"TO COMPARE THE EFFECT OF LIGNOCAINE, EPHEDRINE AND COMBINED LIGNOCAINE AND EPHEDRINE PRETREATMENT ON PAIN ON INJECTION DUE TO PROPOFOL IN ADULT PATIENTS UNDERGOING GENERAL ANAESTHESIA- A ONE YEAR HOSPITAL BASED RANDOMIZED CLINICAL TRIAL."

By

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Dissertation

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M.D.
IN
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Under the Guidance of

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JAWAHARLAL NEHRU MEDICAL COLLEGE

BELAGAVI, KARNATAKA

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DR. NEHA SANJEEV ADHYAPAK

LIST OF ABBREVIATIONS USED

1. HR= Heart Rate
2. SBP=Systolic Blood Pressure
3. DBP= Diastolic Blood Pressure
4. MAP =Mean Arterial Pressure
5. CNS= Central Nervous System
6. ICU= Intensive Care Unit
7. GABA= Gamma-Aminobutyric Acid
8. NMDA=N- methyl-D-aspartate
9. EEG= Electroencephalography
10. $CMRO_2$=Cerebral Metabolic Rate for Oxygen
11. ICP= Intracranial Pressure.
12. $PaCO_{2=}$ Partial pressure of carbon dioxide in the blood
13. SVR= systemic vascular resistance
14. PONV=postoperative nausea and vomiting
15. ACTH=adrenocorticotropic hormone
16. BIS= Bispectral Index
17. PRIS =Propofol infusion syndrome
18. MCAD=medium-chain acyl CoA
19. CHF =Congestive Heart Failure
20. Na^+=Sodium
21. ECG= Electroencephalography
22. MAO= monoamine oxidase
23. PPAR-α=peroxisome proliferator-activated receptor-alpha

24. TNF-α=tumor necrosis factor-alpha

25. NaCl=Sodium Chloride

26. ASA=American Society of Anaesthesiologists

27. VRS =verbal rating scale

28. N_2O= Nitrous Oxide

29. Yrs= years

30. Kg= kilogram

31. μg=microgram

32. cms=centimeters

33. S.D=Standard Deviation

34. BI=Before injection of test solution

35. PI=At Propofol injection

36. AP=One minute after Propofol injection

37. CO= Cardiac Output

ABSTRACT

Title: To Compare the Effect of Lignocaine, Ephedrine and Combined Lignocaine and Ephedrine Pretreatment on Pain on Injection due to Propofol in Adult Patients undergoing General Anaesthesia- A One Year Hospital based Randomized Clinical Trial.

Background: The rapid recovery, safety, and minimal organ damage of Propofol, a sedative-hypnotic, is considered the drug of choice for inducing general anaesthesia. It does, however, have some negative effects, including injection discomfort, hypotension, and bradycardia. Propofol injection pain affects 80 percent to 90 percent of subjects. Pretreatment with lignocaine is the most popular way to reduce propofol-induced discomfort. Ephedrine is useful in the treatment of moderate hypotension as it stimulates beta-1 adrenergic receptors. Ephedrine is thought to improve the analgesic action of lignocaine. Thus, a synergistic impact of two drugs results in reduction of doses & adverse effects while increasing efficacy.

Objectives: To compare the effect of lignocaine, ephedrine and combined lignocaine and ephedrine on pain on injection and hemodynamic changes namely heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) in patients posted for elective surgeries receiving i.v. propofol for induction of General Anaesthesia

Methods: In this randomized clinical trial, 120 ASA I & II patients posted for surgery under general anaesthesia, after approval of Institutional Review Board & Ethical Committee and registering with the Clinical Trials Registry- (CTRI/2020/09/027529) were divided into three groups, 40 in each, namely Group A (i.v lignocaine 1.5 mg/kg), Group B (i.v ephedrine

50μg/kg) and Group C (i.v lignocaine 1.5 mg/kg) + ephedrine 30 μg/kg). Pain on propofol injection was assessed using VRS. Hemodynamic changes in HR, SBP, DPB and MAP were recorded at three intervals; before intubation (BI), at propofol injection (PI) and one minute after propofol injection (AP)

Results: In lignocaine group, 52.5% of patients had no pain while 37.5% had mild pain, 10% had moderate pain, none of them had severe pain. In ephedrine group 10% had no pain, 30% had mild pain, 40% had moderate pain and 20% severe pain. In combined lignocaine and ephedrine group, 27.5% had mild pain, while rest of the patients experienced no pain. The difference in MAP changes from the baseline, in the three groups were as follows, a decrease from 99.16±11.45 to 86.61±11.29 in lignocaine group, an increase from 93.93±9.83 to 98.48±7.05 in ephedrine group and an increase from 94±9.33 to 90.93±9.07 in combined lignocaine & ephedrine group. The difference in HR changes were, in lignocaine group a decrease from 79.68±12.70 to 75.43±11.21, in ephedrine group an increase from 79.15±11.21 to 85.15±11.98 and in combined lignocaine & ephedrine group an increase from 79.10±13.79 to 84.53±13.25.

