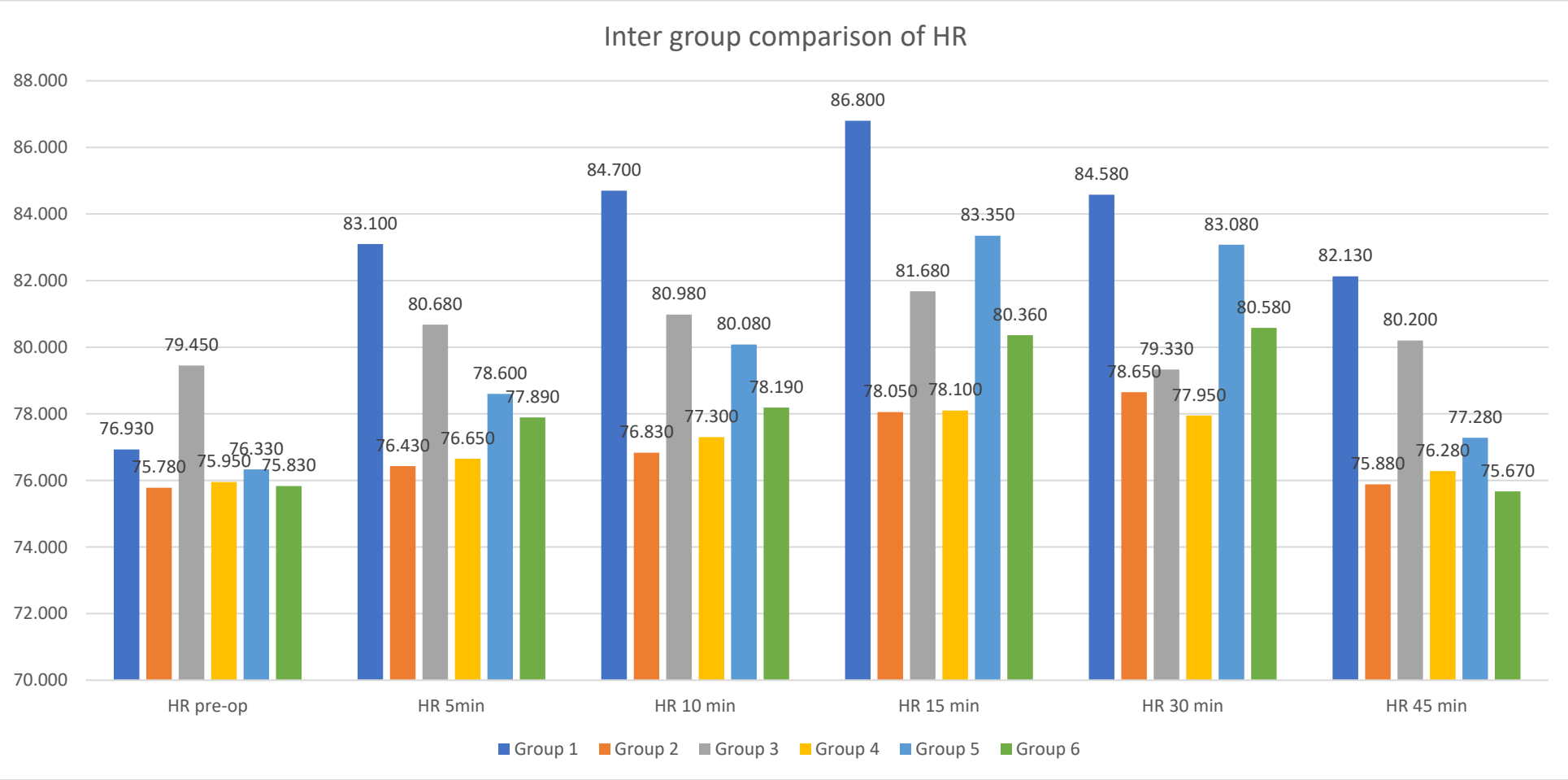
Graph 10:


Inter group comparison of DBP
85.000
84.000
83.000
82.000
81.000
80.000
79.000
78.000
77.000
76.000
80.000
80.750
79.900
80.450
80.150
80.220
81.850
80.900
79.900
80.700
82.000
81.500
82.850
80.900
79.950
80.850
82.200
81.670
83.700
81.400
80.450
80.950
82.150
81.830
82.950
80.850
79.400
80.900
81.800
81.610
82.000
80.900
79.150
80.750
81.080
81.000
DBP pre-op
DBP 5min
DBP 10 min
DBP 15 min
DBP 30 min
DBP 45 min
Group 1
Group 2
Group 3
Group 4
Group 5
Group 6

Graph 11:


Inter group comparison of MABP
99.000
98.000
97.000
96.000
95.000
94.000
93.000
92.000
91.000
90.000
89.000
93.500
93.783
92.817
93.433
93.350
93.352
95.883
94.167
92.833
93.750
94.783
94.519
97.367
94.600
92.983
94.100
95.283
95.056
98.483
95.067
93.617
94.050
95.733
95.537
97.600
94.700
92.300
94.117
95.600
95.167
96.550
93.983
92.167
93.683
94.467
94.259
MABP pre-op
MABP 5min
MABP 10 min
MABP 15 min
MABP 30 min
MABP 45 min
Group 1
Group 2
Group 3
Group 4
Group 5
Group 6

Graph 12:


Inter group comparison of HR
88.000
86.000
84.000
82.000
80.000
78.000
76.000
74.000
72.000
70.000
76.930
75.780
79.450
75.950
76.330
75.830
83.100
76.430
80.680
76.650
78.600
77.890
84.700
76.830
80.980
77.300
80.080
78.190
86.800
78.050
81.680
78.100
83.350
80.360
84.580
78.650
79.330
77.950
83.080
80.580
82.130
75.880
80.200
76.280
77.280
75.670
HR pre-op
HR 5min
HR 10 min
HR 15 min
HR 30 min
HR 45 min
Group 1
Group 2
Group 3
Group 4
Group 5
Group 6

For Adr grp, there was highly significant difference for **Intra-grp comparison using Friedman's test** (**Tables 8.1, 8.2, 8.3, 8.4)** and for **pair-wise comparison with pre-op values**, using Wilcoxon Signed rank test (**Table 9)**

Mean SBP was 120.50±3.672 pre-op, 123.95±3.987 at 5min, 128.05±3.374 at 10 min, 127.90±3.388 at 15min, 126.90±3.448 at 30min, 121.80±2.857 at 45 min post-injection, (**Table 8.1)** (**Graph 13)**

Mean DBP was 80±1.812 pre-operatively, 81.85±1.777 at 5min, 83.55±1.395 at 10min, 83.45±1.358 at 15min, 82.30±1.786 at 30min and 80.90±1.566 at 45min post-injection. (**Table 8.2)** (**Graph 14)**

Mean MABP was 93.50±2.035 pre-op, 95.88±1.996 at 5min, 98.383±1.5089 at 10min, 98.26667±1.390239 at 15min, 97.16667±1.574367 at 30min, 94.53333±1.409775 at 45min post-injection. (**Table 8.3)** (**Graph 15)**

Mean HR was 77.08±2.223 pre-op, 83.10±2.872 at 5min, 83.00±3.351 at 10min, 81.65±2.931 at 15min, 79.93±2.859 at 30min, 78.78±3.634 at 45min post-injection. (**Table 8.4)** (**Graph 16)**

Table 8: Intra group comparison in group 1 (Friedman's test)

8.1 SBP

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
SBP pre-op	40	120.50	3.672	112	128	120.00	1.36		
SBP 5min	40	123.95	3.987	116	132	124.00	2.93		
SBP 10 min	40	128.05	3.374	122	136	128.00	5.19	155.980	0.000**
SBP 15 min	40	127.90	3.388	118	134	128.00	5.06		
SBP 30 min	40	126.90	3.448	120	134	126.00	4.34		
SBP 45 min	40	121.80	2.857	116	126	122.00	2.13		

**** = highly significant**

8.2 DBP

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
DBP pre-op	40	80.00	1.812	76	84	80.00	1.70		
DBP 5 min	40	81.85	1.777	78	84	82.00	3.41		
DBP 10 min	40	83.55	1.395	82	86	84.00	4.94	110.605	0.000**
DBP 15 min	40	83.45	1.358	80	86	84.00	4.80		
DBP 30 min	40	82.30	1.786	78	86	82.00	3.64		
DBP 45 min	40	80.90	1.566	78	84	82.00	2.51		

**** = highly significant**

8.3 MABP

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
MABP pre-op	40	93.50000	2.035301	89.333	98.000	93.33333	1.31		
MABP 5 min	40	95.88333	1.996507	90.667	99.333	96.00000	3.08		
MABP 10 min	40	98.38333	1.508853	95.333	101.333	98.66667	5.26	154.461	0.000**
MABP 15 min	40	98.26667	1.390239	94.667	101.333	98.66667	5.21		
MABP 30 min	40	97.16667	1.574367	92.667	100.667	97.33333	4.01		
MABP 45 min	40	94.53333	1.409775	91.333	96.667	94.66667	2.13		

**** = highly significant**

8.4 HR

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
HR pre-op	40	77.08	2.223	70	82	77.50	1.91		
HR 5min	40	83.10	2.872	76	89	83.50	4.49		
HR 10 min	40	83.00	3.351	75	88	83.00	4.56	71.244	0.000**
HR 15 min	40	81.65	2.931	76	86	82.00	4.29		
HR 30 min	40	79.93	2.859	74	84	81.00	3.05		
HR 45 min	40	78.78	3.634	73	89	79.00	2.70		

**** = highly significant**

Table 9: Pair wise comparison of cardiac variables using Wilcoxon Signed Ranks Test in Grp1

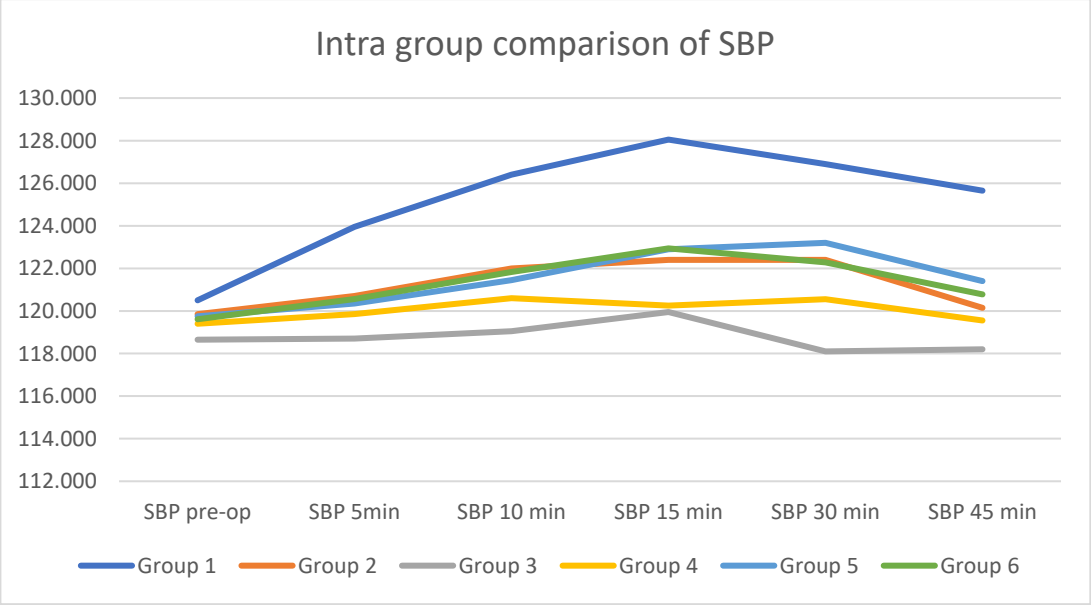
	Z value	p value of Wilcoxon Signed Ranks Test
SBP 5min - SBP pre-op	-5.463	0.000**
SBP 10 min - SBP pre-op	-5.569	0.000**
SBP 15 min - SBP pre-op	-5.549	0.000**
SBP 30 min - SBP pre-op	-5.419	0.000**
SBP 45 min - SBP pre-op	-2.567	0.010*
DBP 5 min - DBP pre-op	-5.336	0.000**
DBP 10 min - DBP pre-op	-5.457	0.000**
DBP 15 min - DBP pre-op	-5.247	0.000**
DBP 30 min - DBP pre-op	-4.198	0.000**
DBP 45 min - DBP pre-op	-2.149	0.032*
MABP 5 min - MABP pre-op	-5.485	0.000**
MABP 10 min - MABP pre-op	-5.528	0.000**
MABP 15 min - MABP pre-op	-5.522	0.000**
MABP 30 min - MABP pre-op	-5.451	0.000**
MABP 45 min - MABP pre-op	-2.824	0.005**
HR 5min - HR pre-op	-5.529	0.000**
HR 10 min - HR pre-op	-5.163	0.000**
HR 15 min - HR pre-op	-4.956	0.000**
HR 30 min - HR pre-op	-3.685	0.000**
HR 45 min - HR pre-op	-2.513	0.012*

 # = non-significant

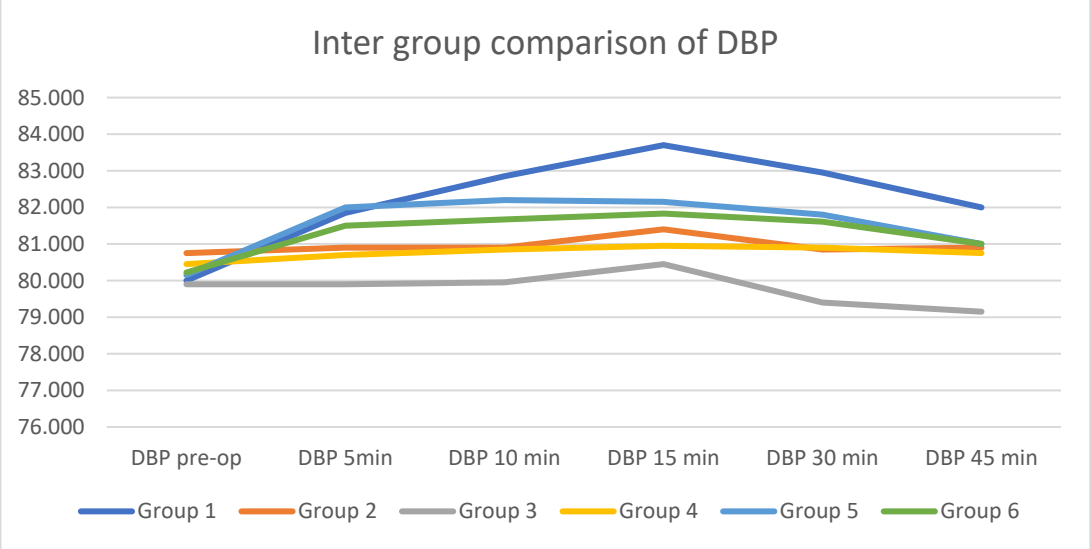
***= significant**

****= highly significant**

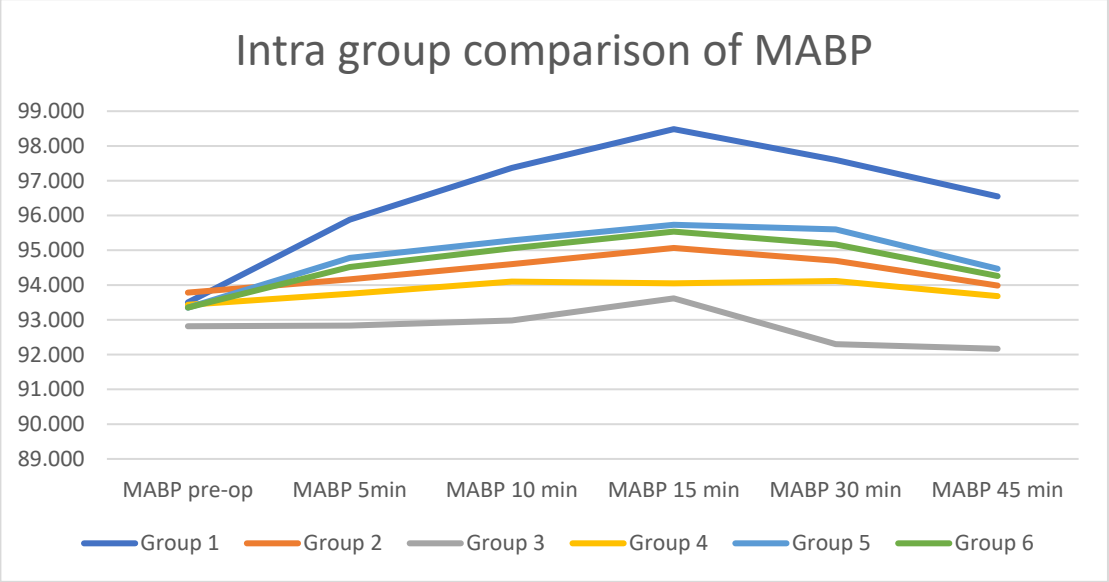
Graph 13:



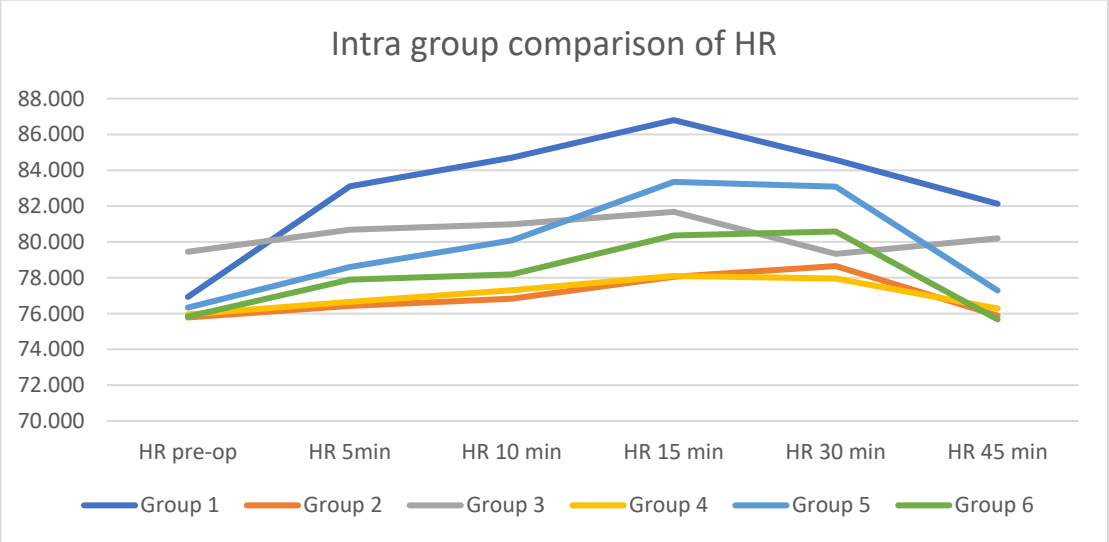
Graph 14:



Graph 15:



Graph 16:



For plain Lig. grp, there was no significant difference for **Intra-grp comparison using Friedman's test** (**Tables 10.1, 10.2, 10.3, 10.4)** and for **pair-wise comparison with pre-op values**, using Wilcoxon Signed rank test **(Table 11)**

Mean SBP was 120.20±1.964 pre-op, 120.70±1.951 at 5min, 120.95±1.867 at 10 min, 120.70±2.003 at 15min, 120.10±1.865 at 30min, 120.10±1.9727 at 45 min post-injection, (**Table 10.1)** (**Graph 13)**

Mean DBP was 80.10±2.307 pre-op, 80.50±1.854 at 5min, 80.60±1.128 at 10min, 80.65±1.994 at 15min, 80.50±2.112 at 30min, 80.20±1.800 at 45min post-injection. (**Table 10.2)** (**Graph 14)**

Mean MABP was 93.46667±1.599145 pre-op, 93.90000±1.436599 at 5min, 94.05000±1.028234 at 10min, 94.00000±1.539601 at 15min, 93.70000±1.660330 at 30min, 93.50000±1.34820 at 45min post-injection. (**Table 10.3)** (**Graph 15)**

Mean HR was 75.78±3.246 pre-op, 76.43±3.876 at 5min, 76.45±4.006 at 10min, 76.55±3.170 at 15min, 76.53±3.366 at 30min, 75.88±3.784 at 45min post-injection. (**Table 10.4)** (**Graph 16)**

Table 10: Intra group comparison in group 2 (Friedman's test)

10.1 SBP

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
SBP pre-op	40	120.20	1.964	116	124	120.00	3.20		
SBP 5min	40	120.70	1.951	116	124	122.00	3.75		
SBP 10 min	40	120.95	1.867	116	124	122.00	4.08	10.999	0.051#
SBP 15 min	40	120.70	2.003	116	124	122.00	3.69		
SBP 30 min	40	120.10	1.865	116	124	120.00	3.18		
SBP 45 min	40	120.10	1.972	116	124	120.00	3.11		

 # = non-significant

10.2 DBP

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
DBP pre-op	40	80.10	2.307	74	84	80.00	3.40		
DBP 5 min	40	80.50	1.854	78	88	80.00	3.43		
DBP 10 min	40	80.60	1.128	78	82	80.00	3.73	2.557	0.768#
DBP 15 min	40	80.65	1.994	78	88	80.00	3.68		
DBP 30 min	40	80.50	2.112	76	88	80.00	3.53		
DBP 45 min	40	80.20	1.800	76	84	80.00	3.25		

 # = non-significant

10.3 MABP

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
MABP pre-op	40	93.46667	1.599145	89.333	96.667	94.00000	3.30		
MABP 5 min	40	93.90000	1.436599	91.333	99.333	94.00000	3.43		
MABP 10 min	40	94.05000	1.028234	92.000	96.000	94.00000	4.03	7.410	0.192#
MABP 15 min	40	94.00000	1.539601	91.333	99.333	94.00000	3.80		
MABP 30 min	40	93.70000	1.660330	91.333	99.333	94.00000	3.35		
MABP 45 min	40	93.50000	1.348208	90.667	96.667	93.33333	3.10		

 # = non-significant

10.4 HR

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
HR pre-op	40	75.78	3.246	70	82	75.50	3.04		
HR 5min	40	76.43	3.876	69	85	76.00	3.49		
HR 10 min	40	76.45	4.006	69	87	76.00	3.69	4.729	0.450#
HR 15 min	40	76.55	3.170	72	82	76.00	3.68		
HR 30 min	40	76.53	3.366	71	83	76.00	3.79		
HR 45 min	40	75.88	3.784	70	82	75.00	3.33		

 # = non-significant

Table 11: Pair wise comparison of cardiac variables using Wilcoxon Signed Ranks Test for grp 2

	Z value	p value of Wilcoxon Signed Ranks Test
SBP 5min - SBP pre-op	-1.720	0.085#
SBP 10 min - SBP pre-op	-1.936	0.053#
SBP 15 min - SBP pre-op	-1.200	0.230#
SBP 30 min - SBP pre-op	-0.254	0.800#
SBP 45 min - SBP pre-op	-0.357	0.721#
DBP 5 min - DBP pre-op	-0.882	0.378#
DBP 10 min - DBP pre-op	-1.277	0.201#
DBP 15 min - DBP pre-op	-0.701	0.483#
DBP 30 min - DBP pre-op	-0.716	0.474#
DBP 45 min - DBP pre-op	-0.313	0.754#
MABP 5 min - MABP pre-op	-1.177	0.239#
MABP 10 min - MABP pre-op	-2.161	0.031#
MABP 15 min - MABP pre-op	-1.108	0.268#
MABP 30 min - MABP pre-op	-0.054	0.957#
MABP 45 min - MABP pre-op	-0.086	0.931#
HR 5min - HR pre-op	-1.071	0.284#
HR 10 min - HR pre-op	-0.835	0.404#
HR 15 min - HR pre-op	-0.898	0.369#
HR 30 min - HR pre-op	-0.748	0.455#
HR 45 min - HR pre-op	-0.386	0.699#

 # = non-significant

For Clonidine grp, there was no significant difference for **Intra-grp comparison using Friedman's test** (**Tables 12.1, 12.2, 12.3, 12.4)** and for **pair-wise comparison with pre-op values**, using Wilcoxon Signed rank test (**Table 13)**

Mean SBP was 120.10±2.262 pre-op, 119.80±2.633 at 5min, 119.70±3.314 at 10 min, 119.70±2.244 at 15min, 119.80±1.682 at 30min, 119.75±2.687 at 45 min post-injection, (**Table 12.1)** (**Graph 13)**

Mean DBP was 79.90±2.122 pre-op, 79.80±2.431 at 5min, 79.70±2.053 at 10min, 79.70±2.003 at 15min, 79.75±1.932 at 30min, 79.75±1.645 at 45min post-injection. (**Table 12.2)** (**Graph 14)**

Mean MABP was 93.30000±1.439769 pre-op, 93.13333±1.812901 at 5min, 93.03333±2.069725 at 10min, 93.03333±1.546617 at 15min, 93.10000±1.277016 at 30min, 93.08333±1.389316 at 45min post-injection. (**Table 12.3)** (**Graph 15)**

Mean HR was 77.00±3.523 pre-op, 77.88±3.383 at 5min, 77.95±3.202 at 10min, 77.83±2.986 at 15min, 77.73±2.918 at 30min, 77.68±3.832 at 45min post-injection. (**Table 12.4)** (**Graph 16)**

Table 12: Intra group comparison in group 3 (Friedman's test)

12.1 SBP

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
SBP pre-op	40	120.10	2.262	116	124	120.00	3.60		
SBP 5min	40	119.80	2.633	112	124	120.00	3.61		
SBP 10 min	40	119.70	3.314	110	124	120.00	3.60	1.239	0.941#
SBP 15 min	40	119.70	2.244	114	124	120.00	3.31		
SBP 30 min	40	119.80	1.682	116	122	120.00	3.35		
SBP 45 min	40	119.75	2.687	110	124	120.00	3.53		

 # = non-significant

12.2: DBP

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
DBP pre-op	40	79.90	2.122	76	84	80.00	3.63		
DBP 5 min	40	79.80	2.431	74	84	80.00	3.50		
DBP 10 min	40	79.70	2.053	74	84	80.00	3.44	701	0.983#
DBP 15 min	40	79.70	2.003	76	82	80.00	3.58		
DBP 30 min	40	79.75	1.932	76	82	80.00	3.53		
DBP 45 min	40	79.75	1.645	76	84	80.00	3.34		