Conclusion: Pretreatment with lignocaine & ephedrine combination decreased pain and had better hemodynamic stability due to propofol injection compared to lignocaine or ephedrine alone during induction of general anaesthesia.

Key words: propofol, lignocaine, ephedrine, pain

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INTRODUCTION

Propofol, a sedative-hypnotic is considered to be the drug of choice for induction of general anaesthesia, essentially because of its rapid recovery, safety and minimal organ toxicity. However, it has some side effects which include pain on injection, hypotension, bradycardia. Pain from propofol injection occurs in 80% - 90% of patients.[1] Inspite an unclear pain etiology, there are two advocated causes. The immediate pain may be caused by phenol due to local irritation on the vein. Second, kininogens released at the endothelium of nerve terminals between the tunica intima and the tunica media of the vessel create delayed pain by eliciting a painful stimulus (after 10-20 secs). [2]

Previous studies have shown that percentage of patients to recall undesirable pain is high. Several measures such as using additive like lignocaine, warming or cooling propofol, adding a diluent, preference for a larger vein for injection and administration of drugs like fentanyl, clonidine, ephedrine, thiopentone sodium, ketamine, magnesium sulfate and paracetamol before giving propofol have been suggested to limit this pain.[21]

Though premedication has little effect on the incidence, it may reduce the severity of pain. The site of injection also plays significant role. Several studies have reported reduced pain when the antecubital fossa vein was used.

Lignocaine pretreatment is the most common drug used to decrease propofol-induced pain. As the pain fibres are free nerve endings in the vasa-vasorum intimal layers, they are instantly blocked by lignocaine and block the propofol induced pain on injection.[40] Propofol is known to cause fall in BP and increase in HR and CO (initially) , eventually this will decrease than baseline.[3] This effect can be aggravated by lignocaine. Dose related neurological effects are drowsiness, nausea, paraesthesia, blurred vision, disorientation, nystagmus, twitching and seizures. There is no cardiovascular effect at a

plasma concentration of less than 5 mg/mL. Seizures occur when plasma levels are between 5 and 10 mg/mL. When plasma concentrations

exceed 10 mg/mL, CNS depression, apnoea, and cardiac arrest occur. During the administration of lidocaine, the convulsive threshold is reduced. The convulsive threshold of lignocaine is decreased in the presence of arterial hypoxia, hyperkalemia or acidosis. Thus, monitoring these parameters during continuous lignocaine infusion to patients to suppress ventricular arrhythmias.

Another drug used to relieve pain after a propofol injection is ephedrine, an adrenergic agonist. It is known to cause vein dilation and enhanced permeability, as well as increasing the interaction between the propofol aqueous phase and free nerve endings..[2]Ephedrine is useful in the treatment of moderate hypotension, especially when it is accompanied by bradycardia, due to its beta-1 adrenergic stimulating properties..[11] Ephedrine can enhance analgesic effect of lignocaine. In general, a synergistic impact of two drugs would allow both agents' doses to be reduced, reducing adverse effects while increasing efficacy. Adverse effects of ephedrine include insomnia, anxiety, tremor, headache, dysrhythmias, nausea and vomiting, palpitations, tachycardia, acute myocardial infarction, cardiac arrest, sudden death and haemorrhagic and ischemic strokes.

As a result, giving lignocaine and ephedrine together before inducing anaesthesia with propofol may help to reduce pain & hypotension due to propofol.[5] To date, there is no study done to determine efficacy of a combination of ephedrine and lignocaine to decrease the adverse effects of injection of propofol. Here in the present study we have compared lignocaine, ephedrine and combination of lignocaine & ephedrine on pain due to injection of propofol.

Aims & Objectives:

The objectives of this study were,

To compare the effect of lignocaine, ephedrine and combined lignocaine and ephedrine on:

1.) Pain on injection

2.) Hemodynamic changes namely heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP).

in patients receiving Propofol for General Anaesthesia.

BASIC SCIENCES

PROPOFOL:

Propofol (Diprivan) is an alkylphenol, 2,6-disopropylphenol. It is highly soluble in lipid but not water and is formulated as an aqueous emulsion with Intralipid, specifically an isotonic 1% solution with 10% soya bean oil, 2.25% glycerol, and 1.2% purified egg phosphatide. This is stable at room temperature and not light sensitive.[32] The addition of disodium edetate (0.005%) suppresses bacterial growth without compromising the clinical safety, efficacy, and stability of propofol.

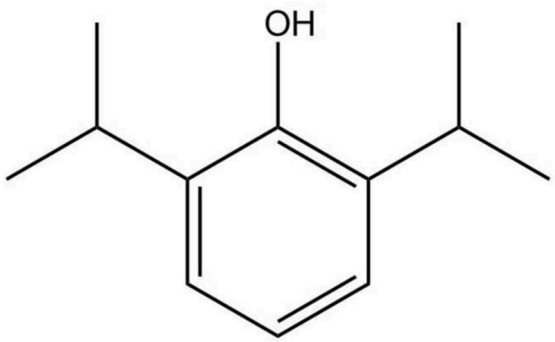

Figure 1: Structure of propofol

Pharmacokinetics and Pharmacodynamics:

1.5 to 2.5 mg/kg IV of propofol as a rapid IV injection, produces unconsciousness within about 30 seconds. The more rapid return of consciousness with minimal residual central nervous system (CNS) effects is one of the most important advantages of propofol compared with alternative drugs administered for the same purpose.[33]

Propofol is oxidized to 1,4-diisopropyl quinol in the liver. Propofol and 1,4-diisopropyl quinol are conjugated with glucuronic acid to propofol-1-glucuronide, quinol-1-

glucuronide and quinol-4-glucuronide, which is excreted by the kidneys. After a $2^{1}/_{2}$ hour patients excrete propofol and propofol metabolites for over 60 hours.[34] Less than 1% propofol is excreted unchanged in urine, and only 2% is excreted in faeces. The metabolites of propofol are thought to be inactive. Because clearance of propofol (>1.5 L/min) exceeds hepatic blood flow, other routes of elimination may occur. [34,37]

The context-sensitive half-time of propofol infusions lasting up to 8 hours is less than 40 minutes.[34] When the infusion is discontinued, this influx from tissues is not sufficient to retard the decrease in plasma concentrations of the drug. However, when used as a sedative for prolonged intensive care unit (ICU) care, the context-sensitive half-time is highly relevant and should be considered.

The pharmacodynamic profile includes pleasant sedation and onset of anaesthesia and a demonstrable antiemetic effect with few side-effects or adverse reactions. The decline in propofol plasma concentration that follows an intravenous bolus can be fitted to a typical three-compartment model. The initial volume of distribution is 20-40L and the initial distribution half-life being l-8min. [32]

Effects on Central Nervous System:

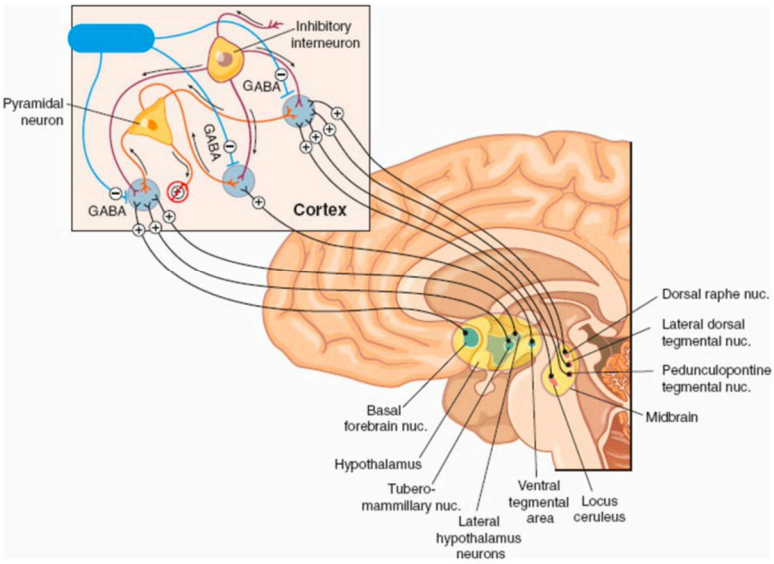

Figure 2: Mechanism of action of propofol [37]

The sedative-hypnotic action of propofol is mediated by enhancing γ-aminobutyric acid (GABA)-induced chloride current through its binding to the β-subunit of $GABA_A$receptor. Sites on the β_1-subunit, β_2-subunit, and β_3- subunit of the transmembrane domains are crucial for the hypnotic action of propofol.[34]

Other neuroreceptors have been linked to propofol activity, including α-adrenergic receptors and N- methyl-D-aspartate (NMDA) receptors. Alteration of the central cholinergic transmission by propofol may also play a role in achieving a state of unconsciousness. The neurotransmission target is the vast array of interneurons involved within the cerebral cortex, brain stem, and thalamus that ultimately play a critical role in arousal.

On increasing propofol concentration, the EEG shows a transient followed by a concentration-dependent decrease in median EEG frequency and an increase in EEG amplitude, leading to burst suppression at high blood concentrations greater than 8μg/mL

Propofol decreases cerebral metabolic rate for oxygen ($CMRO_2$), cerebral blood flow, and intracranial pressure (ICP). Administration of propofol to produce hypnosis in patients with intracranial space-occupying lesions does not increase ICP.[33] However, large dose propofol may decrease systemic blood pressure sufficiently to decrease cerebral perfusion pressure. Cerebrovascular autoregulation in response to changes in systemic blood pressure and reactivity of the cerebral blood flow to changes in $PaCO_2$ are not affected by propofol.