 # = non-significant

12.3 MABP

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
MABP pre-op	40	93.30000	1.439769	89.333	96.000	93.33333	3.69		
MABP 5 min	40	93.13333	1.812901	89.333	96.667	93.33333	3.40		
MABP 10 min	40	93.03333	2.069725	88.000	96.667	93.33333	3.35	1.358	0.929#
MABP 15 min	40	93.03333	1.546617	89.333	96.000	93.33333	3.44		
MABP 30 min	40	93.10000	1.277016	91.333	95.333	93.33333	3.69		
MABP 45 min	40	93.08333	1.389316	88.667	96.000	93.00000	3.44		

 # = non-significant

12.4: HR

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
HR pre-op	40	77.00	3.523	70	83	78.00	3.35		
HR 5min	40	77.88	3.383	72	85	77.00	3.51		
HR 10 min	40	77.95	3.202	73	83	77.50	3.60	.797	0.977#
HR 15 min	40	77.83	2.986	73	83	78.00	3.44		
HR 30 min	40	77.73	2.918	72	84	78.00	3.44		
HR 45 min	40	77.68	3.832	71	84	79.00	3.66		

 # = non-significant

Table 13: Pair wise comparison of cardiac variables using Wilcoxon Signed Ranks Test in grp 3

	Z value	p value of Wilcoxon Signed Ranks Test
SBP 5min - SBP pre-op	-0.594	0.552#
SBP 10 min - SBP pre-op	-0.606	0.544#
SBP 15 min - SBP pre-op	-0.969	0.332#
SBP 30 min - SBP pre-op	-0.722	0.470#
SBP 45 min - SBP pre-op	-0.655	0.512#
DBP 5 min - DBP pre-op	-0.010	0.992#
DBP 10 min - DBP pre-op	-0.488	0.625#
DBP 15 min - DBP pre-op	-0.446	0.655#
DBP 30 min - DBP pre-op	-0.302	0.762#
DBP 45 min - DBP pre-op	-0.406	0.685#
MABP 5 min - MABP pre-op	-0.459	0.646#
MABP 10 min - MABP pre-op	-0.932	0.352#
MABP 15 min - MABP pre-op	-0.799	0.424#
MABP 30 min - MABP pre-op	-0.702	0.483#
MABP 45 min - MABP pre-op	-0.625	0.532#
HR 5min - HR pre-op	-0.668	0.504#
HR 10 min - HR pre-op	-1.208	0.227#
HR 15 min - HR pre-op	-0.924	0.355#
HR 30 min - HR pre-op	-0.408	0.683#
HR 45 min - HR pre-op	-0.771	0.441#

 # = non-significant

For KCl grp, there was no significant difference for **Intra-grp comparison using Friedman's test** (**Tables 14.1, 14.2, 14.3, 14.4)** and for **pair-wise comparison with pre-op values**, using Wilcoxon Signed rank test (**Table 15)**

Mean SBP was 119.50±2.253 pre-op, 119.80±2.255 at 5min, 120.00±1.695 at 10 min, 119.80±1.911 at 15min, 119.60±1.878 at 30min, 119.50±2.112 at 45 min post-injection (**Table 14.1)** (**Graph 13)**

Mean DBP was 79.95±1.894 pre-op, 80.05±1.467 at 5min, 80.10±1.751 at 10min, 80.10±2.023 at 15min, 80.25±1.984 at 30min, 79.90±1.809 at 45min post-injection. (**Table 14.2)** (**Graph 14)**

Mean MABP was 93.13333±1.368760 pre-op, 93.30000±1.178632 at 5min, 93.40000±1.430637 at 10min, 93.33333±1.667521 at 15min, 93.36667±1.625649 at 30min, 93.10000±1.420645 at 45min post-injection. (**Table 14.3)** (**Graph 15)**

Mean HR was 75.95±3.637 pre-op, 76.08±3.415 at 5min, 76.15±3.606 at 10min, 76.10±3.350 at 15min, 75.98±3.977 at 30min, 75.93±3.526 at 45min post-injection. (**Table 14.4)** (**Graph 16)**

Table 14: Intra group comparison in group 4 (Friedman's test)

14.1 SBP

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
SBP pre-op	40	119.50	2.253	114	122	120.00	3.34		
SBP 5min	40	119.80	2.255	114	124	120.00	3.63		
SBP 10 min	40	120.00	1.695	116	122	120.00	3.76	2.187	0.823#
SBP 15 min	40	119.80	1.911	116	124	120.00	3.56		
SBP 30 min	40	119.60	1.878	116	124	120.00	3.35		
SBP 45 min	40	119.50	2.112	114	124	120.00	3.36		

 # = non-significant

14.2 DBP

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
DBP pre-op	40	79.95	1.894	76	84	80.00	3.39		
DBP 5 min	40	80.05	1.467	78	84	80.00	3.51		
DBP 10 min	40	80.10	1.751	76	84	80.00	3.51	2.847	0.724#
DBP 15 min	40	80.10	2.023	74	84	80.00	3.48		
DBP 30 min	40	80.25	1.984	74	84	80.00	3.85		
DBP 45 min	40	79.90	1.809	74	84	80.00	3.26		

 # = non-significant

14.3 MABP

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
MABP pre-op	40	93.13333	1.368760	89.333	96.667	93.00000	3.29		
MABP 5 min	40	93.30000	1.178632	91.333	96.000	93.33333	3.41		
MABP 10 min	40	93.40000	1.430637	89.333	96.000	93.33333	3.74	4.481	0.482#
MABP 15 min	40	93.33333	1.667521	88.000	96.667	93.33333	3.53		
MABP 30 min	40	93.36667	1.625649	88.667	96.000	93.33333	3.88		
MABP 45 min	40	93.10000	1.420645	90.000	96.667	93.33333	3.16		

 # = non-significant

14.4 HR

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
HR pre-op	40	75.95	3.637	70	83	76.00	3.10		
HR 5min	40	76.08	3.415	69	85	76.50	3.48		
HR 10 min	40	76.15	3.606	69	87	75.50	3.68	3.356	0.645#
HR 15 min	40	76.10	3.350	70	83	75.00	3.80		
HR 30 min	40	75.98	3.977	71	83	76.00	3.50		
HR 45 min	40	75.93	3.526	70	82	75.50	3.45		

 # = non-significant

Table 15: Pair wise comparison of cardiac variables using Wilcoxon Signed Ranks Test in grp 4

	Z value	p value of Wilcoxon Signed Ranks Test
SBP 5min - SBP pre-op	-1.000	0.317#
SBP 10 min - SBP pre-op	-1.332	0.183#
SBP 15 min - SBP pre-op	-1.000	0.317#
SBP 30 min - SBP pre-op	-0.304	0.761#
SBP 45 min - SBP pre-op	-0.127	0.899#
DBP 5 min - DBP pre-op	-0.279	0.780#
DBP 10 min - DBP pre-op	-0.588	0.557#
DBP 15 min - DBP pre-op	-0.501	0.616#
DBP 30 min - DBP pre-op	-0.897	0.370#
DBP 45 min - DBP pre-op	-0.061	0.952#
MABP 5 min - MABP pre-op	-0.756	0.450#
MABP 10 min - MABP pre-op	-1.117	0.264#
MABP 15 min - MABP pre-op	-0.866	0.386#
MABP 30 min - MABP pre-op	-0.797	0.425#
MABP 45 min - MABP pre-op	-0.079	0.937#
HR 5min - HR pre-op	-0.703	0.482#
HR 10 min - HR pre-op	-0.369	0.712#
HR 15 min - HR pre-op	-0.434	0.664#
HR 30 min - HR pre-op	-0.007	0.994#
HR 45 min - HR pre-op	-0.015	0.988#

 # = non-significant

For Dexamethasone grp, there was no significant difference for **Intra-grp comparison using Friedman's test** (**Tables 16.1, 16.2, 16.3, 16.4)** and for **pair-wise comparison with pre-op values**, using Wilcoxon Signed rank test (**Table 17)**

Mean SBP was 119.75±3.176 pre-op, 119.85±2.327 at 5min, 119.90±1.751 at 10min, 119.95±2.050 at 15min, 119.95±2.417 at 30min, 119.90±1.972 at 45min post-injection (**Table 16.1)** (**Graph 13)**

Mean DBP was 80.15±1.594 pre-op, 80.10±1.865 at 5min, 80.15±1.942 at 10min, 80.10±2.170 at 15min, 80.05±2.148 at 30min, 80.05±1.535 at 45min post-injection. (**Table 16.2)** (**Graph 14)**

Mean MABP was 93.35000±1.412097 pre-op, 93.35000±1.193405 at 5min, 93.40000±1.177181 at 10min, 93.38333±1.527618 at 15min, 93.35000±1.684435 at 30min, 93.33333±1.159625 at 45min post-injection. (**Table 16.3)** (**Graph 15)**

Mean HR was 76.33±2.654 pre-op, 76.75±2.539 at 5min, 76.70±3.314 at 10min, 76.35±3.613 at 15min, 76.30±3.123 at 30min, 76.20±3.884 at 45min post-injection. (**Table 16.4)** (**Graph 16)**

Table 16: Intra group comparison in group 5 (Friedman's test)

16.1 SBP

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
SBP pre-op	40	119.75	3.176	112	124	120.00	3.50		
SBP 5min	40	119.85	2.327	114	124	120.00	3.64		
SBP 10 min	40	119.90	1.751	116	122	120.00	3.43	.703	0.983#
SBP 15 min	40	119.95	2.050	116	124	120.00	3.38		
SBP 30 min	40	119.95	2.417	116	124	120.00	3.60		
SBP 45 min	40	119.90	1.972	116	124	120.00	3.46		

 # = non-significant

16.2 DBP

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
DBP pre-op	40	80.15	1.594	78	82	80.00	3.33		
DBP 5 min	40	80.10	1.865	76	82	80.00	3.58		
DBP 10 min	40	80.15	1.942	76	84	80.00	3.50	.749	0.980#
DBP 15 min	40	80.10	2.170	76	84	80.00	3.56		
DBP 30 min	40	80.05	2.148	76	84	80.00	3.59		
DBP 45 min	40	80.05	1.535	78	82	80.00	3.45		

 # = non-significant

16.3 MABP

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
MABP pre-op	40	93.35000	1.412097	89.333	96.000	93.33333	3.43		
MABP 5 min	40	93.35000	1.193405	91.333	95.333	93.33333	3.55		
MABP 10 min	40	93.40000	1.177181	90.667	96.000	93.33333	3.59	.393	0.996#
MABP 15 min	40	93.38333	1.527618	90.000	96.000	93.66667	3.45		
MABP 30 min	40	93.35000	1.684435	89.333	96.000	93.33333	3.58		
MABP 45 min	40	93.33333	1.159625	91.333	95.333	93.33333	3.41		

 # = non-significant

16.4: HR

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
HR pre-op	40	76.33	2.654	68	82	77.00	3.83		
HR 5min	40	76.75	2.539	71	81	76.00	3.79		
HR 10 min	40	76.70	3.314	70	84	77.00	3.58	4.312	0.505#
HR 15 min	40	76.35	3.613	71	88	76.00	3.19		
HR 30 min	40	76.30	3.123	71	83	76.00	3.30		
HR 45 min	40	76.20	3.884	70	84	75.00	3.33		

 # = non-significant

Table 17: Pair wise comparison of cardiac variables using Wilcoxon Signed Ranks Test in grp 5

	Z value	p value of Wilcoxon Signed Ranks Test
SBP 5min - SBP pre-op	-0.428	0.668#
SBP 10 min - SBP pre-op	-0.295	0.768#
SBP 15 min - SBP pre-op	-0.222	0.825#
SBP 30 min - SBP pre-op	-0.250	0.803#
SBP 45 min - SBP pre-op	0.000	1.000#
DBP 5 min - DBP pre-op	-0.243	0.808#
DBP 10 min - DBP pre-op	-0.162	0.871#
DBP 15 min - DBP pre-op	-0.099	0.921#
DBP 30 min - DBP pre-op	-0.190	0.850#
DBP 45 min - DBP pre-op	-0.509	0.611#
MABP 5 min - MABP pre-op	-0.008	0.994#
MABP 10 min - MABP pre-op	-0.054	0.957#
MABP 15 min - MABP pre-op	-0.223	0.823#
MABP 30 min - MABP pre-op	-0.109	0.913#
MABP 45 min - MABP pre-op	-0.267	0.789#
HR 5min - HR pre-op	-1.119	0.263#
HR 10 min - HR pre-op	-0.319	0.750#
HR 15 min - HR pre-op	-0.996	0.319#
HR 30 min - HR pre-op	-0.173	0.862#
HR 45 min - HR pre-op	-0.262	0.793#

 # = non-significant

For CPM grp, there was highly significant difference for **Intra-grp comparison using Friedman's test** for SBP and MABP (**Tables 18.1 and 18.3**), whereas, there was no statistically significant difference for DBP and HR (**Tables 18.2 and 18.4**). For **pair-wise comparison with pre-op values**, using Wilcoxon Signed rank test, there was significant difference for SBP at 10 and 15min, for DBP at 5 and 10min, for MABP at 5,10,15min. However no statistically significant difference was obtained for HR for all intervals compared with pre-op (**Table 19)**.

Mean SBP was 120.33±2.217 pre-op, 120.17±1.935 at 5min, 118.00±2.484 at 10min, 118.33±2.268 at 15min, 118.72±17.456 at 30min, 120.17±2.360 at 45 min post-injection, (**Table 18.1)** (**Graph 13)**

Mean DBP was 80.22±1.899 pre-op, 79.22±1.987 at 5min, 79.00±2.318 at 10min, 79.44±1.827 at 15min, 79.56±1.978 at 30min, 80.00±1.586 at 45min post-injection. (**Table 18.2)** (**Graph 14)**

Mean MABP was 93.59259±1.436732 pre-op, 92.87037±1.423784 at 5min, 92.00000±1.520234 at 10min, 92.40741±1.354853 at 15min, 92.61111±5.677860 at 30min, 93.38889±1.238278 at 45min post-injection. (**Table 18.3)** (**Graph 15)**

Mean HR was 75.83±2.783 pre-op, 75.86±2.949 at 5min, 75.89±2.755 at 10min, 75.92±4.108 at 15min, 75.81±4.302 at 30min, 75.67±4.309 at 45min post-injection. (**Table 18.4)** (**Graph 16)**

Table 18: Intra group comparison in group 6 (Friedman's test)

18.1 SBP

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
SBP pre-op	36	120.33	2.217	116	124	120.00	3.90		
SBP 5min	36	120.17	1.935	116	124	120.00	3.76		
SBP 10 min	36	118.00	2.484	114	122	118.00	2.36	46.059	0.000**
SBP 15 min	36	118.33	2.268	112	122	118.00	2.53		
SBP 30 min	36	118.72	17.456	18	126	122.00	4.63		
SBP 45 min	36	120.17	2.360	114	124	120.00	3.82		

**** = highly significant**

18.2 DBP

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
DBP pre-op	36	80.22	1.899	76	84	80.00	3.97		
DBP 5 min	36	79.22	1.987	76	82	80.00	3.17		
DBP 10 min	36	79.00	2.318	76	82	80.00	3.00	9.652	0.086#
DBP 15 min	36	79.44	1.827	76	82	80.00	3.40		
DBP 30 min	36	79.56	1.978	76	82	80.00	3.56		
DBP 45 min	36	80.00	1.586	76	82	80.00	3.90		

 # = non-significant

18.3 MABP

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
MABP pre-op	36	93.59259	1.436732	89.333	96.000	94.00000	4.19		
MABP 5 min	36	92.87037	1.423784	90.667	95.333	92.66667	3.49		
MABP 10 min	36	92.00000	1.520234	88.667	94.667	92.00000	2.29	34.177	0.000**
MABP 15 min	36	92.40741	1.354853	89.333	94.667	92.66667	2.83		
MABP 30 min	36	92.61111	5.677860	60.667	96.667	93.33333	4.04		
MABP 45 min	36	93.38889	1.238278	90.667	95.333	93.33333	4.15		

**** = highly significant**

18.4: HR

	N	Mean	Std. Deviation	Minimum	Maximum	Median	Mean rank	Chi-Square value	p value of Friedman Test
HR pre-op	36	75.83	2.783	71	82	76.00	3.42		
HR 5min	36	75.86	2.949	69	83	76.00	3.63		
HR 10 min	36	75.89	2.755	69	82	76.00	3.88	2.435	0.786#
HR 15 min	36	75.92	4.108	70	87	75.00	3.33		
HR 30 min	36	75.81	4.302	71	86	74.00	3.35		
HR 45 min	36	75.67	4.309	70	85	75.00	3.40		

 # = non-significant

Table 19: Pair wise comparison of cardiac variables using Wilcoxon Signed Ranks Test in grp 6

	Z value	p value of Wilcoxon Signed Ranks Test
SBP 5min - SBP pre-op	-0.588	0.556#
SBP 10 min - SBP pre-op	-3.520	0.000**
SBP 15 min - SBP pre-op	-3.520	0.000**
SBP 30 min - SBP pre-op	-1.692	0.091#
SBP 45 min - SBP pre-op	-0.411	0.681#
DBP 5 min - DBP pre-op	-2.373	0.018*
DBP 10 min - DBP pre-op	-2.339	0.019*
DBP 15 min - DBP pre-op	-1.600	0.110#
DBP 30 min - DBP pre-op	-1.277	0.202#
DBP 45 min - DBP pre-op	-0.662	0.508#
MABP 5 min - MABP pre-op	-2.409	0.016*
MABP 10 min - MABP pre-op	-4.105	0.000**
MABP 15 min - MABP pre-op	-3.308	0.001**
MABP 30 min - MABP pre-op	-0.394	0.693#
MABP 45 min - MABP pre-op	-0.736	0.462#
HR 5min - HR pre-op	-0.301	0.764#
HR 10 min - HR pre-op	-0.334	0.738#
HR 15 min - HR pre-op	-0.113	0.910#
HR 30 min - HR pre-op	-0.051	0.959#
HR 45 min - HR pre-op	-0.041	0.967#

 # = non-significant

***= significant**

****** **= highly significant**

Pair wise comparisons using Mann-Whitney Test for non-cardiac variables ie, number of injections used, Onset in sec, Rescue analgesic taken after (min), VAS score, total blood lost, no. of analgesics taken in 3days were done. The results have been summarized in **Tables 20.1 to 20.15.**

There were highly significant results in most of the pair-wise comparisons **except,**

a. For number of injections used: in Adr- Cloni, Adr- KCl, Adr- Dexa, Lig-CPM, Cloni-KCl, Cloni-Dexa, and KCl-Dexa grps
b. For Rescue analgesic taken: Adr- CPM, KCl- Dexa grps
c. For VAS score: Adr- Cloni, Adr- KCl, Adr- Dexa, Cloni-KCl, Cloni-Dexa, and KCl-Dexa grps
d. For total blood lost: Adr- Cloni, Adr-CPM, Cloni-Dexa, and Cloni-CPM grps.
e. For no. of analgesics in 3days: Adr- plain lig and Cloni-KCl, grps

Tables for Pair wise comparisons using Mann-Whitney Test for non-cardiac variables

{# = non-significant, *= significant, ** = highly significant for all tables }

20.1 Between group 1 vs 2

	Mann-Whitney U value	**Z value**	**p value of Mann-Whitney U test**
number of injections used	520.000	-3.725	0.000**
Onset in sec	0.000	-7.702	0.000**
Rescue analgesic taken after (min)	0.000	-7.723	0.000**
VAS score	94.500	-7.156	0.000**
total blood lost (a+b)	89.000	-6.848	0.000**
no. of analgesics in 3days	644.000	-1.602	0.109#

20.2 Between group 1 vs 3

	Mann-Whitney U value	Z value	p value of Mann-Whitney U test
number of injections used	800.000	0.000	1.000#
Onset in sec	401.000	-3.845	0.000**
Rescue analgesic taken after (min)	0.000	-7.729	0.000**
VAS score	780.500	-0.203	0.839#
total blood lost (a+b)	706.000	-0.907	0.364#
no. of analgesics in 3days	155.500	-6.464	0.000**

20.3 Between group 1 vs 4

	Mann-Whitney U value	Z value	p value of Mann-Whitney U test
number of injections used	780.000	-0.585	0.559#
Onset in sec	0.000	-7.702	0.000**
Rescue analgesic taken after (min)	0.000	-7.718	0.000**
VAS score	764.000	-0.375	0.708#
total blood lost (a+b)	199.500	-5.786	0.000**
no. of analgesics in 3days	363.000	-4.376	0.000**

20.4 Between group 1 vs 5

	Mann-Whitney U value	Z value	p value of Mann-Whitney U test
number of injections used	780.000	-0.585	0.559#
Onset in sec	26.000	-7.454	0.000**
Rescue analgesic taken after (min)	0.000	-7.751	0.000**
VAS score	671.000	-1.347	0.178#
total blood lost (a+b)	585.000	-2.081	0.037*
no. of analgesics in 3days	104.000	-6.929	0.000**

20.5 Between group 1 vs 6

	Mann-Whitney U value	Z value	p value of Mann-Whitney U test
number of injections used	476.000	-3.594	0.000**
Onset in sec	0.000	-7.495	0.000**
Rescue analgesic taken after (min)	687.000	-0.347	0.729#
VAS score	58.000	-7.062	0.000**
total blood lost (a+b)	69.500	-1.699	0.060#
no. of analgesics in 3days	0.000	-7.606	0.000**

20.6 Between group 2 vs 3

	Mann-Whitney U value	Z value	p value of Mann-Whitney U test
number of injections used	520.000	-3.725	0.000**
Onset in sec	0.000	-7.705	0.000**
Rescue analgesic taken after (min)	0.000	-7.715	0.000**
VAS score	108.000	-7.031	0.000**
total blood lost (a+b)	102.500	-6.719	0.000**
no. of analgesics in 3days	104.000	-6.929	0.000**

20.7 Between group 2 vs 4

	Mann-Whitney U value	Z value	p value of Mann-Whitney U test
number of injections used	500.000	-4.074	0.000**
Onset in sec	0.000	-7.702	0.000**
Rescue analgesic taken after (min)	0.000	-7.704	0.000**
VAS score	108.000	-7.031	0.000**
total blood lost (a+b)	569.500	-2.224	0.026*
no. of analgesics in 3days	272.000	-5.256	0.000**

20.8 Between group 2 vs 5

	Mann-Whitney U value	Z value	p value of Mann-Whitney U test
number of injections used	500.000	-4.074	0.000**
Onset in sec	0.000	-7.705	0.000**
Rescue analgesic taken after (min)	0.000	-7.737	0.000**
VAS score	81.000	-7.270	0.000**
total blood lost (a+b)	192.500	-5.863	0.000**
no. of analgesics in 3days	4.000	-7.845	0.000**

20.9 Between group 2 vs 6

	Mann-Whitney U value	Z value	p value of Mann-Whitney U test
number of injections used	712.000	-0.098	0.922#
Onset in sec	0.000	-7.496	0.000**
Rescue analgesic taken after (min)	0.000	-7.523	0.000**
VAS score	303.000	-4.622	0.000**
total blood lost (a+b)	297.000	-4.409	0.000**
no. of analgesics in 3days	0.000	-7.611	0.000**

20.10 Between group 3 vs 4

	Mann-Whitney U value	Z value	p value of Mann-Whitney U test
number of injections used	780.000	-0.585	0.559#
Onset in sec	0.000	-7.704	0.000**
Rescue analgesic taken after (min)	419.000	-3.674	0.000**
VAS score	784.000	-0.166	0.868#
total blood lost (a+b)	217.500	-5.613	0.000**
no. of analgesics in 3days	625.500	-1.800	0.072#

20.11 Between group 3 vs 5

	Mann-Whitney U value	Z value	p value of Mann-Whitney U test
number of injections used	780.000	-0.585	0.559#
Onset in sec	0.000	-7.707	0.000**
Rescue analgesic taken after (min)	263.000	-5.249	0.000**
VAS score	695.000	-1.094	0.274#
total blood lost (a+b)	648.500	-1.467	0.142#
no. of analgesics in 3days	237.000	-5.908	0.000**

20.12 Between group 3 vs 6

	Mann-Whitney U value	Z value	p value of Mann-Whitney U test
number of injections used	476.000	-3.594	0.000**
Onset in sec	0.000	-7.498	0.000**
Rescue analgesic taken after (min)	276.000	-4.650	0.000**
VAS score	57.500	-7.044	0.000**
total blood lost (a+b)	71.500	-1.678	0.062#
no. of analgesics in 3days	23.000	-7.454	0.000**

20.13 Between group 4 vs 5

	Mann-Whitney U value	Z value	p value of Mann-Whitney U test
number of injections used	800.000	0.000	1.000#
Onset in sec	0.000	-7.704	0.000**
Rescue analgesic taken after (min)	735.000	-0.629	0.530#
VAS score	712.000	-0.918	0.359#
total blood lost (a+b)	340.000	-4.442	0.000**
no. of analgesics in 3days	224.500	-5.809	0.000**

20.14 Between group 4 vs 6

	Mann-Whitney U value	Z value	p value of Mann-Whitney U test
number of injections used	458.000	-3.953	0.000**
Onset in sec	0.000	-7.495	0.000**
Rescue analgesic taken after (min)	154.000	-5.912	0.000**
VAS score	56.000	-7.057	0.000**
total blood lost (a+b)	495.000	-2.346	0.004**
no. of analgesics in 3days	31.000	-7.268	0.000**

20.15 Between group 5 vs 6

	Mann-Whitney U value	Z value	p value of Mann-Whitney U test
number of injections used	458.000	-3.953	0.000**
Onset in sec	0.000	-7.498	0.000**
Rescue analgesic taken after (min)	92.000	-6.590	0.000**
VAS score	45.000	-7.186	0.000**
total blood lost (a+b)	430.500	-3.031	0.012*
no. of analgesics in 3days	144.000	-6.262	0.000**

Chapter 7

DISCUSSION

DISCUSSION

The six groups in this study were evaluated and compared on the basis of the following:
Demographic details (age and gender of the subjects)
Number of injections used
Onset of anesthesia (sec)
Duration of analgesia (min)
Depth of anesthesia (intra-operative VAS score)
Total blood lost (gauze pieces+ suction jar)
Number of analgesics taken in 3 days
Systolic, Diastolic, Mean Arterial blood pressure and heart rate measured pre-operatively, 5,10,15,30 and 45 min post-injection

The mean **age** of all the subjects in this study was 31.82± 4.694. Inter-group comparison with one way ANOVA (**Table 4)** showed a statistically non- significant difference ($p>0.05$) between the groups as regards age of the subjects. (**Graph 1)**
This study comprised of 99 females (41.9%) and 137 males (58.1%). There was a statistically non-significant difference seen for the frequencies between the groups ($p>0.05$) as regards **gender (Table 5).** (**Graph 2)**
Thus, the groups were **demographically similar.** So, it is expected that there is no gender or age-related bias affecting the results.