Effects on Respiratory System:

The respiratory depressant effects are also dose-dependent. Apnea is relatively common (25%-30%) with a higher induction dose yet a normal partial pressure of carbon dioxide in the blood ($PaCO_2$) at induction in the absence of surgical stimulation.[34] Metabolic depression further prevents the $PaCO_2$ to increase.

A typical maintenance dose (100 μg/kg/min) results in diminished tidal volumes (40%) and increased respiratory rate (20%). Doubling the infusion rate from 100 to 200 μg/ kg/min causes a further moderate decrease in tidal volume but no change in respiratory frequency. Propofol (50-120 μg/kg/min) also depresses the ventilatory response to hypoxia by a direct action on carotid body chemoreceptors.[34]

It is a potent bronchodilator, primarily because of its direct effects on intracellular calcium homeostasis. It decreases the prevalence of wheezing after induction of anaesthesia and

tracheal intubation in healthy and asthmatic patients. However, a newer formulation of propofol uses metabisulfite as a preservative, which may cause bronchoconstriction in asthmatic patients.

Effects on the Cardiovascular System:

The hemodynamic effects of propofol are dose-dependent and more significant after an induction dose than during a continuous infusion. There is a characteristic drop in systolic and diastolic blood pressure without the expected increase in heart rate. An induction dose of 2- 2.5 μg/kg produces a 25% to 40% reduction of systolic blood pressure.[34] The observed blood pressure drop results from a decrease in cardiac output (myocardial depression and reduced ventricular filling pressures), stroke volume, and systemic vascular resistance (SVR).

Propofol decreases sympathetic activity and leads to indirect arterial vasodilation and venodilation. This effect is enhanced by direct effects on smooth muscle and depressant effects on the myocardium, affecting intracellular calcium balance and influx. The decreased sympathetic tone is also coupled with direct inhibition of the baroreceptor response, leading to a diminished reflex increase in heart rate and a more pronounced hemodynamic effect. Heart rate does not change significantly despite the fall in aortic pressure.[33] Although coronary perfusion pressure is reduced, the global myocardial oxygen supply-demand ratio is preserved by a parallel decrease in left ventricular stroke work and preservation of the diastolic perfusion period. has a minimal direct effect on sinoatrial node function or on nor- mal atrioventricular and accessory pathway conduction.

The decrease in cardiac output after propofol administration may be via its action on sympathetic drive to the heart. The hemodynamic response to propofol lags significantly behind that of the hypnotic effect. The effect-site equilibration half-life of propofol is in the order of 2 to 3 minutes for the hypnotic effect and about 7 minutes for the hemodynamic depressant effect.[37]

High concentrations of propofol abolish the inotropic effect of α- but not β-adrenoreceptor stimulation and enhance the lusitropic (relaxation) effect of β stimulation. Stimulation produced by direct laryngoscopy and intubation of the trachea reverses the blood pressure effects of Propofol. These effects may be exaggerated in hypovolemic patients, elderly patients, and patients with compromised left ventricular function.[32] Adequate hydration before rapid IV administration of propofol is recommended to minimize the blood pressure reduction.

Antiemetic Effects:

The incidence of postoperative nausea and vomiting (PONV) is decreased when propofol is administered, regardless of the anaesthetic technique. Subhypnotic doses of 10 to 15 μg/kg iv may be used in the post anaesthesia care unit to treat nausea and vomiting, particularly if it is not of vagal origin. In the postoperative period, the advantage is its rapid onset of action and the absence of serious side effects. It is generally efficacious in treating PONV at plasma concentrations that do not produce significant sedation. When administered to induce and maintain anaesthesia, it is almost as effective as ondansetron in preventing PONV.

Antipruritic Effects:

Propofol, 10 μg iv, is effective in the treatment of pruritus associated with neuraxial opioids or cholestasis. The mechanism of the antipruritic effect may be related to the drug's ability to depress spinal cord activity. Intrathecal opioids produce pruritus by segmental excitation within the spinal cord.

Anticonvulsant property:

Propofol possesses antiepileptic properties, due to GABA-mediated presynaptic and postsynaptic inhibition of chloride ion channels. If given in doses of greater than 1 μg/kg iv, it decreases seizure duration 35% to 45% in patients undergoing electroconvulsive therapy.

Other effects:

Propofol produces a greater degree of relaxation of laryngeal muscles and better conditions for airway instrumentation. Especially when used in combination with alfentanil or remifentanil to achieve tracheal intubation without neuromuscular block. Neither drug potentiates neuromuscular blockade nor affects the evoked electromyogram or twitch tension. Propofol does not trigger malignant hyperpyrexia and has been used to provide safe anaesthesia for muscle biopsy. It is also considered safe to use in patients with porphyria.