Number of injections used in the six groups showed a statistically highly significant difference between the groups ($p<0.01$) (**Table 6),** (**Graph 3)** with maximum numbers in plain lignocaine group (1.40± 0.496) followed by CPM grp (1.39±0.494) and least numbers in KCl (1.03±0.158) and Dexa (1.03±0.158) groups. Clinically, when the surgical procedure was initiated, 16 subjects in the plain LA grp and 18 from CPM grp, complained of pain and inadequacy of effect of anesthesia despite having subjective symptoms of tingling numbness in the ipsilateral lower lip and tongue, hence, a second injection (with the same drug) had to be administered, thereby increasing the number of injections in these groups. In the CPM grp, in spite of reinjection, four subjects complained of pain on tissue manipulation and had to be withdrawn from the CPM grp

and the surgical procedure was carried out using the standard Lig with Adr. Two subjects each from Adr and Cloni grps and one subject each from KCl and Dexa grps had to be reinjected.

A statistically highly significant difference between the groups ($p<0.01$) (**Table 6),** (**Graph 4)** was noted for the **onset of action**. In this study, time elapsed in sec from the time of injection to the onset of first tingling sensation on the lower lip was considered as onset of action of LA. The order of onset noted was, KCl (44.20±5.450sec) < Dexa (78.10±4.012sec) < Cloni (95.60±4.056sec) < Adr(102.60±9.803sec) < plain Lig (143.68±4.875sec) < CPM (224.75±10.608sec).

Onset depends on diffusibility of the solution, lipid solubility and dissociation constant of the local anesthetic, anatomic barriers and variations, concentration of anesthetic molecules, pH of the solution and pH of the tissues in which it is injected.[2] Amongst these, the factors not in control of the clinician are diffusibility of the solution, lipid solubility, dissociation constant of the local anesthetic and anatomic barriers and variations. As per inclusion criteria, subjects with no active infection on the day of surgery and even for a week prior, were included. Hence, normal tissue pH ie, 7.4 was presumed in all subjects.

The pH of plain Lignocaine is 6.8, whereas, pH of Lignocaine with Adr is 4.2 due to sodium metabisulphite added as preservative for Adr.[2] pH of Clonidine used is approximately 6 [129], giving little or no change when added to plain Lig. KCl being a salt, is neutral and does not alter the pH. Hence, pH of Lig-KCl is similar to plain Lig. Addition of Dexa, (pH 8.5)[90] makes Lig more alkaline. pH of chlorpheniramine is 4-5 [99], addition of which decreases the pH of plain lig. Study of pH was not an objective in this study, hence exact pH values of the formulations i.e. study drugs with Lig have not been calculated/mentioned. pK_a of lignocaine is 7.7.[2] The more alkaline the solution, faster will be the onset of Lig action since proportionately more unionized lipophilic base (RN) rather than cation RNH^+ will be available for penetration into the nerve membrane, leading to faster onset as per Henderson-Hasselbalch equation, Log (base/acid) =pH-pK_a .[2]

With this background, onset of action of Lig with Adr is expected to be slower than plain Lig, however, the mean onset in Adr grp was 102.60±9.803sec and in Lig grp was 143.68±4.875sec and was statistically significant (**table 20.1).** This is in contrast to that stated by Malamed.[2] Statistically delayed onset in plain Lig grp was also noted by

Anurag et al.[130] This may be explained by the fact that the vasoconstrictive effect of Adr maintains more Lig in proximity with the nerve membrane than in plain Lig, hence the increased concentration of RN leads to faster onset.

The addition of Clonidine shortens the onset of action.[67,70] In this study, the onset in Cloni grp was (95.60±4.056sec), compared to 102.60±9.803sec in Adr grp. Pair wise comparison using Mann-Whitney Test between Adr and Cloni grps did show a statistically significant difference between the grps as regards onset of action. (**Table 20.2**) However, this difference was not clinically very significant. Although both Adr and Cloni are potent vasoconstrictors, the marginal difference in onset between the two grps could be because of pH difference. Addition of Cloni to Lig does not change the pH of Lig, ie approx. 6.8. whereas pH of Adr-Lig is more acidic. A close to neutral pH with added vasoconstrictive action may be a possible reason for such a difference. However, Patil et al did not obtain any statistically significant difference in onset in their study.[69]

Addition of KCl does not alter the pH of the solution which is nearly neutral.[79] This grp showed the fastest onset of action (44.20±5.450sec). This can be explained on the basis of increased extracellular potassium ions which can depolarise nerve membrane and cause blockage in nerve impulse.[79,131] Sidon et al have proposed the mechanism by which addition of KCl to Lig shortens the onset and prolongs the duration of action.[79] Studies on brachial plexus nerve blocks with KCl added to bupivacaine have shown that there is a considerable reduction in onset.[82,83]

Since addition of Dexa raises the pH, rendering more unionised entities (RN), onset is faster than Lig-Adr. This is consistent with studies by Bhargava et al[90,92] and Sahu et al.[132] This shorter onset of action due to Dexa can also be attributed to its vasoconstrictive action and increasing the inhibitory activity of potassium channels on C-fibres.[90]

The onset of anesthesia with CPM was (224.75±10.608sec), which was the longest in this study. A study on mandibular teeth extraction by Welborn et al showed that the onset of action with diphenhydramine was considerably longer and a larger volume of solution required to be injected for the desired effect.[133] However, no study comparing the use of chlorpheniramine for pterygomandibular nerve blocks has been reported in literature for comparison with this study. A possible explanation for delayed onset could also be the dilution of Lig in the CPM-Lig solution.

3 ml of 2% Lig-Adr and 3 ml of 2% plain Lig yielded (21.3mg/ml) 63.9 mg of Lig perineurally. In Cloni, KCl and Dexa grps, 2ml of 2% Lig was used with 1ml of the study drug solution yielding 42.6mg (ie 14,2mg/ml) Lig perineurally. In the CPM grp, 2ml of 2% Lig was mixed with 1.5 ml of CPM solution yielding 42.6mg (ie 12.17mg/ml) Lig perineurally. 1.5 ml of 10mg/ml CPM had to be used because when a pilot study was conducted, comparing addition of 0.5 ml and 1 ml of 10mg/ml CPM solution, no effect was obtained as 1.5 ml of CPM solution. It was hence presumed that at least 15mg of CPM is required perineurally for some clinical effect. Even then, the onset in CPM grp was slowest, possibly due to, comparatively lower conc. of Lig available. The volume of this mixture (3.5 ml) in contrast to other mixtures (3ml), also would have hinted the operator about the drug contained and could have possibly served as a source of bias. However, the observer was kept unaware about this volume discrepancy and hence, it has been assumed that the observations were unbiased.

In this study**, duration of analgesia** was measured in min from the onset of first tingling sensation on the lower lip to the first recue analgesic taken by the subject. A statistically highly significant difference ($p<0.01$) (**Table 6)** (**Graph 5)** was obtained between the groups ($p<0.01$), the order being, plain Lig grp (74.50$\pm$5.966min) < Adr (136.95$\pm$9.403min) < CPM (147.78$\pm$30.809min) < Cloni (183.75$\pm$13.291min) < KCl (205.20$\pm$28.399min) <Dexa grp (206.10$\pm$18.854min).

Duration of action depends on the degree of protein binding of the drug, its vasodilatory activity, vascularity of the tissue in which it is injected, and addition of a vasoconstrictor. [2]

Since Lig was common to all grps, and pterygomandibular nerve blocks were used in all healthy subjects, the first three factors were the same. The difference in the duration noted between grps was thus a function of the additive used. The time of rescue analgesic taken is also different from subject to subject and affects the outcome of duration. However, with adequate sample size as in this study, the bias from this factor is minimized.

Pair wise comparison using Mann-Whitney Test showed a statistically significant difference between all the grps except Adr (136.95$\pm$9.403min) and CPM (147.78$\pm$30.809min), KCl (205.20$\pm$28.399min) and Dexa (206.10$\pm$18.854min). **(Tables 20.5, 20.13)**

Lignocaine is a known vasodilator (table 2).[2] Vasoconstrictor added to Lig retards its systemic absorption, thereby decreasing its systemic toxicity and providing adequate Lig entities for adequate duration of action at the injection site/nerve membranes.[2] However, as discussed, the disadvantages of adrenaline had to be considered and rationale for use of the study drugs was evaluated. A common point between Cloni, KCl, Dexa, CPM were their vasoconstrictive properties. So, the difference in duration of action between the grps may be attributed to the degree of vasoconstriction provided by these added drugs to keep Lig in situ and exert its action.

Since no additive was used in plain Lig grp, the duration was the least (74.50±5.966min).

A greatly prolonged and statistically significant duration of action obtained with Dexa was due to vasoconstrictive and multi-modal anti-inflammatory effects of dexamethasone there by leading to minimal release of inflammatory mediators like leukotrienes and prostaglandins.[90,92] This was consistent with the studies by Sahu et al[132], Chong et al[134] and Bhargava et al[90,92]

An equivalent duration seen with KCl (205.20±28.399min) can be attributed not only to additional extracellular potassium ions present which prevented repolarization,[79] but also, to a possible vasoconstrictive property of KCl.[73,81] Aldrete has shown that KCl exerts prolonged effects on digital, ulnar blocks which lasted 1.5-1.8 times that of plain lig.[77,78] Similar results on prolonged duration of action were obtained with brachial plexus blocks.[83,135,136]

In this study, duration in Cloni grp was 183.75±13.291min. There was a statistically significant difference in the duration of action as compared to Adr grp **(table 20.2).** This was not consistent with other studies [67,69,72] which did not report any significant difference between Cloni and Adr grps. Prolonged duration of action with Clonidine in comparison to plain Lig has been reported by Reinhart et al for peripheral nerve blocks.[137] The possible mechanisms discussed were- decreased vascular reabsorption of Lig (α-1 effect), direct action on neural tissues, systemic mechanism via brainstem.[137]

No statistically significant difference in duration of action between Adr (136.95±9.403min) and CPM (147.78±30.809min) **(table 20.5**) implies that the vasoconstrictor activity could be similar, hence maintaining Lig entities at the site of injection for longer period of time. Studies on vasoconstrictive effect by Abramson et al[113] and Altura et al[116] show equipotent vasoconstrictive effects of CPM and

adrenaline. No clinical study with CPM in Lig in oro-facial region however is available for comparison in this regard.

Depth of anesthesia is determined by lipid solubility, its vasodilator activity, vascularity of the tissue in which it is injected, presence of infection/mediators of inflammation and addition of a vasoconstrictor.[2] Lig was common to all grps, and pterygomandibular nerve blocks were used in all healthy subjects, in which absence of infection and inflammation was ascertained before the initiation of the surgical procedure, hence, the first four factors were common to all grps. In this study, VAS score was used to determine the depth of anesthesia during the procedure. This subjective measure had to be used because there is no instrument that can measure pain experience directly. Considering that an ample number of subjects were recruited in this study, there does not seem to be an experience or subjective bias due to this. There was a statistically highly significant difference between all the grps ($p<0.01$) (**Table 6)** (**Graph 6)**. The mean VAS scores were CPM 4.28$\pm$1.059> plain Lig 3.35$\pm$.533> Adr 1.85$\pm$.700> Cloni 1.83$\pm$.747> KCl 1.80$\pm$.758> Dexa 1.65$\pm$ .736.

Thus, the best intra-operative pain control was reported for Dexa grp (1.65$\pm$ .736) and least for CPM grp (4.28$\pm$1.059). These findings are also in accordance with the number of injections used (most for CPM, least for Dexa). In fact, pain control in CPM grp intra-operatively was so poor that four patients had to be withdrawn from this grp as stated earlier.

There was no statistically significant difference in VAS scores in Adr and Cloni (**table 20.2**) Adr and KCl (**table 20.3)**, Adr and Dexa (**table 20.4)**, Cloni and KCl (**table 20.10)**, Cloni and Dexa (**table 20.11)** and KCl and Dexa (**table 20.13)** using Pair wise comparison with Mann-Whitney Test. This implies that Adr, Cloni, KCl and Dexa as Lig additives are equivalent in their effectiveness and provide good depth of anesthesia and intra-operative pain control. Poor pain control in Plain Lig grp could be attributed to wash out of Lig entities from the site of injection with a possibly increased blood flow due to dilatory action of Lignocaine.

Antihistamines in general, have been described as “antinociceptives based on a) possible interaction with opioid receptor sites, b) action at presynaptic histamine auto-receptors resulting in consequent inhibition of histamine release, c) through antagonism of histamine released by Substance P, d) other putative mechanisms like cholinergic, adrenergic, dopaminergic and serotonergic neurotransmission, anti-inflammatory or

spasmolytic action, or an effect on cyclic nucleotides" [119] or activation of a signal transduction mechanism operated by Gi proteins.[120]

Poor pain control in CPM grp could be due to a smaller number of Lig (RN) entities available due to a more dilute solution as discussed earlier or the amount of CPM required for the desired effect was inadequate. Since no study describing perineural use of CPM is available, use of a still higher concentration carried a possibility of perineural damage and hence the use was restricted to 1.5 ml of 10 mg/ml CPM. The maximum permissible daily dose of 10-25mg/ day[138] also had to be taken into consideration. 1.5 ml of 10 mg/ml CPM hence was justified and considered safe knowing the adverse effects it could possibly cause by exceeding this dose limit. Based on pre-clinical studies on safety of perineural CPM, in future may be, a higher dose could be used in further human studies with certainty. CPM itself has been shown to have antinociceptive properties in a dose-dependent manner when compared to bupivacaine in rat skin.[126] Hence, the dose used may be inadequate for the desired effect. With the used dose, no local or systemic adverse effects were noted. No similar study as this is available in literature for comparison.

The results of this study as regards pain control with Dexa are consistent with Bhargava et al [92,97] Chong et al[134] and Deo et al[139] and may be attributed to the multimodal anti-inflammatory action.

Cloni has been shown to have anxiolytic effects which makes it suitable for use in dental as well as medical procedures.[140,141] Analgesic effect of clonidine was reported to be similar to that of morphine. Hence its use for surgeries under local anesthesia is highly advantageous and recommended.[142] Thus, a fairly good intra-operative pain control in Cloni grp is attributed to these properties. The results of this study are consistent with Brkvoic.[67]

Tainter et al stated that the local anesthetic action of K^+ salts is comparable to procaine.[74] Good depth of anesthesia with KCl could be explained on the surplus K^+ ions which prevented repolarization, pH close to neutral and anesthetic potency of KCl itself. Since there was no statistically significant difference between KCl and Adr grp, it could imply that this combination is as effective as Adr-Lig. This is also consistent with study conducted by Sidon et al,[79] Shreedhar et al[136] and Ramaiah et al[83]

The amount of blood lost was calculated indirectly using difference in weights of gauze pieces pre-op and post-operatively added to the volume of blood lost in the

suction jar. This was an indirect indicator of **vasoconstrictive effect**. Lig is a vasodilator. But due to action of the added drug, loss of blood may be minimized. In this study, there was a statistically highly significant difference in the total amount of blood lost in all grps ($p<0.01$) (**Table 6),** (**Graph 7)** in the order, plain Lig 70.25±7.270ml> KCl 66.45±6.656ml> Dexa 59.38±6.376ml> CPM 57.89±5.942ml> Cloni 57.53±4.750ml> Adr 55.80 ±6.653ml.

Thus, the least amount of blood loss was measured in Adr grp and least with plain Lig grp since Lig itself is a vasodilator. No study till date has compared Cloni, KCl, Dexa and CPM with Adr with regards intra-operative blood lost in mandibular third molar extraction surgeries. There was no statistically significant difference between Adr and Cloni (**table 20.2**), Adr and Dexa (**table 20.4)**, Adr and CPM (**table 20.5)**, Cloni and Dexa (**table 20.11)**, Cloni and CPM (**table 20.12)**, Dexa and CPM (**table 20.15)**.

Adr acts on α receptors **(table 3)** and is a known most-potent vasoconstrictor, most-commonly used with LA and hence used as standard in this study for comparison.

Cloni exerts agonist effects on peripheral postsynaptic α2 adrenoceptors and produces vasoconstriction of the peripheral blood vessels. By central activation of presynaptic α2 adrenoceptors, clonidine decreases blood pressure and causes central analgesic activity as well as sedation.[72] Since the amount of blood loss in Cloni and Adr was similar, vasoconstrictive properties of Cloni may be considered similar to Adr, without any corresponding systemic rise in cardiovascular parameters.

Although Mathison[73] and Consigny[83] mention about the vasoconstrictive effects of KCl, these studies were carried out under experimental conditions, do not pertain to oro-facial region and date back to 1911 and 1991 respectively. Mathison has discussed about the controversy in literature on the vasodilatory/constrictive action.[73] Definitive vasoconstrictive effects of KCl need to be evaluated with studies directed to oro-facial region and specially in mandibular third molar surgeries to conclude about the same. In this study, the loss of blood in KCl grp was almost similar to plain Lig grp, however, it was not clinically bothersome or unmanageable.

Dexa has been shown to have vasoconstrictive properties by augmenting vascular tone via actions of vasoconstrictor hormones and direct actions on vascular smooth muscle cells.[143] Although clinically, blood loss in Dexa grp was marginally more than Adr grp, there was no statistically significant difference.

Altura studied the vasoconstrictive effects of CPM on rat meso-appendix and reported that it is equipotent as Adr.[116] CPM competitively inhibits histamine (which is a

mediator of inflammation and potent vasodilator) invariably secreted as a result of tissue trauma. This could possibly explain the comparable amount of blood loss in the CPM grp as in Adr and Cloni and Dexa grps.

Post-operative pain control was indirectly assessed by the total number of analgesics consumed by the subjects in three post-operative days. There was a statistically highly significant difference between the 6 grps ($p<0.01$) (**Table 6),** (**Graph 8)** in the order CPM (4.03±.878) < Dexa (5.50±.555) < Cloni (6.50±.641) < KCl (6.88±1.042) < Adr (7.93±.764) < plain Lig (8.20±.758).

Post-operative pain is dependent on surgical difficulty, tissue trauma caused, analgesics prescribed, intra-operative drugs used and patient factors like compliance of post-surgical instructions and healing abilities. The first three factors were standardized ie, all cases were moderately difficult as per Pederson's index, with same operating surgeon carrying out the surgical procedure, so similar tissue trauma in all cases and same prescription was given to all subjects. Patient factors are beyond operator's control but have been minimized by blinding, randomization and adequate sample size. It was also made sure that the patients were followed up adequately and no under-reporting of the data was made. Intra-operative drugs used may thus be responsible for the difference in the total amount of analgesics consumed.

There was no statistically significant difference in number of analgesics consumed between Adr and plain Lig (**table 20.1**), Cloni and KCl (**table20.10)**

Although very poor intra-operative pain control was observed in CPM grp, this drug led to least intake of post-operative analgesics. This may be due to its delayed effect on histamine secretion which occurs after tissue trauma. As explained by Chiu that the peak effect obtained with CPM was at 40.9 ± 4.0min compared with bupivacaine, 34.3 ± 4.8 min for cutaneous analgesia in rats. Schayer stated that "Inducible histamine (intrinsic histamine) is continuously being synthesized in certain tissues".[144,145] It was also shown that following injection of endotoxin, systemic infection, allergic reactions, and thermal injury, there is an increase in the enzymatic activity of histidine decarboxylase, leading to increased histamine synthesis.[144,145] Antihistamine CPM blocks this mediator of inflammation in the post-operative period, thus leading to good pain control. Another possible explanation is role of CPM in activation of a signal transduction mechanism operated by Gi proteins, which are also involved in facilitation of analgesic effects of opioids, tricyclic antidepressants, and a2-adrenoceptor

agonists.[119,120] Thus, the post-op pain control was better and need for analgesics was minimized. Further studies in this regard may provide still better explanation on the same.

Post-operative pain control with Dexa has been attributed to its multi-modal anti-inflammatory property even with a single dose (a. block the enzymatic activation of phospholipase A2 which inhibits arachidonic acid release by the cell membrane, thereby inhibiting synthesis of prostaglandins, leucotrienes or thromboxane, b. block superoxide production and lysosomal enzyme release in human polymorphonuclear neutrophils c. inhibiting vascular dilatation, reducing liquid transudation and edema formation, decreasing cell exudates, and reducing fibrin deposit.[92,97,98] Chong established superiority of perineural administration in comparison with iv administration for post-operative pain control.[134]

Cloni has been shown to have analgesic and sedative properties acting on central preganglionic adrenergic ganglia that decreased the need for postoperative analgesics.[69]

In addition to its central analgesic action, peripheral antinociception is achieved by an α_2 adrenoceptor-mediated local release of encephalin-like substances.[146] The post-operative pain control was fair in the Cloni grp and consistent with other studies.[69,137]

The number of analgesics consumed in KCl grp were comparable to Cloni grp and less as compared to Lig and Lig Adr. The need of post-operative analgesics was also reported to be minimal in KCl grp in Brachial plexus blocks.[83]

With Inter group comparison for Cardiovascular variables, there was no significant difference for pre-op SBP, DBP, MABP and HR, indicating that the groups were similar pre-operatively. There was a statistically highly significant difference for all these variables at all time intervals, ie. 5min, 10min,15min, 30min and 45min. (**Table 7)** (**Graphs 9, 10, 11, 12)**

For Adr grp, there was highly significant difference for Intra-grp comparison and for pair-wise comparison with pre-op values, (**Tables 8.1, 8.2, 8.3, 8.4 and 9)**

Mean SBP was 120.50$\pm$3.672 pre-op, 123.95$\pm$3.987 at 5min, 128.05$\pm$3.374 at 10 min, 127.90$\pm$3.388 at 15min, 126.90$\pm$3.448 at 30min, 121.80$\pm$2.857 at 45 min post-injection, (**Table 8.1)** (**Graph 13)**

Mean DBP was 80±1.812 pre-operatively, 81.85±1.777 at 5min, 83.55±1.395 at 10min, 83.45±1.358 at 15min, 82.30±1.786 at 30min and 80.90±1.566 at 45min post-injection. (**Table 8.2)** (**Graph 14)**

Mean MABP was 93.50±2.035 pre-op, 95.88±1.996 at 5min, 98.383±1.5089 at 10min, 98.26667±1.390239 at 15min, 97.16667±1.574367 at 30min, 94.53333±1.409775 at 45min post-injection. (**Table 8.3)** (**Graph 15)**

Mean HR was 77.08±2.223 pre-op, 83.10±2.872 at 5min, 83.00±3.351 at 10min, 81.65±2.931 at 15min, 79.93±2.859 at 30min, 78.78±3.634 at 45min post-injection. (**Table 8.4)** (**Graph 16)**

In this study, it is evident that there was a statistically significant increase in SBP, DBP, MABP and HR following Lig-Adr injection, with maximum rise at 10 and 15min post-injection. However, these changes were clinically not significant. These results were similar to those reported previously[6,8,35] The exogenously administered Adr is metabolised and eliminated in approximately 10 min by COMT, following which, the hemodynamic variables are normalised.[42] It has been stated that serum Adr concentration relates to the amount of solution, ie Adr used for injections. With careful injection techniques, if intravascular injection is prevented, there is no dramatic rise in Epi levels and thereby no significant increase in the cardiovascular variables, especially in healthy individuals[37,42]. A marginal increase in these variables in normotensive subjects in this study was uneventful. However, changes in BP and HR in cardiac pts need to be evaluated with due ethical approvals.

For plain Lignocaine, Clonidine, Potassium chloride and Dexamethasone grps, there were no significant differences for Intra-grp comparison of all the variables and for their respective pair-wise comparisons with pre-op values within the grps (**Table 10 to Table 17), (Graphs 13, 14, 15, 16)**

In all these grps there was a marginal rise of BP and HR which was not clinically and statistically significant and mostly attributable to apprehension for the procedure. As noted, the readings came down to pre-op levels mostly within 30min post-injection, that also corresponded to the time when the procedure was completed.

In Lig grp, (no vasoconstrictor used), there was good hemodynamic stability. Yadav et al compared Lig with and without Adr, and showed hemodynamic stability in plain Lignocaine grp.[55]. Similar findings were also reported by Meral et al[47] and Knoll-Kohler et al[37]

Clonidine has vasoconstrictive effects locally[68]. However, when used systemically, it helps in lowering sympathetic tone by inhibiting release of NE at synaptic junctions, thereby lowering HR and BP.[66] Very stable hemodynamics were observed in the Clonidine grp. This was consistent with previous studies.[67,68,69]

Systemic supplementation with potassium salts, decreases the doses of antihypertensives required[148]. Although reported to have vasoconstrictive effects locally[73,81], Potassium salts used systemically, lower BP. No significant changes in cardiovascular variables were obtained in this study. No similar study has been reported in the literature for comparison.

Although corticosteroids augment vascular tone, and foster hypertension, a single dose of systemic Dexamethasone does not lead to any significant change in the hemodynamic variables.[143, 147]. No significant changes in the hemodynamic variables were noted in this study. This may be due to small dose of just 4mg of Dexa which was injected cautiously (no intravascular injection) in the pterygomandibular space. No previous study pertaining to comparison of hemodynamic variables in 3rd molar surgeries with added Dexa in Lig is available for comparison.

For CPM grp, there was highly significant difference for Intra-grp comparison for SBP and MABP (**Tables 18.1 and 18.3**), whereas, there was no statistically significant difference for DBP and HR (**Tables 18.2 and 18.4**). For pair-wise comparison with pre-op values, there was significant difference for SBP at 10 and 15min, for DBP at 5 and 10min, for MABP at 5,10,15min. However no statistically significant difference was obtained for HR for all intervals compared with pre-op (**Table 19)**.