It does not affect corticosteroid synthesis or alter the normal response to adrenocorticotropic hormone (ACTH) stimulation. Neither does it alter the hepatic, hematologic, or fibrinolytic function. But it inhibits platelet aggregation that is induced by

proinflammatory lipid mediators including thromboxane $A_2$and platelet-activating factor.[34]

It is associated with significant decreases in intraocular pressure that occur immediately after induction of anaesthesia and are sustained during tracheal intubation. This becomes significant during laparoscopic surgeries.

Propofol has potent antioxidant properties that resemble those of the endogenous antioxidant vitamin E. Like vitamin E, it contains a phenolic hydroxyl group that scavenges free radicals and inhibits lipid peroxidation. The neuroprotective effect may be at least partially related to the antioxidant potential of propofol's phenol ring structure[32]

Uses:

Table 1: [32]

Uses and Doses of intravenous propofol	
Induction of General Anaesthesia	1-2.5 mg/kg iv, dose reduced with increasing age
Maintenance of General Anaesthesia	50-150 μg/kg/min iv combined with N_2O or an opiate
Sedation	25-75 μg/kg/min iv
Antiemetic action	10-20 μg/kg iv can repeat every 5-10 min or start infusion of 10 μg/kg/min

Induction and maintenance of anaesthesia:

Age, lean body mass and central blood volume are used to determine the appropriate induction dose. Propofol may be titrated on the basis of the BIS value for maintenance of anaesthesia and to assure adequacy of anaesthesia and prevention of overdosing. Premedication with an opiate or a benzodiazepine or both markedly reduces the necessary induction dose. Children require higher induction doses, presumably reflecting a larger central distribution volume and higher clearance rate. Elderly patients require a lower induction dose (25% to 50%) as a result of a smaller central distribution volume and decreased clearance rate and increased pharmacodynamic activity [37]. The complete awakening without residual CNS effectsis the principal reason this drug has replaced thiopental for induction of anaesthesia.

In cardiac surgeries, using titrated infusion rates of 50 to 200 μg/kg/min combined with an opioid for maintenance, propofol provides intraoperative hemodynamic control and ischemic episodes similar to those with either enflurane/opioid or a primary opioid technique.

Alfentanil decreases the elimination clearance of propofol from 2.1 L/min to 1.9 L/min, the distribution clearance from 2.7 L/min to 2.0 L/ min, and the peripheral volume of distribution from 179 L to 141 L. The pharmacokinetic parameters of propofol are affected by cardiac output, heart rate, and plasma alfentanil concentration. Similarly, midazolam reduces propofol's metabolic clearance from 1.94 to 1.61 L/min, Cl_2 from 2.86 to 1.52 L/min, and $Cl_3$from 0.95 to 0.73 L/min [34]. Consequently, in the presence of both midazolam and alfentanil propofol concentrations become elevated by 20% to 30%.

Shock results in slower inter-compartmental clearances and shock shifts the concentration effect relationship to the left, demonstrating a 2.7-fold decrease in the effect-site concentration required to achieve 50% of the maximal effect in the BIS. Haemorrhagic shock decreases the effect-site concentration that produced 50% of the maximal BIS effect from 11.6 ± 3.8 to 9.1 ± 1.7 μg/mL and that producing a 50% probability of movement from 26.8 ± 1.0 to 20.6 ± 1.0 μg/mL. [32,35]

Sedation:

The short context-sensitive half-life, combined with its short effect-site equilibration time, makes it a readily titratable drug for production of i.v sedation. The prompt recovery without residual sedation and low incidence of PONV makes propofol particularly well suited for ambulatory conscious sedation.[33] Increased requirement occurs with repeated anaesthetic administration in a limited time period in individual patients and an increased infusion requirement when propofol is infused for prolonged periods.

The pharmacokinetic profile of propofol makes it a suitable choice for long-term sedation. This should always be weighed, though, against the hemodynamic side effects, tolerance, metabolic acidosis or arrhythmias, rare occurrences of hypertriglyceridemia (and potential pancreatitis) or propofol infusion syndrome.[34] Maintaining the smallest possible dose required for the desired level of sedation with potential "sedation holidays" should be considered as part of a long-term propofol sedation regimen.[32]

Drugs other than propofol should be considered for patients with escalating vasopressor or inotrope requirements or cardiac failure during large-dose propofol infusions. The recommended maximal dose of propofol infusion rate is 80 μg/kg/min (<5 mg/kg/h).[33]

A conventional patient-controlled analgesia delivery system set to deliver 0.7 mg/kg doses of propofol with a 3-minute lockout period has been used as an alternative to continuous IV sedation techniques.[35]

Propofol has emerged as the agent of choice for sedation for brief gastrointestinal endoscopy procedures. Extensive design and testing have gone in to creation of a computer-assisted personalized sedation for upper endoscopy and colonoscopy, called SEDASYS.[37]

Adverse Effects and Contraindications:

Most of the adverse effects like bradycardia, risk of infection, pain on injection, hypertriglyceridemia with prolonged administration, potential for pulmonary embolism are attributed to the oil in water emulsion formulation. Myoclonus, apnoea, hypotension and thrombophlebitis(rare) of the vein into which propofol is injected can also occur.[34] Prolonged or repetitive exposure to the developing fetal brain may lead to neurotoxicity.

Pain on injection:

Pain on injection is the most common side effect which causes discomfort especially in awake patients. It occurs in fewer than 10% of patients when the drug is injected into a large vein rather than a dorsum vein on the hand. Preceding with 1% lidocaine, using the same injection site, or by prior administration of a potent short- acting opioid decreases the incidence of discomfort experienced by the patient and is most commonly used.[36] Pre-treatment with a small dose of propofol, opiates, nonsteroidal anti-inflammatory drugs, ketamine, esmolol/metoprolol, magnesium, a flash of light, clonidine/ ephedrine

combination, dexamethasone, and metoclopramide are the other drugs which have been tested with variable efficacy.[37]

The incidence of thrombosis or phlebitis is usually less than 1%. Changing the composition of the carrier fat emulsion for propofol to long and medium chain triglycerides decreases the incidence of pain on injection.[32] Accidental intraarterial injection of propofol has been described as producing severe pain but no vascular compromise.

Hypotension:

As explained in the cardiovascular effects, hypotension is one of the major adverse effects of propofol during induction of anaesthesia. This decrease in arterial blood pressure is associated with a decrease in cardiac output/cardiac index (±15%), stroke volume index (±20%), systemic vascular resistance (15%-25%), left ventricular stroke work index (±30%).[33] It also produces a marked reduction in the slope of the right ventricular end-systolic pressure- volume relationship.

This can be minimized by adequate preoperative hydration and the slow, controlled titration of propofol dose to achieve the desired effect.[34] However, patients with limited cardiovascular reserve, whether caused by hypovolemia, concurrent myocardial depressant or vasodilating drugs, or cardiac disease with reduced cardiac output may demonstrate exaggerated hypotension requiring immediate recognition and treatment.[36]

Bradycardia-related death:

Profound bradycardia and asystole have been described in healthy adult patients, despite prophylactic anticholinergics. The risk of bradycardia-related death during propofol

anaesthesia has been estimated to be 1.4 in 100,000. Heart rate responses to i.v administration of atropine are attenuated in patients receiving propofol.[37] This decreased responsiveness to atropine cannot be effectively overcome by larger doses of atropine suggesting that propofol may induce suppression of sympathetic nervous system activity. Treatment of propofol-induced bradycardia may require treatment with a direct β-agonist such as epinephrine.[34]

Allergic Reactions:

The phenyl nucleus and diisopropyl side chain are said to be the allergents. Patients who develop evidence of anaphylaxis on first exposure to propofol may have been previously sensitized to the diisopropyl radical, which is present in many dermatologic preparations. Likewise, the phenol nucleus is common to many drugs. Anaphylaxis to propofol during the first exposure to this drug has been observed in patients with a history of other drug allergies (eg; neuromuscular blocking drugs).[35]

Abuse Potential:

Intense dreaming activity, amorous behaviour, and hallucinations have been reported during recovery from low-dose infusions of propofol. Addiction to virtually all opioids and hypnotics, including propofol, has been described.

Bacterial Growth:

It strongly supports the growth of Escherichia coli and Pseudomonas aeruginosa, whereas the solvent (Intra- lipid) appears to be bactericidal for these same organisms and bacteriostatic for Candida albicans. Clusters of post- operative surgical infections

manifesting as temperature elevations have been attributed to extrinsic contamination of propofol.[33]

Disodium edetate or metabisulfite has been added to the formulation of propofol in an attempt to retard such bacterial growth. Strict aseptic technique still must be observed.[33]

Proconvulsant Activity:

Propofol-induced "seizures" during induction of or emergence from anaesthesia can occur and reflect spontaneous excitatory movements of subcortical origin. These responses are not thought to be due to cortical epileptic activity. Prolonged myoclonus associated with meningismus has been associated with its ministration. But there appears to be no reason to avoid propofol for sedation, induction, and maintenance of anaesthesia in patients with known seizures.[36]

Propofol infusion syndrome (PRIS):

PRIS is an extremely rare, but potentially deadly side effect of propofol that was first described in children in the 1990s and subsequently in adults after its use for sedation in the ICU setting. It is associated with infusion of propofol at 4 mg/kg/h or more for 48 hours or longer. The mechanism for sporadic propofol-induced metabolic acidosis is unclear but may reflect poisoning (cytopathic hypoxia) of the electron transport chain and impaired oxidation of long chain fatty acids by propofol or a propofol metabolite in uniquely susceptible patients. Currently the rate of mortality from PRIS is still close to 50%.[43]