Mean SBP was 120.33±2.217 pre-op, 120.17±1.935 at 5min, 118.00±2.484 at 10min, 118.33±2.268 at 15min, 118.72±17.456 at 30min, 120.17±2.360 at 45 min post-injection, (**Table 18.1)** (**Graph 13)**

Mean DBP was 80.22±1.899 pre-op, 79.22±1.987 at 5min, 79.00±2.318 at 10min, 79.44±1.827 at 15min, 79.56±1.978 at 30min, 80.00±1.586 at 45min post-injection. (**Table 18.2)** (**Graph 14)**

Mean MABP was 93.59259±1.436732 pre-op, 92.87037±1.423784 at 5min, 92.00000±1.520234 at 10min, 92.40741±1.354853 at 15min, 92.61111±5.677860 at 30min, 93.38889±1.238278 at 45min post-injection. (**Table 18.3)** (**Graph 15)**

Mean HR was 75.83±2.783 pre-op, 75.86±2.949 at 5min, 75.89±2.755 at 10min, 75.92±4.108 at 15min, 75.81±4.302 at 30min, 75.67±4.309 at 45min post-injection. (**Table 18.4)** (**Graph 16)**

It is evident from the above that CPM grp experienced a slight fall in SBP until 30min post-injection. This was not significant clinically. Chua et al studied cardiovascular effects of oral CPM 4mg in hypertensives and concluded that antihistamines do not cause cardiovascular changes.[149]. No study is available for comparison for CPM used as an additive to Lignocaine in oro-facial region.

None of the injections used in this study had benzyl alcohol or other preservative which interferes with nerve function on perineural use. On follow ups, wound healing was not found to be negatively affected in any grp. Sloughing, wound dehiscence, dry socket, signs of infection, secondary hemorrhage, dry mouth, oral ulceration, pain at the site of surgery/injection, (although not the primary objectives), were not observed in any subject. None of the subjects showed any signs of toxicity or allergy to any of the drugs. Post-operative nausea, sedation, giddiness, diplopia, confusion or variations in cardiovascular variables were also not noted. None of the subjects experienced any untoward local and /or systemic adverse effects. All the drugs used, are already approved for use in humans, were kept well within their therapeutic range and were administered by experienced hands using a slow and careful injection technique and double aspiration in all the included subjects.

Chapter 8

CONCLUSION

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With the above results, it is evident that

- Adrenaline, does cause hemodynamic changes when used with Lignocaine in normotensive subjects. So, it can be expected that these changes may be more pronounced and deleterious in ASA-III and ASA-IV subjects. However, use of careful and slow injection technique to avoid intravascular injection cannot be overstated.
- Plain Lignocaine does not provide sufficient duration and depth of anesthesia. Lack of good hemostasis is also a concern, since, it does not provide a clean and bloodless field for surgery. Inadequate effect requires re-injection, increased amount of administered Lignocaine, which might lead to untoward systemic effects. Also, inadequate depth of anesthesia/poor pain control will lead to an increased secretion of endogenous catecholamines, which may have dire consequences in higher ASA classes. It is thus preferable to use a vasoconstrictor with local anesthetic rather than using lignocaine alone. However, the vasoconstrictor should have a preferential local effect without causing a systemic vasoconstrictive phenomenon leading to an untoward rise in systemic resistance, heart rate and blood pressure.
- Clonidine serves the above criteria, since, it has local constrictor effects, an analgesic action on nerve membranes and systemic anti-hypertensive as well as anxiolytic actions. Additional advantages of faster onset, prolonged duration, optimum bleeding control, better post-op pain control and good hemodynamic stability, makes it a good alternative to Adr especially in ASA-III and IV pts with absolute contraindications to Adrenaline.
- KCl, a physiologic salt, when used in physiologically acceptable doses, provides good onset, depth and duration of anesthesia, good post-op analgesia and hemodynamic stability in comparison to Adr. However, poor control of bleeding is a disadvantage.

- Similarly, Dexamethasone, provides early onset, prolonged duration and very good post-op pain control (because of its established anti-inflammatory actions), fair bleeding control and minimal hemodynamic changes.
- Chlorpheniramine did not yield adequate depth of anesthesia. Onset was longer, reinjection was required and four subjects had to be shifted to Adr grp. Post-operative pain control was excellent. However, this drug cannot be totally relied upon.

No subject in this study experienced any adverse local and/or systemic effects.

Single dose of Dexamethasone or Clonidine may serve as good replacement to Adrenaline, in cases where Adrenaline is contra-indicated.

Similar studies may be planned in future.

Chapter 9

LIMITATIONS AND FUTURE SCOPE

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The volume of solution used for CPM grp was 3.5 ml, which was different from other grps (3ml). Although the operator could have known the drug content with this volume discrepancy, but the observer was kept unaware with this regard and hence, the possibility of bias was eliminated.

This study had to be restricted to ASA-I subjects, However, further studies can be considered in ASA-II, ASAIII AND ASA IV subjects with ethical approval. Similarly, blood levels of the drugs attained, was not a variable in this study due to ethical concerns and may be checked with due ethical approvals in future.

This study was performed on pterygomandibular nerve blocks. In future, other nerve blocks in Oro-facial region may be involved. Similarly, the same drugs may be used in different doses and compared. Also, drugs from other grps or other drugs from the grps used (steroids/salts/α agonists/antihistamines) may be tested.

Study of pH and chemical stability of admixtures, were not primary objectives and results from relevant studies in literature were used as references. Freshly prepared solutions were used in this study, however, stability of stored solutions of such admixtures can be checked in future.

Concentration of Chlorpheniramine was used arbitrarily. Perineural safety with various concentrations may be checked in future. Studies on vasoconstrictive effects of the same in Oro-facial region may be planned.

This study was conducted to evaluate only the clinical effects. Studies may be designed to understand mechanism of actions at molecular/receptor levels.

Conflict of interest: NONE

Funding: NONE

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APPENDICES

Appendix 1: IEC Clearance letter

Y.M.T. Dental College & Hospital
Institutional Ethics Committee (IEC)

Decision Letter for Research Proposal

Ref No. YMTDC/IEC/2018/077 Date: 04/01/2018

To,

Dr. Rinku Kalra

The Institutional Ethics Committee (IEC) has reviewed and discussed your application to conduct the _____ entitled "Comparative Evaluation of Quality of Anesthesia vasoconstrictive Effects, Hemodynamic Response and pain control with Additives in 2% Lignocaine Hydrochloride For pterygomandibular and blocks for adult patients undergoing Surgical extraction of impacted mandibular third molar - A Randomized Controlled Study"

All the documents pertaining to the study were reviewed:

The following members of the ethics committee were present at the meeting held on _____ (Date, Time, Place)

Dr. Sanjeev Yadav. Chairman of the Ethics Committee

Dr. Dheeraj K. Member secretary of the Ethics Committee

Dr. Amar K., Dr. Rizwan. S., Dr. Mrunali K. Members

We approve the study to be conducted in its

- ✓ Presented form
- o Minor changes needed _____
- o Major changes needed _____
- o Clarification to the following points needed

— NIL —

- o Study not approved & not allowed to be started / conducted due to the following reasons

The Institutional Ethics Committee expects to be informed about the progress of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report. The reference number & date need to be cited in all future communications

Yours sincerely,

Member Secretary, Ethics Committee

Dr. Sanjeev Yadav
Chairman
Institutional Ethics Committee
Y M T Dental College & Hospital
Kharghar Navi Mumbai

Navi Mumbai IEC

Appendix 2: Case Record Sheet

Case No: **Date:**
Name: **Occupation:**
Age/Sex:
Address:

Chief complaint:

History of present illness:

Past Medical history:

Past Dental history:

Personal and habit history:

Clinical Examination:
General examination
Temperature: Respiratory rate:
Pulse: Blood pressure:
Pallor/Icterus/Cyanosis/Clubbing/Pedal edema/Lymphadenopathy-

Local Examination:
Extra Oral:

a) Facial Asymmetry: Present/Absent
b) Mouth Opening:
c) T.M.J:
d) Lymphadenopathy
e) Any other relevant finding

Intra Oral:
Mucosa: Normal/ Abnormal
Lip: Normal/ Abnormal
Cheek: Normal/ Abnormal
Floor of the mouth: Normal/ Abnormal
Vestibule : Normal/ Abnormal
Tongue : Normal/ Abnormal
Palate : Normal/ Abnormal

Provisional Diagnosis :

Investigations:
1) Radiographs
2) Blood investigations: Complete Blood Count
Bleeding Time and Clotting Time
Fasting Blood Sugar

Final Diagnosis :

Treatment Plan:

Surgical Procedure:

Follow Up:
Any local/ systemic adverse event/finding:

Appendix 3:

Appendix 3 a.: Participant Information Sheet

Dear sir/ madam,

I, Dr. Rinku Kalra, have undertaken a study on "Comparative Evaluation of Effects of Additives to 2% Lignocaine for Surgical Extraction of Impacted Mandibular Third Molars: A Randomized Controlled Clinical Study". In this study, I will be comparing and evaluating effectiveness of some commonly used drugs vs Adrenaline with local anesthesia for injection in your surgical extraction of mandibular third molar.

This study involves assessment of characteristics of local anesthesia, amount of blood loss, BP, HR and postoperative pain control.

You will be evaluated on the day of surgery and then telephonically thereafter. You will have to follow up for removal of stitches on 7^{th} day after surgery. If you are facing any type of problem pertaining to the procedure conducted, or any health-related issues, kindly feel free to contact me and visit the OPD at the earliest.

General information will be collected regarding name, age, address, education, occupation and income. Previous medical and dental history and oral hygiene practices will be recorded.

As such there are no side effects observed in previous studies with the used drugs. However, in a rare situation, in the event of any adverse reaction, prompt treatment will be facilitated by the principal investigator and the principal investigator will bear the charges.

My contact details in case of emergency are:

Primary Investigator: Dr Rinku Kalra

Phone No: 9167391340

Email ID: drrinkukalra@gmail.com

There is no harm involved in this procedure and you may opt out of the study at any point of time. I request you to kindly participate in this study.

Signature of The Primary Investigator

Signature of the participant

Appendix 3.b: प्रतिभागी सूचना पत्र

य महोदय / महोदया,

मैं, डॉ. रिंकू कालरा ने "प्रभावित निचला अक़ल ढ़ाड़ के सर्जिकल एक्सट्रैक्शन के लिए 2% लिग्नोकेन के एडिटिव्स के प्रभावों का तुलनात्मक मूल्यांकन: एक यादृच्छिक नियंत्रित नैदानिक अध्ययन" पर एक अध्ययन प्रारंभ किया है। इस अध्ययन में, मैं आपके निचला अक़ल ढ़ाड़ के सर्जिकल निष्कर्षण में इंजेक्शन के लिए स्थानीय एनेस्थीसिया के साथ कुछ सामान्य रूप से उपयोग की जाने वाली दवाओं बनाम एड्रेनालाईन की प्रभावशीलता की तुलना और मूल्यांकन करूँगा। इस अध्ययन में स्थानीय संज्ञाहरण, रक्त हानि की मात्रा, बीपी, एचआर और पश्चात दर्द नियंत्रण की विशेषताओं का मूल्यांकन शामिल है।

सर्जरी के दिन आपका मूल्यांकन किया जाएगा और उसके बाद टेलीफोन द्वारा। सर्जरी के बाद 7वें दिन आपको टांके हटाने के लिए फॉलो-अप करना होगा। यदि आप आयोजित प्रक्रिया से संबंधित किसी भी प्रकार की समस्या का सामना कर रहे हैं या किसी भी स्वास्थ्य संबंधी समस्या का सामना कर रहे हैं, तो कृपया मुझसे बेझिझक संपर्क करें और जल्द से जल्द ओपीडी में जाएँ।

नाम, आयु, पता, शिक्षा, व्यवसाय और आय के संबंध में सामान्य जानकारी एकत्र की जाएगी। पिछला चिकित्सा और दंत इतिहास और मौखिक स्वच्छता प्रथाओं को दर्ज किया जाएगा।

जैसे कि पिछले अध्ययनों में प्रयुक्त दवाओं के साथ कोई दुष्प्रभाव नहीं देखा गया है। हालांकि, एक दुर्लभ स्थिति में, किसी भी प्रतिकूल प्रतिक्रिया की स्थिति में, प्रमुख अन्वेषक द्वारा शीघ्र उपचार की सुविधा प्रदान की जाएगी और प्रमुख अन्वेषक आरोपों को वहन करेगा।

दुर्लभ मामलों में यदि कोई प्रतिकूल प्रतिक्रिया होती है, तो प्रधान अन्वेषक द्वारा शीघ्र उपचार किया जाएगा और प्रधान अन्वेषक आरोपों को वहन करेगा।

आपात स्थिति के मामले में मेरे संपर्क विवरण हैं:

प्राथमिक अन्वेषक: डॉ. रिंकू कालरा

फोन नंबर: 9167391340

ईमेल आईडी: drrinkukalra@gmail.com

इस प्रक्रिया में कोई नुकसान नहीं है और आप किसी भी समय अध्ययन से बाहर हो सकते हैं। मेरा आपसे अनुरोध है कि कृपया इस अध्ययन में भाग लेने की कृपा करें।

प्राथमिक अन्वेषक के हस्ताक्षर

प्रतिभागी के हस्ताक्षर

Appendix 4

4 a. Consent Form (English)

Consent Form

I _____ authorize the performance of the following procedure(s) _____

The doctor has fully explained to me the kind of procedure she will perform in the language that I can understand & has answered my questions about my condition & the procedure to my satisfaction.

The doctor has also explained about the medications given to me. This I consent to be my own free act and will.

I consent to the observing, photographing or televising of the procedure to be performed for medical, scientific or educational purposes provided my identity is not revealed by the pictures.

I agree to co-operate fully with my doctor and to follow, to the best of my ability, her instructions and recommendations about my care and treatment.

Witnessed by Patient's signature

4 b. Consent Form (Hindi)

सहमति पत्र

1. मैं_____ प्रस्तुत प्रक्रिया/चिकित्सा/शस्त्रक्रिया _____ करने की पूरी अनुमति दे रहा/रही हूँ|

2. मुझे डॉक्टरने यह प्रक्रिया/चिकित्सा/शस्त्रक्रिया के बारे में मैं समझ सकूं ऐसी भाषा में पूरी जानकारी दी है और मेरे सारे सवालों के जवाब भी दिए हैं|

3. मुझपर किये जानेवाले इलाज के बारे में पर्याप्त जानकारी मुझे डॉक्टरने दी है| यह जिम्मेदारी पूरी तरहसे मेरी रहेगी|

4. मुझे अनामिक रखकर शैक्षणिक, वैज्ञानिक या वैद्यक-संबंधी उद्देश्य से किया जानेवाला प्रक्रिया/चिकित्सा/शस्त्रक्रिया का चित्रीकरण, निरिक्षण या चलचित्रिकरण को मै अनुमति दे रहा/रही हूँ|

5. मेरी सेहत और इलाज के बारे में मुझे जो सूचनाएं डॉक्टरद्वारा दी गयी हैं, मैं उन सबका पालन करूँगा/करुँगी और उन्हें पूरी तरहसे सहकार्य करूँगा/करुँगी |

गवाह के हस्ताक्षर रुग्ण के हस्ताक्षर

Appendix 4 c.

CERTIFICATE OF TRANSLATION

I, Hindi teacher of a recognized school, have translated and cross checked the above, consent form and participant information sheet.

I certify that there is no change in the meaning of the above stated documents after translation.

Signature

Appendix 5

MASTER CHARTS

5.1 Lignocaine-Adrenaline

	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN	AO
1	Age	Sex	Amount of solution injected	number of injections used	Onset in sec	SBP pre-op	SBP 5min	SBP 10 min	SBP 15 min	SBP 30 min	SBP 45 min	DBP pre-op	DBP 5 min	DBP 10 min	DBP 15 min	DBP 30 min	DBP 45 min	MABP pre-op	MABP 5 min	MABP 10 min	MABP 15 min	MABP 30 min	MABP 45 min	HR pre-op	HR 5min	HR 10 min	HR 15 min	HR 30 min	HR 45 min	Rescue analgesic taken after (hrs)	Rescue analgesic taken after (min)	VAS score	Weight of gauze pre-op(gm)	Weight of gauze post - op(gm)	oe in weight of gauze pre-op and post op(gm)	Total volume(ml) in the jar at the end of the procedure	Quantity (ml)of normal saline used for irrigation	Volume (ml)of blood lost in suction jar (b)	total blood lost (a+b)	no. of analgesics in 3days
2	32	F	3	1	102	120	122	126	132	128	122	80	84	86	84	82	82	93.33	96.67	99.33	100.00	97.33	95.33	76	80	83	85	80	82	2.2	132	3	10	25	15	500	475	25	50	8
3	36	F	3	1	98	112	116	122	118	120	116	78	78	82	84	86	82	89.33	90.67	95.33	95.33	97.33	93.33	70	84	85	86	81	75	2.1	126	2	15	30	15	430	410	20	50	7
4	30	M	3	1	100	118	120	124	124	124	122	80	82	84	84	80	80	92.67	94.67	97.33	97.33	94.67	94.00	78	85	86	78	76	76	2	120	1	10	22	12	300	280	20	42	8
5	35	F	3	1	103	116	118	122	126	126	120	78	82	86	86	84	82	90.67	94.00	98.00	99.33	98.00	94.67	80	81	82	83	79	89	2.3	138	3	11	27	16	330	300	30	57	9
6	40	F	3	1	120	120	122	128	128	124	124	80	82	84	86	82	82	93.33	95.33	98.67	100.00	96.00	96.00	76	78	83	84	83	80	2.5	150	2	10	28	18	370	335	35	63	8
7	32	F	3	1	111	120	124	128	128	122	124	80	82	82	84	82	78	93.33	96.00	97.33	98.67	95.33	93.33	80	82	85	86	79	85	2.4	144	2	11	30	19	350	325	25	55	8
8	36	M	3	1	89	126	130	136	134	134	124	80	82	82	82	82	82	95.33	98.00	100.00	99.33	99.33	96.00	78	85	83	85	80	83	2	120	2	10	25	15	360	340	20	45	7
9	35	F	3	1	87	124	128	132	132	130	124	78	80	84	86	84	82	93.33	96.00	100.00	101.33	99.33	96.00	82	84	85	79	77	79	2.5	150	1	12	25	13	330	310	20	45	8
10	36	F	3	1	100	126	126	132	128	126	118	84	84	86	86	82	82	98.00	98.00	101.33	100.00	96.67	94.00	78	86	87	86	83	75	2	120	1	10	31	21	440	420	20	51	8
11	33	F	3	1	115	124	126	128	128	128	124	82	84	84	84	82	80	96.00	98.00	98.67	98.67	97.33	94.67	79	85	75	81	78	76	2.4	144	3	10	25	15	300	280	20	45	9
12	30	M	3	1	118	114	118	124	124	124	118	78	80	82	84	80	80	90.00	92.67	96.00	97.33	94.67	92.67	77	88	87	76	75	74	2.2	132	2	11	35	24	310	285	25	60	8
13	29	F	3	1	103	116	120	126	124	124	118	78	80	82	84	82	82	90.67	93.33	96.67	97.33	96.00	94.00	75	86	87	78	81	82	2.2	132	1	10	23	13	315	290	25	48	9
14	35	M	3	1	118	124	124	130	128	128	124	78	80	84	84	80	82	93.33	94.67	99.33	98.67	96.00	96.00	76	85	78	83	80	81	2.6	156	3	11	34	23	280	250	30	64	7
15	33	M	3	1	103	128	132	132	132	134	124	80	82	82	84	82	82	96.00	98.67	98.67	100.00	99.33	96.00	76	85	86	80	77	79	2.2	132	2	11	30	19	300	270	30	60	7
16	31	M	3	1	109	120	126	130	128	126	124	82	84	84	84	84	80	94.67	98.00	99.33	98.67	98.00	94.67	77	86	87	77	78	80	2.2	132	2	10	25	15	350	330	20	45	9
17	39	M	3	1	104	122	124	130	128	134	122	82	82	84	84	84	82	95.33	96.00	99.33	98.67	100.67	95.33	78	87	88	80	82	81	2.3	138	1	11	28	17	360	330	30	58	9
18	42	F	3	1	99	118	120	126	128	126	120	78	82	86	84	84	80	91.33	94.67	99.33	98.67	98.00	93.33	80	89	78	84	76	73	2.4	144	2	10	36	26	360	340	20	56	8
19	35	M	3	1	76	118	122	126	124	126	116	80	80	82	82	84	80	92.67	94.00	96.67	96.00	98.00	92.00	76	82	79	82	81	80	2.4	144	1	11	34	23	320	290	30	64	7
20	33	M	3	1	109	122	124	126	128	122	126	80	82	84	84	84	82	94.00	96.00	98.00	98.67	96.67	96.67	78	84	78	78	76	76	2.5	150	2	10	30	20	300	275	25	55	7
21	31	M	4	2	104	124	126	130	132	130	118	82	82	82	82	82	78	96.00	96.67	98.00	98.67	98.00	91.33	72	85	79	84	84	77	2.3	138	1	12	35	23	500	470	30	65	9
22	30	F	3	1	103	124	130	132	132	132	124	82	84	84	80	80	78	96.00	99.33	100.00	97.33	97.33	93.33	78	84	85	81	83	76	2.2	132	2	10	30	20	430	400	30	60	7
23	29	M	3	1	111	120	124	126	128	130	122	80	82	84	84	82	82	93.33	96.00	98.00	98.67	98.00	95.33	77	83	77	79	82	80	2.1	126	3	11	28	17	300	275	25	53	8
24	28	M	3	1	91	120	124	128	126	126	122	80	82	82	82	80	82	93.33	96.00	97.33	96.67	95.33	95.33	76	82	86	76	81	74	2.3	138	2	10	35	25	330	300	30	65	7
25	26	M	3	1	109	122	124	126	126	126	122	80	84	86	84	86	82	94.00	97.33	99.33	98.00	99.33	95.33	78	85	83	83	80	84	2.5	150	3	12	30	18	360	340	20	50	8
26	24	F	3	1	106	122	128	132	132	128	122	82	84	86	82	84	84	95.33	98.67	101.33	98.67	98.67	96.67	78	83	84	81	74	78	2.4	144	2	13	28	15	350	330	20	48	8
27	23	F	4	2	92	120	128	128	130	126	126	78	80	82	84	82	80	92.00	96.00	97.33	99.33	96.67	95.33	76	80	85	83	84	83	2.3	138	2	10	32	22	360	340	20	52	9
28	28	M	3	1	94	116	118	124	126	122	118	82	84	82	82	78	82	93.33	95.33	96.00	96.67	92.67	94.00	78	85	82	85	81	74	2.2	132	2	11	35	24	330	300	30	65	8
29	35	M	3	1	102	122	124	126	126	124	124	78	80	82	84	84	80	92.67	94.67	96.67	98.00	97.33	94.67	77	83	84	81	77	79	2.1	126	1	12	32	20	440	415	25	57	9
30	34	M	3	1	104	120	126	128	126	124	124	82	82	84	84	82	82	94.67	96.67	98.67	98.00	96.00	96.00	78	81	83	85	78	75	2.2	132	1	10	28	18	300	265	35	63	7
31	33	M	3	1	108	114	116	122	120	122	122	80	82	84	82	82	82	91.33	93.33	96.67	94.67	95.33	95.33	79	81	86	83	75	76	2	120	2	10	30	20	310	285	25	55	8
32	36	F	3	1	104	118	120	126	124	126	116	78	80	82	82	84	80	91.33	93.33	96.67	96.00	98.00	92.00	77	83	85	77	81	75	2.4	144	1	10	35	25	300	275	25	60	9
33	34	M	3	1	92	122	130	134	132	130	124	82	84	84	84	82	78	95.33	99.33	100.67	100.00	98.00	93.33	75	81	83	85	83	82	2.3	138	2	11	30	19	280	250	30	60	8
34	36	F	3	1	89	124	126	128	130	128	122	82	84	84	84	84	80	96.00	98.00	98.67	99.33	98.67	94.00	78	79	78	81	83	81	2.4	144	1	10	28	18	300	275	25	53	7
35	34	M	3	1	112	128	130	134	132	132	126	80	82	84	82	80	82	96.00	98.00	100.67	98.67	97.33	96.67	76	80	81	82	81	78	2.2	132	2	11	28	17	350	320	30	58	7
36	33	M	3	1	119	118	120	128	128	126	124	82	84	84	84	84	82	94.00	96.00	98.67	98.67	98.00	96.00	77	86	87	81	84	79	2.5	150	2	12	30	18	360	340	20	50	8
37	32	M	3	1	104	122	126	132	130	128	122	82	82	84	84	82	82	95.33	96.67	100.00	99.33	97.33	95.33	78	79	86	83	83	81	2.2	132	3	10	30	20	360	325	35	65	7
38	30	F	3	1	101	120	122	128	128	128	124	80	82	84	82	80	78	93.33	95.33	98.67	97.33	96.00	93.33	72	76	79	82	81	83	2.4	144	2	10	31	21	320	290	30	61	8
39	29	M	3	1	90	120	126	128	128	126	122	78	82	84	82	80	80	92.00	96.67	98.67	97.33	95.33	94.00	76	82	81	83	81	74	2.3	138	1	10	32	22	300	270	30	62	9
40	24	M	3	1	93	118	124	126	128	126	118	76	78	82	82	82	82	90.00	93.33	96.67	97.33	96.67	94.00	78	79	81	83	83	76	2.2	132	2	11	28	17	510	480	30	58	8
41	26	M	3	1	112	118	124	128	130	130	120	78	78	82	82	82	78	91.33	93.33	97.33	98.00	98.00	92.00	79	85	83	77	76	80	2.4	144	1	10	29	19	430	400	30	59	7
42	32.175		3.05	1.05	102.6	120.5	123.95	128.05	127.9	126.9	121.8	80	81.85	83.55	83.45	82.3	80.9	93.5	95.883	98.383	98.267	97.167	94.533	77.075	83.1	83	81.65	79.925	78.775	2.2825	136.95	1.85	10.75	29.675	18.925	353.13	327	26.125	55.8	7.925

5.2 Plain Lignocaine

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN	AO
1	Serial No	Age	Sex	Amount of solution injected	number of injections used	Onset in sec	SBP pre-op	SBP 5min	SBP 10 min	SBP 15 min	SBP 30 min	SBP 45 min	DBP pre-op	DBP 5 min	DBP 10 min	DBP 15 min	DBP 30 min	DBP 45 min	MABP pre-op	MABP 5 min	MABP 10 min	MABP 15 min	MABP 30 min	MABP 45 min	HR pre-op	HR 5min	HR 10 min	HR 15 min	HR 30 min	HR 45 min	Rescue analgesic taken after (hrs)	Rescue analgesic taken after (min)	VAS score	Weight of gauze pre-op(gm)	Weight of gauze post - op(gm)	ce in weight of gauze pre-op and post op(gm)(	Total volume(ml) in the jar at the end of the procedure	Quantity (ml)of normal saline used for irrigation	Volume (ml)of blood lost in suction jar (b)	total blood lost (a+b)	no. of analgesics in 3days
2	1	36	F	3	1	147	122	120	124	122	120	120	80	82	80	82	82	82	94.00	94.67	94.67	95.33	94.67	94.67	72	76	77	75	74	72	1.2	72	3	12	44	32	345	310	35	67	8
3	2	35	F	3	1	141	122	124	120	122	124	118	76	78	80	82	80	80	91.33	93.33	93.33	95.33	94.67	92.67	82	71	74	81	78	72	1.5	65	4	13	45	32	495	460	35	67	8
4	3	35	F	3	1	136	120	120	122	120	118	120	78	78	78	80	78	78	92.00	92.00	92.67	93.33	91.33	92.00	73	78	76	73	78	70	1.4	84	3	10	46	36	385	360	25	61	9
5	4	32	M	5	2	142	118	120	120	118	120	120	82	80	82	78	78	78	94.00	93.33	94.67	91.33	92.00	92.00	80	76	76	74	76	78	1.7	72	4	11	43	32	440	420	20	52	7
6	5	32	M	3	1	143	118	118	120	124	120	118	80	80	80	78	80	80	92.67	92.67	93.33	93.33	93.33	92.67	74	75	75	74	75	75	1.5	66	4	10	45	35	440	400	40	75	9
7	6	35	F	3	1	133	122	122	120	120	120	118	82	82	80	82	82	82	95.33	95.33	93.33	94.67	94.67	94.00	72	76	74	81	76	76	1.6	76	3	12	45	33	445	400	45	78	8
8	7	36	M	3	1	148	122	118	120	124	120	118	76	78	80	78	80	82	91.33	91.33	93.33	93.33	93.33	94.00	72	82	76	77	81	75	1.3	78	3	10	48	38	400	350	50	88	9
9	8	35	M	3	1	143	118	122	122	122	120	120	82	80	82	80	82	82	94.00	94.00	95.33	94.00	94.67	94.67	71	72	75	73	78	70	1.4	84	5	12	44	32	340	300	40	72	7
10	9	35	F	5	2	144	120	120	122	122	120	118	82	80	82	84	80	84	94.67	93.33	95.33	96.67	93.33	95.33	72	74	75	74	74	71	1.6	86	4	10	47	37	345	300	45	82	8
11	10	35	M	3	1	139	120	120	122	120	118	120	80	82	80	80	78	78	93.33	94.67	94.00	93.33	91.33	92.00	76	78	81	72	76	73	1.5	68	3	10	48	38	450	420	30	68	7
12	11	33	M	3	1	146	120	122	122	124	122	122	78	82	80	78	76	76	92.00	95.33	94.00	93.33	91.33	91.33	75	69	69	73	72	73	1.5	70	3	11	48	37	445	400	45	82	8
13	12	36	M	3	1	141	118	118	122	122	120	118	82	82	80	80	80	80	94.00	94.00	94.00	94.00	93.33	92.67	76	77	78	76	71	70	1.3	78	3	12	40	28	390	350	40	68	9
14	13	36	F	4	2	139	118	120	122	122	122	118	80	84	82	82	88	82	92.67	96.00	95.33	95.33	93.33	94.00	71	75	76	75	72	72	1.5	68	3	11	45	34	335	300	35	69	8
15	14	32	F	5	2	147	116	118	120	122	122	116	76	80	80	88	84	80	89.33	92.67	93.33	99.33	96.67	92.00	72	82	74	82	75	74	1.5	65	3	11	46	35	335	300	35	70	9
16	15	33	M	4	2	143	120	122	124	122	122	120	82	80	82	80	82	80	94.67	94.00	96.00	94.00	95.33	93.33	79	80	73	80	73	82	1.5	72	4	10	40	30	390	350	40	70	7
17	16	35	M	3	1	137	122	122	122	122	124	122	84	80	82	80	80	80	96.67	94.00	95.33	94.00	94.67	94.00	75	74	84	74	83	81	1.5	79	3	11	43	32	440	400	40	72	8
18	17	39	F	5	2	135	116	116	116	116	116	116	80	80	80	82	82	78	92.00	92.00	92.00	93.33	93.33	90.67	72	70	76	78	80	73	1.4	84	3	10	47	37	385	350	35	72	9
19	18	42	F	3	1	150	122	122	120	122	118	120	78	80	78	82	78	78	92.67	94.00	92.00	95.33	91.33	92.00	78	78	78	80	74	75	1.4	84	3	11	41	30	340	300	40	70	8
20	19	42	F	5	2	151	118	118	122	120	122	122	82	80	80	78	82	80	94.00	92.67	94.00	92.00	95.33	94.00	75	81	84	72	76	74	1.2	72	3	14	48	34	390	360	30	64	9
21	20	36	M	3	1	145	122	124	120	120	118	122	80	82	80	82	82	78	94.00	96.00	93.33	94.67	94.00	92.67	78	80	78	82	71	76	1.6	76	3	12	40	28	335	300	35	63	9
22	21	33	M	5	2	138	120	118	118	122	118	118	80	80	82	80	78	80	93.33	92.67	94.00	94.00	91.33	92.67	70	71	78	80	82	74	1.5	71	3	12	43	31	345	300	45	76	9
23	22	37	F	3	1	143	118	120	120	118	122	120	82	80	80	80	80	80	94.00	93.33	93.33	92.67	94.00	93.33	81	85	75	76	74	78	1.5	68	3	11	48	37	385	350	35	72	7
24	23	35	M	5	2	146	120	122	124	118	120	122	84	82	80	78	78	78	96.00	95.33	94.67	91.33	92.00	92.67	80	76	70	75	82	81	1.8	80	3	10	42	32	345	310	35	67	9
25	24	36	F	3	1	149	118	120	122	122	122	120	80	80	80	82	80	80	92.67	93.33	94.00	95.33	94.00	93.33	82	75	73	75	80	80	1.7	81	3	12	41	29	395	350	45	74	8
26	25	34	F	5	2	142	118	118	118	120	120	122	76	80	80	80	80	80	90.00	92.67	92.67	93.33	93.33	94.00	78	74	75	82	73	79	1.5	72	4	13	42	29	400	380	20	49	8
27	26	32	F	3	1	138	122	122	118	116	116	122	80	80	80	80	80	80	94.00	94.00	92.67	92.00	92.00	94.00	80	78	78	80	75	78	1.8	82	3	14	43	29	345	310	35	64	8
28	27	31	F	5	2	149	120	118	120	122	120	120	82	80	80	82	82	80	94.67	92.67	93.33	95.33	94.67	93.33	73	78	81	80	74	80	1.5	76	3	11	41	30	340	300	40	70	8
29	28	28	M	3	1	150	120	122	118	122	118	122	82	84	82	80	82	84	94.67	96.67	94.00	94.00	94.00	96.67	79	85	87	80	75	71	1.6	75	4	12	40	28	390	350	40	68	9
30	29	26	M	3	1	151	120	120	122	120	118	118	80	80	80	82	78	78	93.33	93.33	94.00	94.67	91.33	91.33	78	80	71	72	76	78	1.6	74	3	14	46	32	435	400	35	67	8
31	30	24	M	5	2	146	124	120	122	122	120	120	80	80	80	80	82	84	94.67	93.33	94.00	94.00	94.67	96.00	75	72	75	76	77	75	1.5	73	3	10	44	34	385	350	35	69	9
32	31	29	M	3	1	147	122	122	122	120	120	118	80	80	82	82	80	80	94.00	94.00	95.33	94.67	93.33	92.67	77	75	75	76	77	82	1.4	68	4	14	40	26	340	300	40	66	9
33	32	25	M	3	1	138	120	122	122	122	122	120	80	88	82	80	80	82	93.33	99.33	95.33	94.00	94.00	94.67	76	77	74	73	76	70	1.6	73	3	11	42	31	390	350	40	71	7
34	33	25	F	3	1	152	122	122	120	120	122	122	80	80	80	82	82	80	94.00	94.00	93.33	94.67	95.33	94.00	76	78	80	79	81	74	1.5	74	4	10	46	36	335	300	35	71	9
35	34	25	M	3	1	149	120	122	122	118	120	120	84	80	80	82	80	80	96.00	94.00	94.00	94.00	93.33	93.33	78	80	81	74	81	80	1.5	72	3	11	45	34	345	300	45	79	8
36	35	28	M	5	2	142	122	124	122	120	120	124	78	78	82	82	82	82	92.67	93.33	95.33	94.67	94.67	96.00	78	74	76	75	78	82	1.4	84	4	12	45	33	395	350	45	78	7
37	36	26	M	3	1	141	122	122	118	122	122	120	74	80	82	82	80	80	90.00	94.00	94.00	95.33	94.00	93.33	75	80	85	81	83	78	1.6	72	4	14	44	30	335	300	35	65	9
38	37	27	M	4	2	147	124	122	124	120	120	122	80	80	82	80	82	80	94.67	94.00	96.00	93.33	94.67	94.00	74	74	74	75	80	75	1.6	71	4	10	49	39	390	350	40	79	8
39	38	24	M	5	2	138	120	122	122	118	120	122	82	80	80	78	82	82	94.67	94.00	94.00	91.33	94.67	95.33	74	76	75	76	77	79	1.3	78	3	10	46	36	335	300	35	71	7
40	39	23	M	3	1	146	120	122	122	122	120	124	80	80	82	80	80	80	93.33	94.00	95.33	94.00	93.33	94.67	78	70	70	75	72	80	1.4	72	3	11	48	37	385	350	35	72	8
41	40	25	M	5	2	145	122	122	120	118	118	122	80	78	80	78	78	80	94.00	92.67	93.33	91.33	91.33	94.00	74	75	76	76	75	79	1.4	65	3	10	42	32	390	350	40	72	9
42		32.075		3.725	1.4	143.68	120.2	120.7	120.95	120.7	120.1	120.1	80.1	80.5	80.6	80.65	80.5	80.2	93.467	93.9	94.05	94	93.7	93.5	75.775	76.425	76.45	76.55	76.525	75.875	1.495	74.5	3.35	11.375	44.25	32.875	381.88	344.5	37.375	70.25	8.2

5.3 Lignocaine-Clonidine

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN	AO
1	Serial No	Age	Sex	Amount of solution injected	number of injections used	Onset in sec	SBP pre-op	SBP 5min	SBP 10 min	SBP 15 min	SBP 30 min	SBP 45 min	DBP pre-op	DBP 5 min	DBP 10 min	DBP 15 min	DBP 30 min	DBP 45 min	MABP pre-op	MABP 5 min	MABP 10 min	MABP 15 min	MABP 30 min	MABP 45 min	HR pre-op	HR 5min	HR 10 min	HR 15 min	HR 30 min	HR 45 min	Rescue analgesic taken after (hrs)	Rescue analgesic taken after (min)	VAS score	Weight of gauze pre-op(gm)	Weight of gauze post-op(gm)	ce in weight of gauze pre-op and post op(gm)(	Total volume(ml) in the jar at the end of the procedure	Quantity (ml)of normal saline used for irrigation	Volume (ml)of blood loss (b)	total blood lost (a+b)	no. of analgesics in 3days
2	1	29	F	3	1	95	118	116	118	120	122	118	80	82	80	80	78	78	92.67	93.33	92.67	93.33	92.67	91.33	78	73	77	75	78	71	3.5	210	2	15	42	27	400	370	30	57	6
3	2	29	M	3	1	99	116	116	112	116	118	120	76	78	76	76	82	76	89.33	90.67	88.00	89.33	94.00	90.67	70	79	73	78	84	81	3.3	198	1	12	45	33	350	315	35	68	7
4	3	23	M	3	1	98	120	118	118	120	120	118	80	78	80	82	80	80	93.33	91.33	92.67	94.67	93.33	92.67	73	74	75	76	77	76	2.8	168	3	12	42	30	300	270	30	60	7
5	4	28	M	3	1	96	120	118	118	122	120	120	80	80	80	78	82	78	93.33	92.67	92.67	92.67	94.67	92.00	74	77	78	76	78	79	2.8	168	1	15	40	25	320	290	30	55	6
6	5	27	M	3	1	95	118	114	118	118	118	110	82	80	80	80	78	78	94.00	91.33	92.67	92.67	91.33	88.67	77	79	77	80	78	81	3	180	2	12	40	28	360	335	25	53	6
7	6	28	F	3	1	100	118	116	112	120	122	112	78	78	78	80	76	82	91.33	90.67	89.33	93.33	91.33	92.00	72	79	76	78	74	76	2.8	168	2	11	40	29	350	320	30	59	6
8	7	32	F	3	1	102	120	118	120	122	118	120	80	80	82	82	82	80	93.33	92.67	94.67	95.33	94.00	93.33	73	75	78	82	81	79	2.9	174	2	12	35	23	360	335	25	48	7
9	8	32	M	3	1	103	122	120	118	118	120	120	78	76	78	80	80	78	92.67	90.67	91.33	92.67	93.33	92.00	75	85	77	75	78	81	2.8	168	2	10	42	32	330	300	30	62	6
10	9	31	M	3	1	102	120	122	112	122	120	118	76	78	78	80	78	82	90.67	92.67	89.33	94.00	92.00	94.00	80	75	76	76	78	81	3.2	192	3	15	40	25	450	425	25	50	6
11	10	35	M	3	1	99	124	120	122	124	118	120	80	82	82	78	78	78	94.67	94.67	95.33	93.33	91.33	92.00	75	85	73	78	84	84	3.5	210	1	10	35	25	300	275	25	50	6
12	11	33	M	3	1	98	118	122	118	120	120	120	82	82	78	80	82	80	94.00	95.33	91.33	93.33	94.67	93.33	71	83	83	82	76	80	2.9	174	1	14	42	28	310	280	30	58	7
13	12	32	F	3	1	105	118	120	120	124	120	120	82	80	80	82	78	80	94.00	93.33	93.33	96.00	92.00	93.33	83	78	83	78	84	84	3	180	1	11	37	26	300	275	25	51	7
14	13	25	M	3	1	92	124	122	122	124	120	122	80	82	82	76	80	80	94.67	95.33	95.33	92.00	93.33	94.00	76	83	83	82	76	80	2.8	168	3	11	38	27	310	285	25	52	6
15	14	32	M	3	1	91	122	118	116	122	118	118	76	78	78	80	78	80	91.33	91.33	90.67	94.00	91.33	92.67	81	77	78	79	78	75	3.1	186	1	10	42	32	300	270	30	62	6
16	15	30	M	3	1	94	118	112	110	114	118	118	78	78	78	80	78	80	91.33	89.33	88.67	91.33	91.33	92.67	76	79	81	78	84	81	2.9	174	2	10	42	32	350	315	35	67	7
17	16	36	M	3	1	92	120	118	120	122	122	120	80	82	80	76	80	78	93.33	94.00	93.33	91.33	94.00	92.00	77	75	80	79	78	80	3.2	192	2	10	45	35	360	330	30	65	6
18	17	36	F	3	1	95	118	120	118	120	118	122	80	78	82	80	82	78	92.67	92.00	94.00	93.33	94.00	92.67	70	75	83	73	81	81	3.4	204	2	12	40	28	340	315	25	53	7
19	18	32	F	3	1	96	118	120	122	118	120	120	78	78	80	80	82	80	91.33	92.00	94.00	92.67	94.67	93.33	81	79	81	78	76	81	3.2	192	3	11	40	29	320	290	30	59	6
20	19	36	M	3	1	99	120	122	120	122	120	122	80	78	78	80	82	78	93.33	92.67	92.00	94.00	94.67	92.67	78	75	81	74	79	74	2.9	174	1	10	38	28	320	290	30	58	6
21	20	35	M	4.5	2	95	122	118	124	124	122	124	82	80	80	82	78	80	95.33	92.67	94.67	96.00	92.67	94.67	71	77	73	77	76	76	3	180	3	15	45	30	420	390	30	60	7
22	21	25	F	3	1	90	118	122	122	118	120	124	82	80	80	78	82	80	94.00	94.00	94.00	91.33	94.67	94.67	80	72	73	82	76	80	3.2	192	2	10	40	30	430	400	30	60	8
23	22	28	M	3	1	91	124	118	120	118	122	118	78	80	80	78	82	82	93.33	92.67	93.33	91.33	95.33	94.00	79	80	80	78	80	72	3.3	198	1	11	43	32	300	270	30	62	7
24	23	36	F	3	1	95	120	122	122	120	118	120	78	80	82	82	78	80	92.00	94.00	95.33	94.67	91.33	93.33	79	76	76	75	77	78	3.4	204	1	10	40	30	410	380	30	60	6
25	24	36	F	3	1	94	122	122	122	118	120	120	80	80	78	78	82	82	94.00	94.00	92.67	91.33	94.67	94.67	81	78	83	82	76	80	2.9	174	1	12	40	28	360	330	30	58	7
26	25	35	F	3	1	92	118	120	124	120	118	118	82	84	82	82	82	80	94.00	96.00	96.00	94.67	94.00	92.67	78	82	75	83	77	74	3.2	192	3	13	41	28	350	320	30	58	6
27	26	35	F	4	2	95	122	120	122	120	122	120	80	82	80	78	78	78	94.00	94.67	94.00	92.00	92.67	92.00	73	74	78	73	78	71	3.2	192	1	10	38	28	360	330	30	58	6
28	27	32	M	3	1	96	120	120	120	118	116	120	78	80	82	80	82	80	92.00	93.33	94.67	92.67	93.33	93.33	79	77	77	76	78	79	3.1	186	3	11	40	29	310	280	30	59	6
29	28	32	M	3	1	92	122	124	122	120	122	122	82	80	80	78	80	82	95.33	94.67	94.00	92.00	94.00	95.33	78	74	74	75	73	75	3.1	186	1	12	42	30	440	410	30	60	6
30	29	35	F	3	1	91	120	118	120	118	120	120	80	82	78	80	80	80	93.33	94.00	92.00	92.67	93.33	93.33	77	78	77	75	78	72	3	180	3	13	40	27	300	270	30	57	6
31	30	32	M	3	1	90	118	122	122	120	118	118	84	82	82	82	78	80	95.33	95.33	95.33	94.67	91.33	92.67	80	77	79	82	79	80	2.8	168	2	12	40	28	310	280	30	58	7
32	31	35	M	3	1	89	124	124	122	118	122	122	78	76	80	82	80	78	93.33	92.00	94.00	94.00	94.00	92.67	79	76	75	77	74	84	2.7	162	2	10	35	25	300	275	25	50	6
33	32	25	F	3	1	99	122	122	122	118	120	124	78	80	82	82	82	80	92.67	94.00	95.33	94.00	94.67	94.67	80	83	83	78	76	80	2.9	174	2	11	40	29	310	280	30	59	7
34	33	28	M	3	1	102	116	118	120	118	118	122	84	82	80	82	82	82	94.67	94.00	93.33	94.00	94.00	95.33	81	80	80	79	80	73	2.8	168	2	10	39	29	300	275	25	54	8
35	34	36	F	3	1	100	118	122	122	120	122	122	82	82	82	82	78	80	94.00	95.33	95.33	94.67	92.67	94.00	75	76	76	75	77	78	3	180	1	11	40	29	350	325	25	54	6
36	35	36	F	3	1	93	122	122	122	120	122	118	76	78	78	80	80	80	91.33	92.67	92.67	93.33	94.00	92.67	81	77	80	82	76	71	3.4	204	2	12	45	33	350	320	30	63	6
37	36	35	F	3	1	92	118	122	122	118	118	120	82	84	84	82	78	80	94.00	96.67	96.67	94.00	91.33	93.33	80	82	82	83	75	75	3.2	192	1	10	42	32	360	330	30	62	8
38	37	35	F	3	1	91	124	120	120	118	118	120	82	84	78	80	80	84	96.00	96.00	92.00	92.67	92.67	96.00	79	77	77	76	78	79	2.8	168	1	15	40	25	320	290	30	55	7
39	38	32	M	3	1	97	120	122	122	118	120	122	80	74	74	76	78	78	93.33	90.00	90.00	90.00	92.00	92.67	81	84	78	80	78	79	3.2	192	2	10	35	25	300	270	30	55	6
40	39	37	M	3	1	93	122	120	120	118	122	120	82	80	80	78	76	82	95.33	93.33	93.33	91.33	91.33	94.67	76	74	74	75	73	75	3.3	198	2	11	42	31	450	420	30	61	7
41	40	35	F	3	1	96	120	122	122	120	120	118	80	74	76	76	78	78	93.33	90.00	91.33	90.67	92.00	91.33	73	76	75	73	72	71	3	180	2	14	40	26	430	405	25	51	6
42		32.025		3.0625	1.05	95.6	120.1	119.8	119.7	119.7	119.8	119.75	79.9	79.8	79.7	79.7	79.75	79.75	93.3	93.133	93.033	93.033	93.1	93.083	77	77.875	77.95	77.825	77.725	77.675	3.0625	183.75	1.825	11.65	40.3	28.65	347.25	316.38	28.875	57.525	6.5

5.4 Lignocaine-KCl

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN
1	Serial No	Age	Sex	Amount of solution injected	number of injections used	Onset in sec	SBP pre-op	SBP 5min	SBP 10 min	SBP 15 min	SBP 30 min	SBP 45 min	DBP pre-op	DBP 5 min	DBP 10 min	DBP 15 min	DBP 30 min	DBP 45 min	MABP pre-op	MABP 5 min	MABP 10 min	MABP 15 min	MABP 30 min	MABP 45 min	HR pre-op	HR 5min	HR 10 min	HR 15 min	HR 30 min	HR 45 min	Rescue analgesic taken after (min)	VAS score	Weight of gauze pre-op(gm)	Weight of gauze post - op(gm)	ce in weight of gauze pre-op and post op(gm)	Total volume(ml) in the jar at the end of the procedure	Quantity (ml)of normal saline used for irrigation	Volume (ml)of blood lost in suction jar (b)	total blood lost (a+b)	no. of analgesics in 3days
2	1	34	M	3	1	35	120	118	118	120	120	122	78	80	80	80	80	78	92.00	92.67	92.67	93.33	93.33	92.67	70	74	76	75	71	72	180	1	10	37	27	345	300	45	72	6
3	2	35	M	3	1	34	116	120	122	120	122	120	80	82	82	78	82	82	92.00	94.67	95.33	92.00	95.33	94.67	82	80	81	80	78	79	220	2	10	38	28	450	420	30	58	8
4	3	32	F	3	1	38	122	120	122	118	122	120	78	80	80	80	80	80	92.67	93.33	94.00	92.67	94.00	93.33	75	77	75	73	78	76	213	2	11	38	27	445	400	45	72	8
5	4	32	F	3	1	40	118	120	120	118	120	118	80	82	80	78	80	80	92.67	94.67	93.33	91.33	93.33	92.67	83	78	76	82	72	77	176	2	12	40	28	390	350	40	68	9
6	5	32	F	3	1	37	116	118	118	120	120	118	78	82	82	82	82	80	90.67	94.00	94.00	94.67	94.67	92.67	80	78	81	83	76	75	167	1	11	42	31	335	300	35	66	6
7	6	35	M	3	1	42	122	122	120	120	116	118	80	82	80	80	78	82	94.00	95.33	93.33	93.33	90.67	94.00	76	76	75	77	75	79	223	1	11	41	30	335	300	35	65	7
8	7	36	M	3	1	48	116	118	116	116	118	118	76	78	76	74	76	82	89.33	91.33	89.33	88.00	90.00	94.00	72	75	81	77	81	75	245	1	10	40	30	390	350	40	70	7
9	8	35	F	3	1	37	118	122	122	120	120	120	82	80	82	80	82	82	94.00	94.00	95.33	93.33	94.67	94.67	71	72	75	73	78	70	231	3	11	43	32	440	400	40	72	7
10	9	25	M	3	1	36	120	120	122	124	120	118	82	80	82	80	80	76	94.67	93.33	95.33	94.67	93.33	90.00	72	74	75	74	74	71	175	2	10	41	31	385	350	35	66	5
11	10	35	M	3	1	43	118	120	118	122	120	120	80	82	80	80	84	82	92.67	94.67	92.67	94.00	96.00	94.67	76	78	77	80	76	73	179	1	11	41	30	340	300	40	70	8
12	11	33	F	3	1	42	120	122	122	118	122	122	80	82	80	78	78	84	93.33	95.33	94.00	91.33	92.67	96.67	75	69	69	73	72	73	181	1	10	39	29	390	360	30	59	5
13	12	36	M	4.5	2	45	118	118	122	122	120	118	82	82	80	80	80	80	94.00	94.00	94.00	94.00	93.33	92.67	76	77	78	76	71	70	179	1	12	40	28	335	300	35	63	7
14	13	36	F	3	1	39	122	120	120	120	118	118	80	84	82	82	78	82	94.00	96.00	94.67	94.67	91.33	94.00	71	75	76	75	72	72	183	2	12	43	31	345	300	45	76	6
15	14	32	M	3	1	41	116	118	120	118	120	116	84	80	78	82	80	78	94.67	92.67	92.00	94.00	93.33	90.67	73	74	74	75	82	74	183	3	11	41	30	385	350	35	65	7
16	15	33	F	3	1	39	120	120	120	120	118	120	82	80	82	80	82	80	94.67	93.33	94.67	93.33	94.00	93.33	79	80	73	80	73	82	210	1	14	42	28	345	310	35	63	8
17	16	35	F	3	1	40	122	118	122	122	120	122	78	80	82	80	80	80	92.67	92.67	95.33	94.00	93.33	94.00	75	74	76	78	83	81	180	2	12	41	29	395	350	45	74	6
18	17	39	F	3	1	46	118	116	118	120	122	116	80	80	80	82	82	78	92.67	92.00	92.67	94.67	95.33	90.67	71	70	72	78	80	73	203	2	13	42	29	400	380	20	49	7
19	18	42	M	3	1	45	122	122	120	122	120	120	82	80	78	80	80	80	95.33	94.00	92.00	94.00	93.33	93.33	77	78	78	80	72	75	207	3	10	43	33	345	310	35	68	7
20	19	28	F	3	1	45	118	118	122	118	122	122	80	80	80	78	82	80	92.67	92.67	94.00	91.33	95.33	94.00	75	77	80	74	81	76	192	1	11	41	30	340	300	40	70	8
21	20	36	F	3	1	37	122	124	120	120	118	118	78	78	80	82	82	78	92.67	93.33	93.33	94.67	94.00	91.33	78	80	78	72	71	76	199	3	12	40	28	390	350	40	68	6
22	21	33	M	3	1	50	120	118	118	118	118	118	80	80	78	80	80	78	93.33	92.67	91.33	92.67	92.67	91.33	70	71	78	73	75	74	200	2	14	39	25	435	400	35	60	6
23	22	37	F	3	1	53	118	116	120	118	122	118	82	80	80	80	80	80	94.00	92.00	93.33	92.67	94.00	92.67	81	85	75	73	83	78	215	1	10	38	28	385	350	35	63	6
24	23	35	F	3	1	47	120	122	120	120	118	122	76	78	76	74	74	74	90.67	92.67	90.67	89.33	88.67	90.00	80	76	70	75	82	73	176	1	10	40	30	340	300	40	70	6
25	24	36	M	3	1	49	118	120	118	122	122	118	80	80	80	82	80	80	92.67	93.33	92.67	95.33	94.00	92.67	82	72	74	71	77	79	173	1	11	42	31	390	350	40	71	7
26	25	34	M	3	1	52	118	118	118	120	118	120	82	78	80	80	82	80	94.00	91.33	92.67	93.33	94.00	93.33	78	74	75	82	83	79	181	3	10	38	28	335	300	35	63	7
27	26	32	F	3	1	49	122	120	122	120	120	122	78	82	78	80	80	80	92.67	94.67	92.67	93.33	93.33	94.00	71	78	78	73	80	78	193	1	14	41	27	345	300	45	72	8
28	27	31	F	3	1	46	118	118	120	118	124	120	82	80	80	82	82	78	94.00	92.67	93.33	94.00	96.00	92.00	73	78	75	70	74	80	184	3	12	40	28	395	350	45	73	6
29	28	28	M	3	1	45	120	122	120	122	120	122	80	78	84	82	78	80	93.33	92.67	96.00	95.33	92.00	94.00	79	78	87	75	71	71	173	1	14	34	20	335	300	35	55	8
30	29	26	F	3	1	49	120	118	122	118	120	118	78	78	80	80	82	80	92.00	91.33	94.00	92.67	94.67	92.67	78	80	71	72	71	78	211	3	10	39	29	390	350	40	69	7
31	30	24	M	3	1	51	116	118	118	120	118	118	80	78	80	80	82	82	92.00	91.33	92.67	93.33	94.00	94.00	75	72	75	76	77	75	230	2	10	40	30	335	300	35	65	6
32	31	29	M	3	1	53	122	122	120	124	120	118	78	80	78	82	80	80	92.67	94.00	92.00	96.00	93.33	92.67	81	75	75	76	77	82	260	2	11	38	27	385	350	35	62	7
33	32	31	M	3	1	44	120	122	120	122	118	120	80	78	82	80	80	82	93.33	92.67	94.67	94.00	92.67	94.67	76	77	74	73	76	70	271	2	10	42	32	390	350	40	72	6
34	33	25	F	3	1	47	114	114	118	118	116	114	80	80	78	82	82	80	91.33	91.33	91.33	94.00	93.33	91.33	72	78	80	79	81	74	266	2	12	44	32	345	310	35	67	5
35	34	25	M	3	1	48	120	122	122	118	118	120	78	80	80	82	80	78	92.00	94.00	94.00	94.00	92.67	92.00	78	80	81	82	73	80	230	2	12	45	33	495	460	35	68	6
36	35	28	M	3	1	49	122	124	120	120	116	122	78	78	82	82	76	80	92.67	93.33	94.67	94.67	89.33	94.00	80	80	76	75	71	82	244	2	12	39	27	385	360	25	52	6
37	36	26	M	3	1	42	122	120	118	116	120	118	84	80	82	80	80	80	96.67	93.33	94.00	92.00	93.33	92.67	77	80	81	81	75	78	211	1	11	43	32	440	420	20	52	8
38	37	27	F	3	1	47	122	122	120	120	122	122	80	80	78	80	82	80	94.00	94.00	92.00	93.33	95.33	94.00	74	74	74	76	72	75	195	1	10	41	31	440	400	40	71	8
39	38	31	M	3	1	44	120	118	122	118	118	120	82	80	80	78	82	80	94.67	92.67	94.00	91.33	94.00	93.33	75	75	78	77	76	80	254	2	12	40	28	445	400	45	73	7
40	39	33	F	3	1	55	122	122	122	120	120	124	80	80	82	78	80	80	94.00	94.00	95.33	92.00	93.33	94.67	78	70	70	75	72	74	221	3	10	38	28	400	350	50	78	8
41	40	25	M	3	1	39	122	122	118	122	118	122	80	80	80	84	80	80	94.00	94.00	92.67	96.67	92.67	94.00	73	74	73	75	77	78	194	2	12	40	28	340	300	40	68	9
42		31.925		3.0375	1.025	44.2	119.5	119.8	120	119.8	119.6	119.5	79.95	80.05	80.1	80.1	80.25	79.9	93.133	93.3	93.4	93.333	93.367	93.1	75.95	76.075	76.15	76.1	75.975	75.925	205.2	1.8	11.275	40.35	29.075	381.88	344.5	37.375	66.45	6.875