Acute refractory bradycardia leading to asystole, in the presence of one or more of the following: metabolic acidosis (base deficit >10 mmol/ L^{-1}), rhabdomyolysis,

hyperlipidemia, and enlarged or fatty liver.[35] Other features include cardiomyopathy with acute cardiac failure, skeletal myopathy, hyperkalemia, hepatomegaly, and lipemia. The

symptoms and signs are the result of muscle injury and of the release of intracellular toxic contents. The major risk factors for its development are poor oxygen delivery, sepsis, serious cerebral injury, and large propofol dosage. Predisposing factors are genetic disorders impairing fatty acid metabolism, such as medium-chain acyl CoA (MCAD) deficiency and low carbohydrate supply. Because lipemia has been noted, a failure of hepatic lipid regulation, possibly related to poor oxygenation or a lack of glucose, may be the cause.[33]

There are no established guidelines for the treatment for PRIS. The best approach to early diagnosis is being aware that the condition exists, what its clinical features are, and maintaining a high index of suspicion should those clinical features develop in a patient receiving a propofol infusion.[32] Once the diagnosis is made, there is the simultaneous imperative to eliminate propofol from the body and treat the effects of PRIS. There is no antidote, but commencing an infusion of dextrose is unlikely to do harm (as long as blood glucose is monitored and controlled with insulin if necessary) and may have some benefit if propofol infusion syndrome has a mitochondrial aetiology.[36] Metabolic acidosis in its early stages is reversible with discontinuation of propofol administration although cardiogenic shock requiring assistance with extracorporeal membrane oxygenation has been described.

LIGNOCAINE (LIDOCAINE):

Lignocaine is a tertiary amine which is an amide derivative of diethylaminacetic acid with the longest pedigree and the most widely used local anaesthetic in clinical medicine.[37] It is effective in suppressing re-entry cardiac arrhythmias such as premature ventricular contractions and ventricular tachycardia. It has a pKa of 7.6.[32] It is a standard antiarrhythmic agent when given intravenously. Initial dose is 1-1.5 mg/kg iv can be repeated at 0.5-0.75 mg/kg iv every 5-10 min upto maximum cumulative dose of 3mg/kg. Infusion dose is 1-4mg/min (30-50mcg/kg/min).[36]

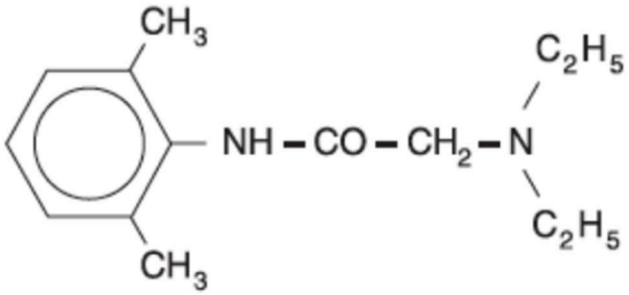

Figure 3: Structure of Lignocaine

It is available in the following forms:

Preservative-free solutions:

1. 2% solution for intravenous use, as an antiarrhythmic agent or to blunt responses to endotracheal intubation;[34]
2. 5%, 'heavy' solution for intrathecal use. It is made hyperbaric by the addition of 7.5% dextrose.[34]

With preservative (methyl paraben):

1. 1%, 2% solutions for use as local anaesthetic – intradermal, subcutaneous injections, epidural anaesthesia and nerve blocks.[32]
2. 2% viscous solution for gargling, 2% jelly for mucosal analgesia.[32]
3. 2% lignocaine with adrenaline (5μg/ml) for local infiltration. This can also be used for peripheral nerve blocks. [33]
4. 4% solution for mucosal analgesia. [36]
5. 4% (provides 4mg/spray) and 10% (provides 10mg/spray) lignocaine spray.[33]

Pharmacokinetics:

Due to high first pass metabolism in liver, it is orally inactive. When given iv bolus, action lasts only for 10–20 min because of rapid redistribution.[37] Lidocaine is metabolized in the liver by N-dealkylation, with subsequent hydrolysis to monoethylglycine and xylidide. Monoethylglycine is further hydrolysed, whilst xylidide undergoes hydroxylation to 4-hydroxy- 2,6-xylidine which is the main metabolite and excreted in the urine.[37] Metabolites of lidocaine may lower the fit threshold, thereby potentiating seizure activity, whilst others have some antiarrhythmic properties.

The $t_{1/2}$ of early distribution phase is 8 min and of elimination phase is nearly 2 hours. Its $t_{1/2}$ is prolonged in Congestive Heart Failure (CHF) due to decrease in volume of distribution and hepatic blood flow.[36]

Mechanism of action:

Diffusion of the uncharged base form through neural sheaths and the axonal membrane to the internal surface of cell membrane of Sodium (Na^+) channels.