5.5 Lignocaine-Dexamethasone

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN	AO
1	Serial No	Age	Sex	Amount of solution injected	number of injections used	Onset in sec	SBP pre-op	SBP 5min	SBP 10 min	SBP 15 min	SBP 30 min	SBP 45 min	DBP pre-op	DBP 5 min	DBP 10 min	DBP 15 min	DBP 30 min	DBP 45 min	MABP pre-op	MABP 5 min	MABP 10 min	MABP 15 min	MABP 30 min	MABP 45 min	HR pre-op	HR 5min	HR 10 min	HR 15 min	HR 30 min	HR 45 min	Rescue analgesic taken after (hrs)	Rescue analgesic taken after (min)	VAS score	Weight of gauze pre-op(gm)	Weight of gauze post-op(gm)	ce in weight of gauze pre-op and post op(gm)	Total volume(ml) in the jar at the end of the procedure	Quantity (ml)of normal saline used for irrigation	Volume (ml)of blood lost in suction jar (b)	total blood lost (a+b)	no. of analgesics in 3days
2	1	23	F	3	1	81	122	122	120	118	122	120	82	80	82	82	82	82	95.33	94.00	94.67	94.00	95.33	94.67	76	80	77	78	76	81	3.2	192	2	10	38	28	430	395	35	63	6
3	2	41	M	3	1	85	116	114	116	116	118	116	80	82	84	84	84	82	92.00	92.67	94.67	94.67	95.33	93.33	79	78	76	75	74	74	3.2	192	3	12	30	18	300	270	30	48	5
4	3	37	F	3	1	78	112	116	118	122	116	120	82	80	80	82	80	80	92.00	92.00	92.67	95.33	92.00	93.33	77	75	80	76	77	72	3.5	210	1	10	43	33	330	305	25	58	5
5	4	26	M	3	1	85	122	124	120	124	120	124	78	78	84	78	80	80	92.67	93.33	96.00	93.33	93.33	94.67	77	78	73	77	80	76	3.2	192	2	11	38	27	360	335	25	52	6
6	5	25	M	3	1	83	124	122	122	120	124	124	80	82	82	82	80	80	94.67	95.33	95.33	94.67	94.67	94.67	70	72	77	84	78	75	3.3	198	1	10	40	30	350	320	30	60	5
7	6	38	F	3	1	80	116	118	120	124	120	118	82	78	82	82	84	82	93.33	91.33	94.67	96.00	96.00	94.00	72	78	79	77	72	74	3.2	192	2	10	38	28	360	335	25	53	5
8	7	42	F	3	1	76	112	114	120	122	122	120	78	80	82	80	82	82	89.33	91.33	94.67	94.00	95.33	94.67	75	78	83	88	82	81	3.5	210	2	10	40	30	330	290	40	70	6
9	8	27	F	3	1	75	122	120	122	120	120	120	80	78	80	80	82	82	94.00	92.00	94.00	93.33	94.67	94.67	68	73	71	74	73	75	3.2	192	1	11	46	35	440	415	25	60	6
10	9	41	F	3	1	74	120	118	122	122	122	120	78	80	78	78	80	78	92.00	92.67	92.67	92.67	94.00	92.00	76	80	82	79	83	84	3.6	216	1	10	39	29	340	315	25	54	5
11	10	35	F	3	1	79	120	118	120	122	122	120	82	82	80	80	82	82	94.67	94.00	93.33	94.00	95.33	94.67	72	71	70	83	76	72	4.3	258	1	11	41	30	340	310	30	60	6
12	11	27	F	3	1	80	124	122	122	120	124	122	82	78	78	76	76	78	96.00	92.67	92.67	90.67	92.00	92.67	78	76	83	79	80	79	3.8	228	1	10	42	32	300	280	20	52	5
13	12	26	F	3	1	81	118	120	118	118	118	120	78	80	80	80	80	80	91.33	93.33	92.67	92.67	92.67	93.33	77	80	84	82	80	76	3.5	210	1	10	36	26	340	315	25	51	5
14	13	31	F	3	1	76	124	118	118	120	122	122	80	82	82	82	82	82	94.67	94.00	94.00	94.67	95.33	95.33	82	75	80	81	78	82	3.2	192	3	11	36	25	300	275	25	50	6
15	14	35	M	3	1	73	120	118	120	120	122	118	80	82	80	78	82	80	93.33	94.00	93.33	92.00	95.33	92.67	76	80	74	75	72	74	3.2	192	1	10	42	32	350	320	30	62	5
16	15	32	M	3	1	80	120	122	122	120	118	124	80	82	80	82	80	80	93.33	95.33	94.00	94.67	92.67	94.67	78	80	77	76	75	73	3.2	192	2	12	39	27	360	335	25	52	5
17	16	29	M	3	1	83	118	120	122	118	120	120	82	78	78	76	78	78	94.00	92.00	92.67	90.00	92.00	92.00	73	74	77	74	76	84	3.3	198	1	11	38	27	360	335	25	52	6
18	17	26	F	3	1	84	120	122	120	118	118	120	78	76	80	80	78	78	92.00	91.33	93.33	92.67	91.33	92.00	78	80	77	74	76	76	3.2	192	2	10	35	25	350	325	25	50	5
19	18	26	F	3	1	76	124	118	118	122	120	120	80	82	78	78	82	80	94.67	94.00	91.33	92.67	94.67	93.33	79	78	76	78	80	78	3.3	198	2	12	42	30	350	320	30	60	5
20	19	35	M	3	1	78	118	122	120	118	122	120	82	82	82	82	80	78	94.00	95.33	94.67	94.00	94.00	92.00	77	78	76	73	73	74	3.2	192	1	10	42	32	400	370	30	62	5
21	20	32	M	3	1	82	118	120	118	120	120	120	82	80	82	82	80	78	94.00	93.33	94.00	94.67	93.33	92.00	75	76	78	73	77	78	3.4	204	2	11	38	27	430	405	25	52	5
22	21	30	M	3	1	81	124	122	120	122	116	118	78	76	80	82	80	80	93.33	91.33	93.33	95.33	92.00	92.67	74	75	72	73	74	78	3.2	192	2	12	44	32	300	275	25	57	6
23	22	35	M	3	1	79	122	122	120	120	118	122	82	78	78	78	76	80	95.33	92.67	92.00	92.00	90.00	94.00	76	76	75	76	71	75	3.5	210	3	10	42	32	330	300	30	62	6
24	23	36	M	3	1	80	120	118	118	118	118	120	80	80	80	82	82	82	93.33	92.67	92.67	94.00	94.00	94.67	77	75	81	77	76	70	3.6	216	1	11	39	28	360	335	25	53	6
25	24	29	M	3	1	82	118	120	118	116	116	116	82	78	80	78	76	82	94.00	92.00	92.67	90.67	89.33	93.33	78	75	75	75	77	73	3.5	210	3	12	42	30	350	320	30	60	5
26	25	30	M	3	1	79	116	120	118	122	116	116	80	82	80	80	80	80	92.00	94.67	92.67	94.00	92.00	92.00	80	81	80	78	76	75	4.1	246	1	13	43	30	360	330	30	60	7
27	26	32	M	3	1	75	120	122	118	120	122	120	82	78	80	80	82	78	94.67	92.67	92.67	93.33	95.33	92.00	76	78	76	76	77	78	4.2	252	1	10	45	35	350	325	25	60	5
28	27	35	M	4.5	2	74	124	120	120	120	120	120	78	80	76	78	80	80	93.33	93.33	90.67	92.00	93.33	93.33	78	76	77	78	75	81	3.4	204	3	10	40	30	400	370	30	60	6
29	28	36	M	3	1	80	118	120	122	118	122	118	80	82	78	76	76	80	92.67	94.67	92.67	90.00	91.33	92.67	79	75	78	78	77	81	3.2	192	1	10	40	30	300	270	30	60	5
30	29	35	F	3	1	81	120	122	118	120	122	118	82	80	80	82	82	80	94.67	94.00	92.67	94.67	95.33	92.67	78	76	77	74	73	71	3.4	204	2	10	40	30	350	320	30	60	5
31	30	33	M	3	1	81	124	122	122	120	122	120	78	80	78	82	78	78	93.33	94.00	92.67	94.67	92.67	92.00	77	76	75	76	76	72	3.2	192	1	12	47	35	380	345	35	70	6
32	31	29	M	3	1	73	122	120	118	120	120	120	80	78	82	82	80	80	94.00	92.00	94.00	94.67	93.33	93.33	76	75	73	73	74	75	3.1	186	1	11	41	30	300	270	30	60	5
33	32	35	M	3	1	72	124	120	122	118	120	122	80	82	80	80	82	82	94.67	94.67	94.00	92.67	94.67	95.33	78	75	77	71	82	74	3.5	210	2	10	47	37	300	275	25	62	6
34	33	34	F	3	1	76	118	116	120	122	124	118	78	82	78	76	76	78	91.33	93.33	92.00	91.33	92.00	91.33	73	76	74	71	72	80	3.2	192	2	10	40	30	350	320	30	60	5
35	34	36	F	3	1	75	120	122	118	122	122	120	80	82	82	82	82	80	93.33	95.33	94.00	95.33	95.33	93.33	76	78	78	78	81	82	4	240	1	10	43	33	360	335	25	58	6
36	35	26	M	3	1	71	116	118	122	116	116	122	82	82	78	82	78	82	93.33	94.00	92.67	93.33	90.67	95.33	78	80	75	74	76	76	3.8	228	1	10	43	33	360	320	40	73	6
37	36	24	M	3	1	72	118	120	122	118	116	118	78	80	80	82	80	80	91.33	93.33	94.00	94.00	92.00	92.67	78	77	78	78	74	72	3.6	216	1	12	44	32	320	285	35	67	5
38	37	25	M	3	1	81	116	118	118	118	122	118	78	82	84	80	80	80	90.67	94.00	95.33	92.67	94.00	92.67	76	72	78	74	81	74	3.2	192	3	10	42	32	350	315	35	67	5
39	38	36	M	3	1	80	122	122	122	122	118	120	80	78	82	82	80	82	94.00	92.67	95.33	95.33	92.67	94.67	77	80	71	72	76	81	3.2	192	1	12	45	33	380	345	35	68	6
40	39	34	M	3	1	71	118	120	122	120	118	120	80	82	78	78	80	78	92.67	94.67	92.67	92.00	92.67	92.00	77	79	74	73	73	70	3.9	234	2	11	41	30	300	260	40	70	6
41	40	37	M	3	1	72	120	122	120	122	120	122	82	80	78	78	78	78	94.67	94.00	92.00	92.67	92.00	92.67	76	75	74	73	73	72	3.1	186	2	10	42	32	350	315	35	67	6
42		32.025		3.0375	1.025	78.1	119.75	119.85	119.9	119.95	119.95	119.9	80.15	80.1	80.15	80.1	80.05	80.05	93.35	93.35	93.4	93.383	93.35	93.333	76.325	76.75	76.7	76.35	76.3	76.2	3.435	206.1	1.65	10.7	40.825	30.125	349.25	320	29.25	59.375	5.5

5.6 Lignocaine-CPM

Serial No	Age	Sex	Amount of solution injected	number of injections used	Onset in sec	SBP pre-op	SBP 5min	SBP 10 min	SBP 15 min	SBP 30 min	SBP 45 min	DBP pre-op	DBP 5 min	DBP 10 min	DBP 15 min	DBP 30 min	DBP 45 min	MABP pre-op	MABP 5 min	MABP 10 min	MABP 15 min	MABP 30 min	MABP 45 min	HR pre-op	HR 5min	HR 10 min	HR 15 min	HR 30 min	HR 45 min	Rescue analgesic taken after (min)	VAS score	Weight of gauze pre-op(gm)	Weight of gauze post-op(gm)	ce in weight of gauze pre-op and post op(gm)(	Total volume(ml) in the jar at the end of the procedure	Quantity (ml)of normal saline used for irrigation	Volume (ml)of blood lost in suction jar (b)	total blood lost (a+b)	no. of analgesics in 3days
1	29	M	3.5	1	226	120	120	118	116	116	122	82	82	82	78	80	78	94.67	94.67	94.00	90.67	92.00	92.67	75	76	78	73	75	78	120	4	10	33	23	345	310	35	58	3
2	27	M	3.5	1	241	124	122	118	118	120	122	78	80	80	82	80	80	93.33	94.00	92.67	94.00	93.33	94.00	74	75	74	87	82	78	180	4	11	41	30	340	310	30	60	6
3	28	M	4.5	2	216	122	122	118	122	124	122	82	82	82	80	78	80	95.33	95.33	94.00	94.00	93.33	94.00	76	76	78	78	85	75	120	6	12	40	28	390	360	30	58	3
4	24	M	4.5	2	212	120	120	118	118	118	120	80	80	80	82	82	82	93.33	93.33	92.67	94.00	94.00	94.67	77	79	73	72	73	70	210	3	14	39	25	435	400	35	60	6
5	36	F	4.5	2	216	118	124	116	118	114	120	82	78	82	80	78	76	94.00	93.33	93.33	92.67	90.00	90.67	78	75	82	80	82	73	180	4	10	38	28	385	350	35	63	3
6	40	F	3.5	1	203	116	120	114	120	120	122	80	76	80	78	80	80	92.00	90.67	91.33	92.00	93.33	94.00	80	75	77	77	76	75	200	5	10	40	30	340	310	30	60	5
7	33	F	4.5	2	221	120	122	114	118	120	120	82	76	80	80	82	78	94.67	91.33	91.33	92.67	94.67	92.00	76	76	75	82	81	78	120	6	11	42	31	390	360	30	61	4
8	40	M	3.5	1	223	124	120	120	122	126	120	78	76	76	78	82	80	93.33	90.67	90.67	92.67	96.67	93.33	78	75	77	78	83	81	180	4	10	38	28	335	300	35	63	4
9	33	F	4.5	2	218	118	116	122	118	122	122	80	78	76	76	78	78	92.67	90.67	91.33	90.00	92.67	92.67	79	75	78	77	78	81	120	5	14	41	27	345	315	30	57	4
10	31	M	3.5	1	220	120	122	116	118	122	124	82	78	80	82	82	80	94.67	92.67	92.00	94.00	95.33	94.67	78	77	74	82	83	71	120	4	12	40	28	395	360	35	63	3
11	20	F	4.5	2	212	124	122	116	116	122	120	78	76	76	80	78	80	93.33	91.33	89.33	92.00	92.67	93.33	77	83	82	86	86	82	180	6	14	34	20	335	300	35	55	5
12	30	F	3.5	1	214	122	120	122	120	122	124	80	78	76	82	80	80	94.00	92.00	91.33	94.67	94.00	94.67	76	73	75	82	81	75	120	5	10	39	29	390	350	40	69	3
13	27	M	4.5	2	231	124	120	118	116	126	122	80	78	80	80	82	82	94.67	92.00	92.67	92.00	96.67	95.33	78	75	77	73	74	74	150	2	10	40	30	335	300	35	65	4
14	28	F	3.5	2	230	118	116	114	118	124	124	78	80	76	76	80	80	91.33	92.00	88.67	90.00	94.67	94.67	73	76	73	71	72	80	120	4	11	41	30	340	300	40	70	5
15	25	F	3.5	1	216	120	118	116	122	122	124	80	78	82	80	82	80	93.33	91.33	93.33	94.00	95.33	94.67	76	78	78	78	72	82	140	4	14	48	34	390	360	30	64	4
16	24	M	4.5	2	218	122	120	118	118	122	122	82	78	78	78	78	78	95.33	92.00	91.33	91.33	92.67	92.67	78	80	77	76	75	76	120	4	12	40	28	335	300	35	63	3
17	36	F	3.5	1	221	118	120	118	114	124	118	78	80	82	82	80	80	91.33	93.33	94.00	92.67	94.67	92.67	78	82	78	79	73	85	150	4	12	43	31	345	310	35	66	4
18	35	F	3.5	1	228	120	120	118	118	122	114	78	82	76	78	76	80	92.00	94.67	90.00	91.33	91.33	91.33	76	72	78	77	76	74	120	3	11	40	29	385	350	35	64	3
19	42	F	3.5	1	231	122	122	122	122	122	120	80	82	80	78	80	82	94.00	95.33	94.00	92.67	94.00	94.67	77	80	77	76	75	81	180	4	10	42	32	345	310	35	67	4
20	35	M	3.5	1	217	120	120	118	120	122	120	80	80	76	78	80	80	93.33	93.33	90.00	92.00	94.00	93.33	77	76	81	74	73	70	120	5	12	41	29	395	360	35	64	5
21	37	M	3.5	1	243	120	122	120	122	126	122	82	78	76	78	76	82	94.67	92.67	90.67	92.67	92.67	95.33	76	73	73	72	73	82	180	4	13	42	29	400	380	20	49	3
22	34	M	3.5	1	231	122	120	118	120	120	120	80	82	80	82	82	82	94.00	94.67	92.67	94.67	94.67	94.67	72	76	77	75	74	72	140	4	14	43	29	345	310	35	64	4
23	28	M	3.5	1	230	122	124	116	118	124	116	76	78	80	82	80	80	91.33	93.33	92.00	94.00	94.67	92.00	82	71	74	72	73	72	200	4	11	41	30	340	310	30	60	3
24	28	F	4	2	217	120	120	118	120	122	120	78	76	78	80	78	78	92.00	90.67	91.33	93.33	92.67	92.00	73	78	76	73	78	70	190	2	12	40	28	390	350	40	68	4
25	32	M	3.5	1	221	118	120	120	118	120	120	82	80	82	78	78	78	94.00	93.33	94.67	91.33	92.00	92.00	80	76	76	75	73	78	200	2	14	40	26	435	400	35	61	5
26	36	M	4	2	221	122	118	120	116	120	118	80	80	80	80	80	80	94.00	92.67	93.33	92.00	93.33	92.67	74	75	75	74	75	75	140	4	10	40	30	385	350	35	65	4
27	22	M	3.5	1	231	124	122	116	116	120	118	82	82	82	78	82	82	96.00	95.33	93.33	90.67	94.67	94.00	72	76	74	71	71	76	140	5	14	40	26	340	300	40	66	3
28	40	M	3.5	1	217	116	118	114	112	120	118	76	78	80	80	80	80	89.33	91.33	91.33	90.67	93.33	94.00	72	73	72	77	73	75	160	4	11	38	27	390	350	40	67	3
29	25	M	4	2	216	118	118	116	118	18	120	82	80	76	80	82	82	94.00	92.67	89.33	92.67	60.67	94.67	71	72	75	73	78	70	120	5	10	38	28	335	300	35	63	4
30	31	M	3.5	1	232	122	120	116	120	120	118	82	80	82	78	76	78	95.33	93.33	93.33	92.00	90.67	91.33	72	74	75	74	74	71	120	5	11	45	34	345	300	45	79	4
31	32	F	4	2	216	120	120	122	118	126	120	80	82	80	80	78	82	93.33	94.67	94.00	92.67	94.00	94.67	76	78	73	72	71	73	120	4	12	45	33	395	350	45	78	4
32	31	F	3.5	1	241	120	122	116	116	122	122	80	78	80	76	78	78	93.33	92.67	92.00	89.33	92.67	92.67	75	69	69	70	72	73	110	6	11	43	32	440	400	40	72	5
33	22	M	3.5	1	234	118	118	122	118	120	118	82	82	78	80	80	80	94.00	94.00	92.67	92.67	93.33	92.67	76	77	78	76	71	70	120	5	10	38	28	440	410	30	58	4
34	28	F	3.5	1	249	118	118	122	118	122	118	80	78	76	82	78	82	92.67	91.33	91.33	94.00	92.67	94.00	71	75	76	75	72	72	140	4	12	45	33	445	410	35	68	4
35	26	M	3.5	1	245	120	118	120	120	122	116	84	80	76	78	76	80	96.00	92.67	90.67	92.00	91.33	92.00	72	74	74	74	73	74	130	4	10	40	30	400	370	30	60	5
36	25	M	4	2	233	120	122	118	118	122	120	82	80	78	80	82	80	94.67	94.00	91.33	92.67	95.33	93.33	79	80	73	72	73	82	160	6	12	44	32	340	300	40	72	5
	30.556		3.7917	1.3889	224.75	120.33	120.17	118	118.33	118.72	120.17	80.222	79.222	79	79.444	79.556	80	93.593	92.87	92	92.407	92.611	93.389	75.833	75.861	75.889	75.917	75.806	75.667	147.78	4.2778	11.583	40.611	29.028	373.89	339.03	34.861	63.889	4.0278

Appendix 6

PUBLICATIONS

Comparative Evaluation of Effectiveness of 2% Lignocaine Hydrochloride with Clonidine Hydrochloride versus 2% Lignocaine Hydrochloride with Adrenaline Bitartrate as Local Anesthetic for Adult Patients Undergoing Surgical Extraction of Impacted Mandibular Third Molars: A Randomized Controlled Clinical Study

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Abstract

Background and Objectives: Clonidine is a common additive to local anesthetics for various regional and local nerve blocks. However, its effectiveness in dentistry has not yet been fully explored. Thus, this study was performed to evaluate the quality of anesthesia, vasoconstrictive effect, hemodynamic response, and pain control using a solution of 2% lignocaine hydrochloride with clonidine hydrochloride in comparison with the standard solution of 2% lignocaine hydrochloride and adrenaline bitartrate for pterygomandibular nerve blocks. Materials and Methods: A parallel arm, triple-blind randomized controlled study was conducted on 152 patients belonging to ASA-I (American Society of Anesthesiologist) category in the age group of 18–45 years, requiring surgical extraction of impacted mandibular third molars. The patients were divided equally into two groups randomly by computer-generated sequence; Group 1: 2% lignocaine hydrochloride with 1 ml of clonidine hydrochloride (150 μg/ml) and Group 2: 2% lignocaine hydrochloride with adrenaline bitartrate 1: 80,000 (12.5 μg/ml). The variables evaluated were systolic, diastolic, and mean arterial blood pressure, heart rate (HR,) blood loss, onset, depth (pain), and duration of anesthesia. Results: There was a statistically nonsignificant difference seen between the two groups ($P > 0.05$) for the onset of anesthesia, pain assessed, and blood loss, whereas a statistically highly significant difference was seen for cardiovascular variables (systolic, diastolic and mean arterial blood pressure, and HR) at various intervals with higher values for Group 2 ($P < 0.001$) and for the duration of action of local anesthesia (LA), with higher values for Group 1 ($P < 0.001$). Conclusions: Clonidine as an additive to lignocaine has proved to have the onset of action, vasoconstrictive properties, and pain control, equivalent to adrenaline. However, with better stability of hemodynamic variables and prolonged duration of action of LA with clonidine, it can be considered as a better, safer, and more effective additive to lignocaine than adrenaline.

Keywords: *Additives, adrenaline, clonidine, hemodynamic variables, local anesthetics*

Introduction

The eternal quest for pain control has stimulated researchers globally for innovation in the field of local anesthesia (LA). The importance of LA cannot be overstated in today's surgical and dental procedures.

The most commonly used local anesthetic agent in dentistry is lignocaine hydrochloride. However, due to its vasodilator properties,[1-4] a vasoconstrictor needs to be added to prolong duration of anesthetic action, to reduce systemic absorption, thereby reducing the systemic toxicity of lignocaine and to provide hemostasis. Adrenaline, a potent vasoconstrictor, serves to achieve these effects![1-4] The commonly available local anesthetic solutions contain adrenaline bitartrate in different concentrations, ranging from 12.5 μg/ml (1:80,000) to 5 μg/ml (1:200,000). Even with small doses of adrenaline, there are significant cardiovascular changes in both healthy and cardiac patients![5,6] Hence, it is prudent to limit or avoid adrenaline in poorly

Submitted : 22-Jul-2020
Revised : 29-Jul-2020
Accepted : 01-Aug-2020
Published : 21-Sep-2021

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Access this article online
Website: www.contemporarydentistry.org
DOI: 10.4103/ccd.ccd_686_20
Quick Response Code:

How to cite this article: Gupte SH, Kalra RD, Dcruz TM, Kamble S, Patnaik RS. Comparative evaluation of effectiveness of 2% lignocaine hydrochloride with clonidine hydrochloride versus 2% lignocaine hydrochloride with adrenaline bitartrate as local anesthetic for adult patients undergoing surgical extraction of impacted mandibular third molars: A randomized controlled clinical study. Contemp Clin Dent 2021;12:308-12.

controlled American Society of Anesthesiologists (ASA)-III and all ASA-IV group of patients.[11] The use of various additives other than adrenaline has been tested in the literature for various regional and local nerve blocks.

Clonidine is both centrally and peripherally acting, selective α-2 adrenoceptor agonist.[14] By central activation of presynaptic, α-2 adrenoceptors, it decreases blood pressure and provides central analgesic activity.[11] Through peripheral activation, peripheral blood vessel vasoconstriction is achieved.[14] Clonidine has been safely used as an additive to anesthetics for a number of regional blocks in adults as well as pediatric age group. Its use in dentistry has still not been thoroughly explored.

The aim of the present clinical study was to evaluate the effectiveness of 2% lignocaine with clonidine versus 2% lignocaine with adrenaline for surgical removal of impacted mandibular third molars. The study tested the null hypothesis which stated that there is no difference in the effectiveness of 2% lignocaine with clonidine and 2% lignocaine with adrenaline in surgical removal for impacted mandibular third molars, for the outcome variables – quality of anesthesia, vasoconstriction effects, hemodynamic response, and pain control.

Materials and Methods

The study design was parallel arm, triple-blind randomized control clinical study, carried out in the Department of Oral and Maxillofacial Surgery at our tertiary care center. The sample size was calculated using the formula, $n = 2 (Z\alpha + Z\beta)^2 [s]^2/d^2$, where $Z\alpha$ is the z variate of alpha error, i.e., a constant with value 1.96, $Z\beta$ having a value of 0.84, considering the mean and standard deviation (SD) from the literature, that concluded approximately 76 patients per group. Approval from the Institutional Ethics Committee was obtained (no. YMTDCH/IEC/OUT/072/2017).

The inclusion criteria were ASA-I patients, between the age group of 18 and 45 years, requiring surgical extraction of impacted mandibular third molars under LA with no history of allergy to the drugs used in this research. The exclusion criteria included pregnant women, lactating mothers, any previous history of cardiovascular conditions, apprehensive patients, and patients with active orofacial infections. Patients with any other contraindication or on any medication that could possibly interact with clonidine/adrenaline were also excluded from the study. It was made sure that the study participants had not been on any medications preoperatively (1 week). Using the above, participants were randomly selected from patients requiring surgical removal of impacted mandibular third molars under LA and randomly allocated to either group by computer-generated sequence. Informed written consent was obtained from all study participants.

In the test group/Group 1, freshly prepared solution made with 9 ml of plain 2% lignocaine with 1 ml of clonidine (150 μg/ml) was used, whereas in the control group/Group 2, a standard solution of 2% lignocaine with adrenaline 1:80,000 (12.5 μg/ml) was used. The entire study was carried out by single operator and single observer who were standardized and blinded. Pterygomandibular nerve blocks were used in all cases with mandatory negative aspiration preinjection. The difficulty index of the impacted mandibular third molars was standardized as moderate level (5–7) as per Pederson's Difficulty Index[11] for both groups.

The outcome variables measured and studied were (a) cardiovascular variables (systolic blood pressure [SBP], diastolic blood pressure [DBP], mean arterial blood pressure [MABP], and heart rate [HR]) and blood loss and (b) quality of anesthesia assessed by onset, duration, and its depth. The cardiovascular variables were measured using a multiparameter monitor (IntelliVue MX 400, Philips, with more than 95% accuracy), just before LA injection and repeated at intervals of 5 min, 10 min, 15 min, 30 min, and 45 min after injection. The estimated volume of blood loss was calculated by subtracting the total quantity of normal saline used for irrigation from the total volume of fluid collected in the suction jar after the procedure. In addition to this, the difference in preoperative and postoperative weights of the used gauze pieces was also used to determine the volume of blood loss. The onset of anesthesia (in minutes) was assessed by subjective and objective symptoms of LA. The duration (in minutes) was recorded from the completion of the pterygomandibular nerve block till the first oral analgesic used by the patient. The depth of anesthesia was evaluated using the visual analog scale (VAS) to determine degree of pain during the procedure.

Statistical procedures

Data obtained were compiled on a MS Office Excel Sheet (v 2010, Microsoft Redmond Campus, Redmond, Washington, United States) and were subjected to statistical analysis using the Statistical Package for the Social Sciences (SPSS v 21.0, IBM). Descriptive statistics such as frequencies and percentage for categorical data and mean and SD for numerical data have been depicted. The normality of numerical data was checked using the Shapiro–Wilk test and was found that the data followed a normal curve; hence, parametric tests have been used for comparisons. Intergroup comparison was done using *t*-test, whereas intragroup comparison up to two observations was done using paired *t*-test. Intragroup comparison was done using repeated measures ANOVA (for >2 observations), followed by *post hoc* test. The comparison of frequencies of categories of variables with groups was done using Chi-square test. For all the statistical tests, $P < 0.05$ was considered to be statistically significant, keeping α error at 5% and β error at 20%, thus giving a power to the study as 80%.

Results

The mean age of the patients was 31.71 + 4.602 (minimum 21 and maximum 45). There were 55 (36.2%) females and 97 (63.8%) male patients.

Intergroup comparison of the mean age of the patients showed a statistically nonsignificant difference ($p > 0.05$) which also ruled out age as a confounding factor. Furthermore, the intergroup comparison of frequencies of sex of the patients showed a statistically nonsignificant difference ($p > 0.05$).

Discussion

Clonidine hydrochloride has been used in different concentrations for improvement of epidural anesthesia, brachial plexus anesthesia, and anesthesia for peripheral nerves. These studies proved and gave effective concentrations at which no significant side effects were observed[9-11] Our study investigated the effectiveness of clonidine hydrochloride in concentration of 1.50 μg/ml when used with 2% lignocaine hydrochloride for pterygomandibular nerve blocks for surgical extractions of impacted mandibular third molars.

The time from completion of nerve block to postoperative consumption of the first analgesic was considered duration of action of LA. It was observed that the average value in the test group was 4 h 42 min (282.53 min), whereas it was 3 h 5 (185.42) min in the control group, both statistically and clinically highly significant. [Table 1], thereby proving that clonidine was more effective in prolonging the duration of action of LA, in comparison with adrenaline. Multiple research papers by Patil *et al.*,[9] Rajkumar *et al.*,[10] and Brkovic *et al.*[11] showed findings consistent with our study.

The onset of anesthesia is a property that mainly depends on the local anesthetic rather than vasoconstrictor.[12-14] In our study, 2% lignocaine was used as a local anesthetic in both the groups, thus the onset of anesthesia was similar and both clinically and statistically nonsignificant. These findings of onset of anesthesia were consistent with the study done by Brkovic *et al.*,[11] Pawan Patil *et al.*,[9] and Chowdhury *et al.*[14]

The cardiovascular variables, SBP, DBP, MABP, and HR, showed a higher statistical significance between the two groups at all time intervals [Table 2]. This suggested that clonidine as compared to adrenaline provides hemodynamic stability after LA injection. The values recorded for HR were significantly stable in the test group. Unlike adrenaline, which is a nonselective alpha and beta agonist, clonidine exhibits a selective α-2 agonist activity without beta side effects on the myocardium, thus leading to no significant fluctuations in HR.[14] Dandriyal *et al.*[15] demonstrated a statistically significant difference between SBP and HR within the two groups, whereas DBP did not show any statistical significance.

The assessment of intragroup cardiovascular variables in each group at different time intervals was done using Scheffe *post hoc* test. In the study group, no statistical significance was seen, indicating stability in blood pressure and HR at various time intervals. In the control group, a statistically significant difference was seen at different time intervals, indicating the recordings to be highly fluctuant. This supports the view that clonidine is a safer and better alternative to adrenaline in terms of maintaining cardiovascular variables.

Table 1: Intergroup comparison of onset, duration, depth, and vasoconstrictive effects of local anesthesia

	Group	*n*	Mean	SD	SEM	*t*	*P* of *t*-test
Onset of local anesthesia (min)	1	75	4.80	0.401	0.046	1.142	0.255*
	2	75	4.72	0.450	0.052		
Completion of nerve block to first analgesic (min)	1	75	282.53	25.219	2.893	24.087	0.000**
	2	75	185.42	20.422	2.343		
VAS score (intraoperative)	1	75	2.506	0.5976	0.0800	−0.731	0.466*
	2	75	2.588	0.5772	0.0776		
Weight of gauze preoperative (g)	1	75	10.51	2.176	0.250	−0.240	0.811*
	2	75	10.58	0.997	0.114		
Weight of gauze postoperative (g)	1	75	12.45	2.294	0.263	−0.137	0.892*
	2	75	12.49	1.039	0.119		
Difference in weight of gauze pre- and postoperative (g)	1	75	1.93	0.957	0.110	0.187	0.852*
	2	75	1.91	0.769	0.088		
Total volume in the jar at the end of the procedure in ml (a)	1	75	441.82	101.949	11.694	7.137	0.000**
	2	75	346.58	55.367	6351		
Quantity of normal saline used for irrigation in ml (b)	1	75	364.71	107.913	12379	6.241	0.000**
	2	75	278.16	54.521	6.254		
Volume of blood loss (a-b ml)	1	75	75.79	32.351	3.711	1.489	0.139*
	2	75	68.95	23.641	2.712		

SD: Standard deviation, SEM: Standard error of mean, VAS: Visual Analog Scale, **Means highly significant, *Means nonsignificant

Table 2: Intergroup comparison of cardiovascular variables

	Group	N	Mean	SD	SEM	t	P of t test
SBP preoperative	1	75	122.49	6.807	0.781	−5.458	0.000**
	2	75	127.30	3.476	0.399		
SBP 5 min	1	75	118.36	5.085	0.583	−32.485	0.000**
	2	75	140.89	3.207	0.368		
SBP 10 min	1	75	118.32	5.076	0.582	−39.324	0.000**
	2	75	144.38	2.761	0.317		
SBP 15 min	1	75	119.84	3.966	0.455	−40.137	0.000**
	2	75	144.03	4.073	0.467		
SBP 30 min	1	75	117.22	6.090	0.699	−27.141	0.000**
	2	75	139.59	3.813	0.437		
SBP 45 min	1	75	121.05	5.356	0.614	−17.566	0.000**
	2	75	133.24	2.503	0.287		
DBP preoperative	1	75	80.70	7.135	0.818	−1.942	0.054#
	2	75	82.53	4.061	0.466		
DBP 5 min	1	75	74.24	8.472	0.972	−13.091	0.000**
	2	75	92.46	4.266	0.489		
DBP 10 min	1	75	77.42	6.587	0.756	−18.908	0.000**
	2	75	94.79	6.030	0.692		
DBP 15 min	1	75	78.53	5.934	0.681	−27.066	0.000**
	2	75	102.32	4.848	0.556		
DBP 30 min	1	75	77.37	4.841	0.555	−21.229	0.000**
	2	75	95.76	5.799	0.665		
DBP 45 min	1	75	78.41	5.335	0.612	−14.441	0.000**
	2	75	88.39	3.056	0.351		
MABP preoperative	1	75	41.79	3.645	0.418	−5.515	0.000**
	2	75	44.38	3.000	0.344		
MABP 5 min	1	75	42.20	5.007	0.574	−6.933	0.000**
	2	75	48.24	5.711	0.655		
MABP 10 min	1	75	40.89	4.163	0.478	−8.509	0.000**
	2	75	47.39	5.453	0.626		
MABP 15 min	1	75	41.33	5.749	0.659	−2.369	0.019*
	2	75	43.43	5.193	0.596		
MABP 30 min	1	75	39.56	4.916	0.564	−4.019	0.000**
	2	75	43.88	6.801	0.780		
MABP 45 min	1	75	42.44	3.999	0.459	−2.869	0.004**
	2	75	44.44	4.492	0.515		
HR preoperative	1	75	82.75	10.172	1.167	2.607	0.010*
	2	75	79.28	5.613	0.644		
HR 5 min	1	75	75.33	9.266	1.063	−10.050	0.000**
	2	75	88.46	6.626	0.760		
HR 10 min	1	75	75.37	9.941	1.140	−12.210	0.000**
	2	75	92.72	7.398	0.849		
HR 15 min	1	75	76.21	7.387	0.847	−23.248	0.000**
	2	75	99.00	4.066	0.466		
HR 30 min	1	75	74.41	5.317	0.610		
	2	75	92.30	8.495	0.974	−15.566	0.000**
HR 45 min	1	75	77.36	4.598	0.527	−6.114	0.000**
	2	75	83.43	7.347	0.843		

*Statistically significant difference ($P<0.05$), **Statistically highly significant difference ($P<0.01$) #Non-significant difference ($P>0.05$) …for both tables. SD: Standard deviation, SEM: Standard error of mean, SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MABP: Mean arterial blood pressure; HR: Heart rate

Two indirect methods, namely suction jar and gauze method were used to compute and assess the vasoconstrictive property of clonidine and adrenaline. With both methods, the calculated amount of blood loss was marginally higher

for the clonidine group. However, there was no statistically significant difference between the two groups. Thus, the vasoconstrictive property of clonidine is equivalent to adrenaline. Patil *et al.* in their study concluded that clonidine could be used as a safer alternative to adrenaline considering the vasoconstrictive property.[11]

The VAS scale was used intraoperatively to evaluate the depth and intensity of LA. Although VAS scores in the clonidine group presented lower values, there was no statistical significance between the two groups. Eisenach *et al.*[12] showed a similar finding on the intensity of anesthesia when evaluated with the VAS scale.

Limitations and future scope

We had to restrict this study to ASA-I category patients based on approval from the Institutional Ethics Committee. However, more studies may be designed with larger sample sizes and including patients in ASA-II, III, and IV categories. Effects of addition of clonidine to LA may be tested with other anesthetic agents and for other orofacial nerve blocks.

Conclusions

Based on the aforementioned results of the current study, it can be concluded that clonidine as an additive to lignocaine is a better, safer, and more effective alternative to adrenaline as it maintains hemodynamic variables stable and prolongs the duration of LA effect without affecting the onset and depth of anesthesia.

Acknowledgment

We profoundly thank Dr. Milind Nayak, Associate Professor, Department of Anesthesiology, YMTD CH, Navi Mumbai, for his valuable contribution towards this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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J Oral Med Oral Surg 2021; 27: 56
https://www.jomos.org
JOMOS
© The authors, 2021
https://doi.org/10.1051/mbcb/2021017

Original Research Article

Comparative evaluation of effectiveness of 2% lignocaine hydrochloride with 1.5% potassium chloride *versus* 2% lignocaine hydrochloride with adrenaline bitartrate *versus* 2% lignocaine hydrochloride as local anaesthetic for adult patients undergoing surgical extraction of impacted mandibular third molars: a randomized controlled clinical study

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(Received: 25 April 2021, accepted: 9 June 2021)

Keywords: Local anaesthetics / lignocaine / potassium chloride / adrenaline / pterygomandibular nerve block

Abstract Background and objectives: Administration of some additives with local anesthetics can prolong pain free period post operatively, thereby reducing need for post operative analgesics and improving patient comfort. Potassium chloride was found to increase duration and quality of anesthesia in various studies on brachial plexus blockade. This study was designed to evaluate and compare the effect of 2% lignocaine with 1.5% potassium chloride, 2% lignocaine with adrenaline and 2% lignocaine (plain) in pterygomandibular nerve blocks. Materials and methods: A triple blind randomized controlled study was conducted on 120 adults, aged 18–46 years in ASA I category, requiring surgical extraction of impacted mandibular third molars. The subjects were divided equally into 3 groups randomly by computer generated sequence; Group 1: 2% lignocaine plus 1.5% solution of potassium chloride, group 2: 2% lignocaine with 1:80,000 adrenaline and group 3: 2% plain lignocaine. Onset, duration, depth (pain) of anesthesia, patient satisfaction, systolic and diastolic blood pressures, heart rate and oxygen saturation, were evaluated and compared. Results: Onset was shortest for group1 and longest for grp3, statistically highly significant difference between the 3 groups ($p < 0.01$). Statistically significant difference ($p < 0.05$) was found in duration of surgery, duration of analgesia and VAS scores between groups 1 & 3. Duration and depth of anesthesia were comparable for groups 1 & 2. There was no statistically significant difference seen for total amount of dose used, SBP, DBP, HR and SpO_2 between the 3 groups ($p > 0.05$). Conclusion: Potassium chloride, a physiological salt is inert and causes no local/systemic adverse effects when injected with lignocaine in physiologically permissible amounts. The combination achieves satisfactory onset, duration, depth of anesthesia without altering hemodynamic variables. Hence, it may be considered as a safe and effective additive.

Introduction

Achieving better, prolonged and deeper regional anesthesia with prolonged post-operative pain control is one of the therapeutic goals for every clinician. Local anesthetic (LA) agents have an inherent vasodilatory effect and when used alone, provide limited duration of action, not so profound sensory block and probable risk of systemic toxicity. In an attempt to counter these, vasoconstrictors like adrenaline (Adr) are commonly added to LA. However, due to detrimental systemic effects of vasoconstrictors and limited permissible dose in patients with certain systemic conditions, many pharmacological agents like opioids, clonidine, neostigmine, hyaluronidase, dexamethasone, sodium bicarbonate, magnesium sulphate, etc. have been tried as additives to anesthetic agents for various regional nerve blocks [1].

Potassium salts have been shown to possess local anesthetic potency which is almost similar to that of procaine, when tested under experimental conditions [2]. It has been stated that, toxicity of LA can be reduced by adding potassium salts, since, the amount of LA required to produce a desired degree of anesthesia is reduced [2].

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Potassium Chloride (KCl) is a physiologic salt, inert, compatible with lignocaine. Addition of KCl to LA increases the extracellular concentration of K^+, depolarizes nerve membrane and blocks the conduction of nerve impulses thereby, shortening the onset, improving quality and duration of anesthesia, without causing any adverse effect on the hemodynamic status of the individual. [3].

Several authors have reported use of KCl as an additive with various LAs for brachial plexus blockade [4–6]. Not many studies have reported the use of KCl as an additive with lignocaine for anesthesia in the maxillofacial region. Tsinter et al. [2] studied and compared the effects of adding potassium sulphate and sodium chloride to 2 per cent procaine hydrochloride with 1:50,000 epinephrine. Sidon et al. [7] studied mandibular nerve blocks as well as supra periosteal injection techniques in surgical patients as well as volunteers [7]. However, the variables assessed were onset, duration and depth.

Hence, this study was designed and conducted to evaluate and compare onset, duration, pain control and hemodynamic effects, using 2% lignocaine hydrochloride with 1.5% KCl, 2% lignocaine hydrochloride with 1:80,000 Adrenaline bitartrate and 2% lignocaine hydrochloride (plain) in pterygomandibular nerve blocks for surgical extractions of impacted mandibular third molars. The study tested the null hypothesis, which stated that there is no difference in the effectiveness of 2% lignocaine with 1.5% KCl, 2% lignocaine with 1:80,000 Adrenaline and 2% lignocaine in pterygomandibular nerve blocks for the outcome variables, quality of anesthesia, hemodynamic response and pain control.

Materials and methods

A triple blinded (operator, observer, subject) randomized controlled trial was designed including patients who visited the department of Oral and Maxillofacial Surgery of recognized dental college for extraction of impacted mandibular third molars.

The sample size was calculated using the formula, $n = 2(Z\alpha + Z\beta)^2 [s]^2/d^2$, where $Z\alpha$ is the z variate of alpha error i.e. a constant with value 1.96, $Z\beta$ having a value of 0.84, considering the mean and standard deviation from the literature, that concluded approximately 40 subjects per group. Approval from Institutional Ethics Committee was obtained (n°. YMTDCH /IEC/CUT/072/2017).

The study included ASA-I category (American Society of Anesthesiologists) subjects of both sexes, aged between 18 and 45 years, requiring surgical extraction of mandibular third molars (with moderate Pederson's difficulty index [8] i.e., 5–7) and willing to consent for the study. Patients with any known medical condition, h/o previous resistance to LA, known drug/food allergy, pregnant or lactating mothers, mentally challenged, uncooperative or apprehensive were excluded from the study. It was ascertained that none of the subjects was suffering from any form of active infection nor consuming any medication one week prior to the procedure.

Thus, a total of 120 patients, who fulfilled the inclusion criteria were randomly selected for this study and divided randomly into three groups (40/per group) using computer generated random numbers. Pterygomandibular nerve blocks were used in all groups. In group 1: 2% lignocaine hydrochloride with 1.5% potassium chloride in the ratio 2:1, in group 2: 2% lignocaine hydrochloride with 1:80,000 adrenaline bitartrate, in group 3: plain 2% lignocaine hydrochloride were used.

The basic protocol followed for every case included a detailed case history, explanation of the procedure to the patient, routine X-rays and blood investigations. A well-informed written consent was obtained from all subjects. All subjects underwent surgical extractions of impacted mandibular third molars under similar conditions by same operating surgeon using standard aseptic and surgical protocol under pterygomandibular nerve blocks. No pre-medications were used in any group. Care was taken to avoid any intra-vascular injection. In the event of a positive aspiration, the solution and the syringe were discarded and a new solution from the same group was used. Neither the subject, nor the operating surgeon was aware of the contents of the solution used for nerve blocks. Routine post-operative medications were prescribed and postoperative instructions were explained. The subjects were kept under observation post-operatively and discharged after all study variables were recorded. All subjects were advised to use prescribed analgesic as required. The time of first rescue analgesic postoperatively was also recorded. Patients were recalled on the next day for follow-up. Postoperative pain and rescue analgesic requirement were noted.

The outcome variables measured were, cardiovascular variables (SBP, DBP, MABP and HR and SPO_2) and quality of anesthesia assessed by onset, duration and its depth. The cardiovascular variables were measured using a multiparameter monitor (Intellivue MX 400, Philips, with more than 95% accuracy), just prior to LA injection and repeated at intervals of 5 min, 10 min, 15 min, 30 min and 45 min after injection. Onset of anesthesia (in seconds) was measured from the time of injection to the onset of first tingling sensation on the lower lip. Duration (in minutes) was recorded from the onset of first tingling sensation on the lower lip till the first prescribed rescue analgesic used by the subject. Clinical signs and symptoms of hyperkalemia like paresthesia of the extremities, listlessness, mental confusion, weakness or heaviness of the legs, flaccid paralysis, cold skin, grey pallor, fall in blood pressure if any, were also specifically looked for. Any other symptoms like nausea, vomiting, sedation, itching, shivering, headache, accidental soft tissue injury was also mentioned in the case file. The duration of surgery (time of injection to the last suture taken) and total amount of dose used were also recorded. Depth of anesthesia was assessed with VAS score which was specifically recorded for pain during extraction.

Data obtained was compiled on a MS Office Excel Sheet (v 2019, Microsoft Redmond Campus, Redmond, Washington, United States). Data was subjected to statistical analysis using Statistical package for social sciences (SPSS v 26.0, IBM).

Descriptive statistics like frequencies and percentage for categorical data, Mean & SD for numerical data has been depicted. Inter group comparison (>2 groups) was done using one way ANOVA followed by pair wise comparison using post hoc test. Intra group comparison was done using repeated measures ANOVA (for >2 observations) followed by post Hoc test. Comparison of frequencies of categories of variables with groups was done using chi square test. For all the statistical tests, $p < 0.05$ was considered to be statistically significant, keeping α error at 5% and β error at 20%, thus giving a power to the study as 80%.

Results

The mean age of the subjects was 32.31±4.902 (Min 21 years, Max 45 years). There were 57 (47.5%) females, 63 (52.5%), male subjects. Inter group comparison of mean age of the subjects showed a statistically non-significant difference ($p > 0.05$) which ruled out age as a confounding factor. Also inter group comparison of frequencies of sex of the subjects showed a statistically non-significant difference ($p > 0.05$).

Table I shows Inter group comparison of Onset, duration, total amount/dose used, duration of surgery, number of injections and depth of anesthesia using VAS scale.

Table II shows Inter group pairwise comparison using Post Hoc Tests for Onset, duration, total amount/dose used, duration of surgery, number of injections and depth of anesthesia using VAS scale.

Table III shows Inter group pairwise comparison of SBP, DBP, Pulse, SpO_2 using Post Hoc Tests.

There was a highly statistically significant difference in the onset of action between 3 groups, grp 3 (mean – 246.65 s) > grp 2 (102.60 s) > grp 1 (44.20 s) (Tabs. I and II). Duration of analgesia was least for group 3 (100.28 min) as compared to Group 1 (205.20 min) and group 2 (222.43 min) (highly statistically significant, Tabs. I and II). Depth of anesthesia (VAS scores) showed statistically significant difference between groups 1 and 3 and non-significant difference between 1 and 2 (Tabs. I and II). There was a statistically non-significant difference seen for SBP, DBP, Pulse and SpO_2 at all the time intervals between all pairs of groups i.e. group 1 *versus* 2, 1 *versus* 3 and 2 *versus* 3 (Tab. III). There was no statistically significant difference in the amount of Lignocaine injected and number of injections used in the 3 groups ($p > 0.05$, Tabs. I and II).

Discussion

A physiologic concentration of potassium, similar to that in extracellular fluid, when added to isotonic solutions of LA, potentiates their effect [9]. Systemic and local toxicity studies conducted by Aldrete *et al.* on animals and volunteers injected with KCl-LA, established its safety [3]. Aldrete *et al.* also showed that there were no consistent or significant alterations in serum potassium levels of patients undergoing bronchoscopies, anesthetized with bilateral superior laryngeal nerve block and trans-cricoid injection, using 8 mL of 1 percent lidocaine plus KCl. [10]. This suggested that when small amount of KCl is used, there is no change in normal balance of the extracellular potassium pool. [3]. A proposed mode of action of potassium ions when added to LA, has been given by Sidon *et al.* [7] and Hurley *et al.* [11].

In the present study, 1mL of 1.5% KCl (2 mEq) was safely added to 2mL of 2% lignocaine (grp1) and its effects were evaluated and compared with 2% lignocaine with 1:80,000 adrenaline (grp2) and 2% lignocaine (grp3) in pterygomandibular nerve blocks for surgical extraction of mandibular third molars.

There was a highly statistically significant difference in the onset of action between 3 groups, grp 3 ((mean – 246.65 s) > grp 2 (102.60 s) > grp 1 (44.20 s) (Tabs. I and II). Thus, the onset was fastest in grp1.

Similarly, in other studies, shorter onset of action was obtained for brachial plexus [4], and epidural blockade [1]. The addition of KCl renders additional extracellular potassium ions, leading to depolarization of nerve membrane and blocks conduction of impulses [4, 7, 11].

As regards duration of surgery, a statistically significant difference was obtained between groups 1 and 3 ($p < 0.05$, Tab. II), which can be explained by the delayed onset in group 3 as compared to earlier onset in group 1.

Duration of analgesia was least for group 3 (100.28 min) as compared to Group 1 (205.20 min) and group 2 (222.43 min) (highly statistically significant, Tabs. I and II). However, the duration of LA with KCl was comparable to LA-Adr and statistically non-significant (Tab. II). Prolonged duration of action with KCl is consistent with previous studies with mandibular nerve blocks and supra-periosteal injections [7], brachial plexus [4] and epidural blockade [12].

Shorter onset and prolonged duration for both sensory and motor nerve blocks were also obtained when KCl was used with bupivacaine [13, 14].

Depth of anesthesia, measured by pain experienced during extraction by the subjects using VAS scale showed statistically significant difference between groups 1 and 3 and non-significant difference between 1 and 2 (Tabs. I and II), indicating that pain control with LA-KCl was comparable to the standard LA-Adr.

There was a statistically non-significant difference seen for SBP, DBP, Pulse and SpO_2 at all the time intervals between all pairs of groups i.e. group 1 *versus* 2, 1 *versus* 3 and 2 *versus* 3 (Tab. III). Thus, there were no differences in hemodynamic effects in the 3 groups.

There was no statistically significant difference in the amount of Lignocaine injected and number of injections used in the 3 groups ($p > 0.05$, Tabs. I and II). There was no need for additional injection and/or alternate technique to be used in any of the subjects in the 3 groups. Thus, the Lignocaine-KCl combination was comparable to the standard Lignocaine-Adr as regards LA dose required.

Table I. Inter group comparison of Onset, duration, total amount/dose used, duration of surgery, number of injections and depth of anesthesia using VAS scale.

	Groups	Mean	Std. deviation	Std. error	95% confidence interval for mean		Minimum	Maximum	F value	P value of one way ANOVA
					Lower bound	Upper bound				
Onset of analgesia (sec)	1	44.20	5.450	0.862	42.46	45.94	34	55	470.702	0.000**
	2	102.60	9.803	1.550	99.46	105.74	76	120		
	3	246.65	51.403	8.128	230.21	263.09	27	301		
Duration of analgesia (min)	1	205.20	28.399	4.490	196.12	214.28	167	271	110.759	0.000**
	2	222.43	61.369	9.703	202.80	242.05	154	456		
	3	100.28	12.770	2.019	96.19	104.36	79	132		
Total amount of dose used	1	2.20	0.608	0.096	2.01	2.39	2	4	2.079	0.130#
	2	2.35	0.770	0.122	2.10	2.60	2	4		
	3	2.55	0.904	0.143	2.26	2.84	2	4		
Duration of surgery (min)	1	15.10	4.460	0.705	13.67	16.53	5	26	2.869	0.061#
	2	18.18	6.201	0.981	16.19	20.16	9	29		
	3	21.25	18.361	2.903	15.38	27.12	10	121		
Number of injections required	1	1.10	0.304	0.048	1.00	1.20	1	2	2.079	0.130#
	2	1.18	0.385	0.061	1.05	1.30	1	2		
	3	1.28	0.452	0.071	1.13	1.42	1	2		
VAS	1	3.50	0.480	0.076	3.28	3.72	2	5	6.452	0.002**
	2	3.73	0.599	0.095	3.53	3.92	2	4		
	3	3.98	0.679	0.107	3.82	4.13	2	5		

* statistically significant difference ($p < 0.05$).
**statistically highly significant difference ($p < 0.01$).
non significant difference ($p > 0.05$).

Table II. Inter group pair wise comparison using post hoc tests.

Dependent variable	(I) group	(J) group	Mean difference (I–J)	Std. Error	p value
Onset of analgesia (sec)	1	2	-58.400*	6.792	0.000**
	1	3	-202.450*	6.792	0.000**
	2	3	-144.050*	6.792	0.000**
Duration of analgesia (min)	1	2	-17.225	8.884	0.132#
	1	3	104.925*	8.884	0.000**
	2	3	122.150*	8.884	0.000**
Total amount of dose used	1	2	-0.150	0.172	0.660#
	1	3	-0.350	0.172	0.109#
	2	3	-0.200	0.172	0.479#
Duration of surgery (min)	1	2	-3.075	2.567	0.457#
	1	3	-6.150*	2.567	0.047*
	2	3	-3.075	2.567	0.457#
Number of injections required	1	2	-0.075	0.096	0.660#
	1	3	-0.175	0.096	0.109#
	2	3	-0.100	0.096	0.479#
VAS	1	2	0.250	0.132	0.146#
	1	3	0.475*	0.132	0.001**
	2	3	0.225	0.132	0.209#

* statistically significant difference ($p < 0.05$).
** statistically highly significant difference ($p < 0.01$).
# non significant difference ($p > 0.05$).

Table III. Inter group pairwise comparison of SBP, DBP, Pulse, SpO_2 using Post Hoc Tests.

Dependent variable	(I) group	(J) group	Mean difference (I–J)	Std. error	p value
SBP preop	1	2	1.000	1.039	0.601#
	1	3	-0.150	1.039	0.999#
	2	1	-1.000	1.039	0.601#
	2	3	-1.150	1.039	0.511#
DBP preop	1	2	0.000	0.554	1.000#
	1	3	0.550	0.554	0.582#
	2	1	0.000	0.554	1.000#
	2	3	0.550	0.554	0.582#
SBP 5 min	1	2	0.300	0.903	0.941#
	1	3	-0.200	0.903	0.973#
	2	1	-0.300	0.903	0.941#
	2	3	-0.500	0.903	0.845#
DBP 5 min	1	2	0.350	0.457	0.725#
	1	3	-0.250	0.457	0.949#
	2	1	-0.350	0.457	0.725#
	2	3	-0.600	0.457	0.391#
SBP 10 min	1	2	1.050	0.977	0.457#
	1	3	-0.350	0.977	0.916#
	2	1	-1.050	0.977	0.457#
	2	3	-1.400	0.977	0.251#
DBP 10 min	1	2	-0.400	0.445	0.642#
	1	3	0.350	0.445	0.712#
	2	1	0.400	0.445	0.642#
	2	3	0.750	0.445	0.215#

Table III. (continued).

Dependent variable	(I) group	(J) group	Mean difference (I–J)	Std. error	p value
SBP 15 min	1	2	0.550	0.946	0.830#
	1	3	-0.050	0.946	0.998#
	2	1	-0.550	0.946	0.830#
	2	3	-0.600	0.946	0.802#
DBP 15 min	1	2	-0.400	0.493	0.697#
	1	3	-0.350	0.493	0.758#
	2	1	0.400	0.493	0.697#
	2	3	0.050	0.493	0.994#
SBP 30 min	1	2	0.450	21.900	1.000#
	1	3	-26.900	21.900	0.439#
	2	1	-0.450	21.900	1.000#
	2	3	-27.350	21.900	0.427#
DBP 30 min	1	2	-0.400	0.451	0.649#
	1	3	-0.400	0.451	0.649#
	2	1	0.400	0.451	0.649#
	2	3	0.000	0.451	1.000#
SBP 45 min	1	2	0.400	0.913	0.900#
	1	3	-0.150	0.913	0.985#
	2	1	-0.400	0.913	0.900#
	2	3	-0.550	0.913	0.819#
DBP 45 min	1	2	-0.550	0.464	0.464#
	1	3	-0.150	0.464	0.944#
	2	1	0.550	0.464	0.464#
	2	3	0.400	0.464	0.665#
Pulse (preop)	1	2	0.200	0.959	0.976#
	1	3	1.975	0.959	0.103#
	2	1	-0.200	0.959	0.976#
	2	3	1.775	0.959	0.157#
Pulse 5 min	1	2	0.025	0.937	1.000#
	1	3	0.675	0.937	0.752#
	2	1	-0.025	0.937	1.000#
	2	3	0.650	0.937	0.769#
Pulse 10 min	1	2	0.350	0.959	0.929#
	1	3	0.500	0.959	0.861#
	2	1	-0.350	0.959	0.929#
	2	3	0.150	0.959	0.987#
Pulse 15 min	1	2	0.550	0.956	0.833#
	1	3	0.925	0.956	0.599#
	2	1	-0.550	0.956	0.833#
	2	3	0.375	0.956	0.919#
Pulse 30 min	1	2	-0.050	0.935	0.999#
	1	3	-1.475	0.935	0.259#
	2	1	0.050	0.935	0.999#
	2	3	-1.425	0.935	0.282#
Pulse 45 min	1	2	-1.400	0.985	0.334#
	1	3	-0.925	0.985	0.617#
	2	1	1.400	0.985	0.334#
	2	3	0.475	0.985	0.880#

Table III. (continued).

Dependent variable	(I) group	(J) group	Mean difference (I-J)	Std. error	p value
SpO_2 preop	1	2	0.075	0.235	0.946#
	1	3	0.150	0.235	0.800#
	2	1	-0.075	0.235	0.946#
	2	3	0.075	0.235	0.946#
SpO_2 5 min	1	2	0.200	0.218	0.631#
	1	3	0.000	0.218	1.000#
	2	1	-0.200	0.218	0.631#
	2	3	-0.200	0.218	0.631#
SpO_2 10 min	1	2	0.225	0.239	0.612#
	1	3	0.200	0.239	0.679#
	2	1	-0.225	0.239	0.612#
	2	3	-0.025	0.239	0.994#
SpO_2 15 min	1	2	0.000	0.202	1.000#
	1	3	-0.125	0.202	0.810#
	2	1	0.000	0.202	1.000#
	2	3	-0.125	0.202	0.810#
SpO_2 30 min	1	2	0.350	0.218	0.247#
	1	3	0.150	0.218	0.771#
	2	1	-0.350	0.218	0.247#
	2	3	-0.200	0.218	0.630#
SpO_2 45 min	1	2	-0.450	0.229	0.126#
	1	3	-0.150	0.229	0.790#
	2	1	0.450	0.229	0.126#
	2	3	0.300	0.229	0.393#

* statistically significant difference ($p < 0.05$).
** statistically highly significant difference ($p < 0.01$).
# non significant difference ($p > 0.05$).

In this study, none of the subjects experienced any untoward reaction, local and/or systemic in the immediate and late post-operative periods. None of the grp1 subjects developed any sign of hyperkalemia.

Conclusion

It can thus be concluded that KCl is inert, causes no local &/or systemic adverse effects when injected with lignocaine in physiologically acceptable amounts. The effectiveness of KCl-Lignocaine is comparable to Lignocaine-Adr and causes no hemodynamic alterations. However, significant advantage of KCl-Lignocaine over Lignocaine-Adr is shorter onset of action.

Future scope

In this study, freshly prepared KCl-Lignocaine solution was used. In future, clinical studies may be designed to evaluate stability and shelf-life of the mixture.

Keeping in view that physiological amounts of KCl used doesn't cause any hemodynamic changes, clinical studies with ASA-2,3 AND 4 patients may be designed to further establish its safety.

Acknowledgements. We profoundly thank Dr. Mukund Nayak, Associate Professor, Department of Anaesthesiology, YMT DCH, Navi Mumbai for his valuable contribution towards this study.

Conflicts of interests: The authors declare that there is no conflict of interest.

Ethical Approval

Ethical Approval was not required.

Funding

This research did not receive any specific funding.

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Appendix 7

ORAL PRESENTATIONS

GALGOTIAS UNIVERSITY

Plot No. 2, Yamuna Expy, Opposite, Buddha International Circuit, Sector 17A, Greater Noida, Uttar Pradesh 203201

Desire

International e-Conference on Forensic Science & Criminology

Bridging the Gap in Criminal Justice System Conference Series: Forensis Agora

This is to certify that Prof./Dr./Mr./Ms./Mrs. Rinku Kalra of Galgotias University has presented a paper entitled Comparative Evaluation of Effectiveness of Dexamethasone and Adrenaline as Additives To Lignocaine For Pterygomandibular Nerve Blocks In Adult Patients: A Randomized Controlled Clinical Study in the conference held on **15th - 16th May, 2021** through online mode.

Dr. Arvind Kr. Jain
Dean School of Basic & Applied Sicences
Galgotias University

Dr. Rajeev Kumar
Program Chair
Division of Forensic Science
Galgotias University

Mrs. Vinny Sharma
Assistant Professor
Organizing Secretary

GALGOTIAS UNIVERSITY

DIVISION OF CHEMISTRY

INTERNATIONAL CONFERENCE ON
ADVANCED MATERIALS FOR NEXT GENERATION APPLICATIONS
AMNGA-2021

Division of Chemistry, School of Basic and Applied Sciences, Galgotias University.

CERTIFICATE OF PRESENTATION

This is to Certify that

RINKU KALRA

has presented in the International Conference on Advanced Materials for Next Generation held on 29th – 30th September, 2021

PROF. (DR) A K JAIN
Conference Chair
Dean SBAS

DR ANJALI GUPTA
Convenor

Appendix 8

Plagiarism certificate

GALGOTIAS UNIVERSITY

University Library

Date: 23 April, 2022

Certificate of Plagiarism

This is to certify that Plagiarism check of Ph.D. Thesis of Mr./Ms. Rinku Kalra, Registration No. 17SCRH301001, Dept. of Clinical Research, School of Basic and Applied Sciences titled "Comparative Evaluation of Effects of Additives to 2% Lignocaine for Surgical Extraction of Impacted Mandibular Third Molars: A Randomized Controlled Clinical Study" has been done through iThenticate and found 10% similarity index.

Thanking you,

(Dr. Debal C. Kar)
University Librarian

Appendix 9

AUTHORS'S CV

Dr. Rinku Kalra

OBJECTIVES

To work for result-oriented, challenging assignments which allow me to utilize my clinical knowledge and skills to the fullest and to evolve in the process.

To keep myself updated about the advances in the field and also add my experiences to the literature.

To impart my knowledge and professional experiences to the younger generation

To fight against Tobacco addiction and its consequences.

EDUCATIONAL QUALIFICATIONS

BDS: **Bachelor of Dental Surgery** (1996-2001) from Rural Dental College and Hospital, Loni, affiliated to University of Pune.

- Was a part of the ***National Service Scheme*** during the same.

Entrance Exams for Post Graduation:

Maharashtra state PGDCET'2007- **RANK 2nd**
ALL INDIA PG Entrance'2007- **RANK 17TH**
AMUPMDC'2007- **RANK 6TH**

MDS: **Master of Dental Surgery** (**in Oral and Maxillofacial Surgery, 2007-2010)** from **Nair Hospital Dental College, Mumbai,** affiliated to Maharashtra University of Health Sciences (MUHS)

Library Dissertation (MDS*)- Condylar Fractures-Open Vs Closed Reduction*

Main Dissertation (MDS)- *Role of Maxillary Distraction Osteogenesis with bilateral intra-oral appliances in Cleft lip/ palate patients for the correction of Maxillary Hypoplasia.*

PhD in Healthcare and Clinical research: Ongoing, from Galgotias University, Greater Noida, U.P

Research Title: *Comparative Evaluation of Effects of Additives to 2% Lignocaine for Surgical Extraction of Impacted Mandibular Third Molars: A Randomized Controlled Clinical Study*

Supervised by Dr Ranjana Patnaik

POST- GRADUATE TRAINING

- Successfully completed **MDS** (Oral and Maxillofacial Surgery) from **2007-2010**, guided by **Dr. Neelam Andrade,** Professor and Head, Dept. of Oral and Maxillofacial Surgery, and Dean, Nair Hospital Dental College, an esteemed Institute and Public Hospital, run by Mumbai Municipal Corporation.
- Performed and attended all routine ward, OPD, OT work and duties, emergency duties, trauma cases, major surgeries
- Performed over 400 minor surgeries during post-graduation.
- Assisted all supra-major surgeries associated with Oral and Maxillofacial region
- Completed oncology posting in Tata Memorial Hospital, Mumbai.
- Attended postings in the Gen. Medicine, Gen. Surgery and Trauma wards in T.N.Medical College and B.Y.L. Nair Hospital, Mumbai.
- Attended many conferences and hands-on workshops.
- Presented papers at national conferences.
- Participated in quiz and won prizes twice.
- Completed 6 months' **Resident House-man Post** at Nair Hospital Dental College, Mumbai.

SCIENTIFIC ACTIVITIES

- Have attended Hands-on workshops on, Distraction Osteogenesis, Magnification in Dentistry, Sinus lift and Block Grafting, Direct Sinus lift and lateral Ridge augmentation, Trauma & Implantology, Introductory seminar by AOCMF, AOCMF course on Principles in Craniomaxillofacial trauma management, Basic mandibular Osteosynthesis techniques, Flap Dissection, ATLS, CPCR, Management of Medically compromised patients in dental practice, Basic suturing techniques, AOCMF TMJ Course.

- Have completed Tobacco Intervention Initiative Training for de-addiction counselling

- Have attended Teachers' Training Program, Biostatistics and Research Methodology courses by AOMSI and MET-MUHS

- Have attended various International, National and State-Level specialty conferences

- Have assisted in organizing various CDE programs at Nair Hospital Dental College and Y.M.T. Dental College and Hospital.

- Delivered lectures at Research Methodology workshops

- Have reviewed scientific papers for peer- reviewed journals

MEMBERSHIPS AND REGISTRATIONS

Registered in Maharashtra State Dental Council in Part A, Regn No. A-9023
Life Member of Association of Oral and Maxillofacial Surgeons of India (AOMSI), Life membership No. 1711.

WORK SUMMARY

Currently working as

1. **Associate Professor and Post-Graduate teacher at Yerala Dental College and Hospital**, Navi Mumbai (Affiliated to the Maharashtra University of Health Sciences), since May 2015.
2. Consultant at **Anandpara Hospital**, Malad East, Mumbai since 2011
3. Consultant at, **Gokuldham Medical Center**, Goregaon East, Mumbai since April 2021
4. Consultant at **St. Joseph's Church Trust**, Juhu, Mumbai since 2012.
5. Consultant at **Nivaan Charitable Trust**, Navi Mumbai since 2018
6. Consultant at many private dental clinics in western Mumbai.

Previously,

Assistant Professor at Yerala Dental College and Hospital, Navi Mumbai (2011-2015)
Consultant at :
Manav Seva Sangh, Sion,
Apollo White Dental Spa and Apollo Hospital, Mumbai and Navi Mumbai
Rotary Medical Center, Borivali/ Dahisar East
Sadbhavna Charitable Trust, Malad (E)

PUBLICATIONS

1. *Development and evolution of distraction devices: Use of indigenous appliances for Distraction Osteogenesis-An overview*, **published** in **Annals Of Maxillofacial Surgery**, January-June 2011, 1(1):58-65.
2. *New protocol to prevent TMJ reankylosis and potentially life-threatening complications in Triad patients*, **published** in the **International Journal of Oral and Maxillofacial Surgery**, Volume 41, Issue 12, Pages 1495–1500.

3. *The Versatility of Distraction Osteogenesis in Cranio-maxillo-facial Region,* **published** in **The Magic, The Official Journal Of Malad Medical Association,** Sept 2011 issue.
4. *"Fore-warned is fore-armed"- A Case-report of Tuberculous Lymphadenitis in the Oro-facial region,* **published** in **Dento-Med Journal**,Vol III, Issue 3, Oct.2011.
5. *Management of Oral Sub mucous Fibrosis- a Review,* **published** in *the* **Indian Journal Of Dental Sciences**, *vol 4, Issue 2, June-2012, 107-14.*
6. *Autologous Osteoblast Implantation- A boon to Bone Augmentation- A case report,* **Published** in **Unique Journal Of Medical And Dental Sciences** 02(01), Jan-Mar 2014, 46-49
7. *Anti-microbial efficacy of tea and coffee extracts against common cariogenic microbes: An in-vitro study,* **published** *in* **The Indian Journal Of Contemporary Dentistry,** *2014;2(2):62-6*
8. Reply to comments on "New protocol to prevent TMJ reankylosis and potentially life-threatening complications in triad patients*",* ***published*** **in the International Journal of Oral and Maxillofacial Surgery***; Volume 43, Issue 11, Pages 1411-1412*
9. *Non – Fluoride remineralisation: A review of the contemporary technologies,* **published in Journal of Dental & Allied Sciences,***2014;3 (1):24-33.*
10. *Bilateral Maxillary Sinus Floor Augmentation Using A Combination Of Tissue Engineered Autologous Osteoblasts And Demineralized Freeze Dried Bone Graft,* **published in Contemporary Clinical Dentistry,** *May 2015; Vol6, Issue 2,243-46.*
11. *Assessment of self-medication among dental students in Pune city, Maharashtra: A cross-sectional survey* **published in Journal of Indian Association of Public Health Dentistry**, Sept 2015; Vol 13(3), 318-323
12. *Assessment of Job Satisfaction among Dental Educators in a dental college at Davangere city, Karnataka: A Cross-sectional Questionnaire based study,* **published in Indian Journal of Public Health Research and Development;** *October2015;6(4):220*

13. *Assessment Of Oral Health Related Quality of Life Using Gohai Pre And Post Dental Rehabilitation: An Analytical Study,* **published in European Journal of Biomedical and Pharmaceutical sciences**, Nov 2016; Vol 3(11), 477-482.
14. *When things go wrong, published in* **The Indian Journal Of Contemporary Dentistry.***July2017, vol 5(2),42-47*
15. *Oro-antral communication and oro-antral fistula:a brief review and report of two cases* **published in International Journal of Development Research,** *January, 2018,Vol. 08 (01),18310-18314.*
16. *Anterior Maxillary Dentigerous Cyst with Supernumerary Tooth- Case Series and Review of Literature* **published in EC Dental Science Journal**. Dec, 2018, vol-17(12): 2239-2248.
17. *Rise and become wise over COVID-19* **published** in **International Journal of Advanced Dental Sciences,**1 (S1), 24-28
18. *Comparative Evaluation of Effectiveness of 2% Lignocaine Hydrochloride with Clonidine Hydrochloride versus 2% Lignocaine Hydrochloride with Adrenaline Bitartrate as Local Anesthetic for Adult Patients Undergoing Surgical Extraction of Impacted Mandibular Third Molars: A Randomized Controlled Clinical Study*, **published** in **Contemporary Clinical Dentistry**, Vol 12(3), July-2021, 308-312
19. *Comparative evaluation of effectiveness of 2% lignocaine hydrochloride with 1.5% potassium chloride versus 2% lignocaine hydrochloride with adrenaline bitartrate versus 2% lignocaine hydrochloride as local anaesthetic for adult patients undergoing surgical extraction of impacted mandibular third molars: a randomized controlled clinical study* **published** in **Journal of Oral Med Oral Surg**, 2021;27:55

TECHNICAL SKILLS

Microsoft Word, Power point & Excel

PERSONAL DETAILS

Address: C/308, Pratap Nagar, Pushpa Park, Daftari Rd, Malad (E), Mumbai - 400097

DOB: 28/10/1978

Tel/email: +91 9167391340 / drrinkukalra@gmail.com

Languages known: English, Hindi, Gujarati, Marathi, Punjabi

Nationality/Citizenship: Indian

- Have a valid Indian Passport and Driving License

Marital Status: Single

FAMILY

Father – Family Physician (retired)

Mother – Home-maker.

Brother– MDS In Public Health Dentistry, also working as Senior lecturer and Dept In-Charge, Dept of Public Health Dentistry, YMTDC, Navi Mumbai

Sister-in-law: Working as a general dentist in Nivaan Charitable Trust, Navi Mumbai

References:

Upon Request