Combination with hydrogen ions to form a cationic species and entry into the internal opening of the Na^+ channel and combination with a receptor.

blockade of the Na^+ channel, thereby decrease in Na^+ conductance which delays the rate of spontaneous phase 4 depolarization by preventing or diminishing the gradual decrease in potassium ion permeability that normally occurs during this phase.[33]

Lidocaine is a blocker of inactivated Na^+ channels more than that of open state.[32] Brevity of atrial action potential and lack of lidocaine effect on channel recovery might explain its lack of efficacy in atrial arrhythmias.[34]

It has minimal effect on normal ECG- QT interval may decrease. It causes little depression of cardiac contractility or arterial BP. [34] There are no significant autonomic actions: all cardiac effects are direct actions.

The most prominent cardiac action of lidocaine is suppression of automaticity in ectopic foci. Enhanced phase-4 depolarization in partially depolarized or stretched PFs, and after-depolarizations are antagonized, but SA node automaticity is not depressed.[34]

Adverse effects:

Dose related neurological effects are drowsiness, nausea, paraesthesia, blurred vision, disorientation, nystagmus, twitching and seizures. When the plasma concentration remains less than 5 mg/mL there is no cardiovascular effect. Seizures occur at plasma concentrations of 5 to 10 mg/mL. CNS depression, apnoea, and cardiac arrest occur when plasma concentrations are greater than 10 mg/mL. The convulsive threshold for lidocaine is decreased during arterial hypoxemia, hyperkalemia, or acidosis, emphasizing the importance of monitoring these parameters during continuous infusion of lidocaine to patients for suppression of ventricular arrhythmias.[35] The dose required to produce cardiovascular toxicity is said to be approximately 7 times higher than that required to produce central nervous system toxicity. [35]

EPHEDRINE:

Ephedrine is a naturally occurring sympathomimetic amine obtained from Ephedra vulgaris. It is the primary active constituent in ephedra which is derived from the aboveground parts of the plant and related species but can also be chemically synthesized.[33]

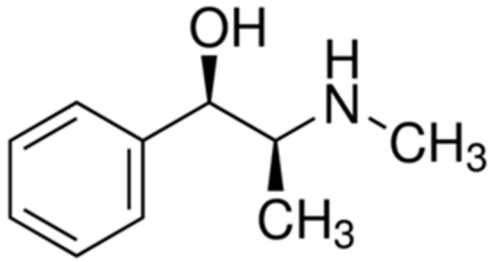

Figure 4: Structure of Ephedrine

Pharmacokinetics and pharmacodynamics:

The recommended intravenous dose in adults is 3–7.5 mg (maximum 9 mg), administered slowly, repeated every 3–4 minutes to a maximum of 30 mg, titrated to response. The adult oral dose is 30 mg 8-hourly, 1–2 drops as a nasal decongestant, may be administered every 4 hours. When administered orally, the drug acts within 60 minutes and has a duration of action of 3–5 hours. It mainly acts indirectly but also has some direct action on α1 and β1 receptors. [32] Endocytosis of ephedrine into α1- and β1-adrenoceptor presynaptic postganglionic nerve terminals displaces norepinephrine from the synaptic vesicles, which is then released to activate the corresponding postsynaptic receptors to cause arterial and venous vasoconstriction resulting in increased myocardial contractility. Hence, repeated injections produce tachyphylaxis (second dose of ephedrine produces a less intense systemic blood pressure response than the first dose). Premedication with clonidine enhances the pressor effects of ephedrine. It lacks selectivity and efficacy is low. [35]

It is resistant to metabolism by monoamine oxidase (MAO) in the gastrointestinal tract and thus permits the drug to be absorbed unchanged into the circulation after oral administration.[36]

Though its initial cardiovascular effects resemble those of adrenaline, because dose-related increases in heart rate, cardiac output and systemic vascular resistance, it is about 100 times less potent than Adrenaline but longer acting. Its action lasts about 4-6 hours. [33] It crosses to the brain and causes stimulation but central: peripheral activity ratio is lower than that of amphetamine. [33]

Up to 40% of a single dose of ephedrine is excreted unchanged in urine. Some of it is deaminated by MAO in the liver and rest undergo hepatic conjugation.[32] The slow inactivation and excretion of ephedrine are responsible for its prolonged duration of action.[32]

Cardiovascular Effects:

Ephedrine has positive inotropic and chronotropic action producing an increase in the cardiac output, myocardial work and myocardial oxygen consumption. Myocardial irritability is increased by the drug. There is increases the coronary blood flow, systolic and diastolic blood pressures, and pulmonary artery pressure. An increase in the circulating volume is seen due to post- capillary vasoconstriction. Renal and splanchnic blood flows are decreased. Its systemic blood pressure–elevating response is less intense and lasts approximately 10 times longer than adrenaline. [37]

Other effects:

It is a respiratory stimulant and causes marked bronchodilatation. Increases the cerebral blood flow. Mydriasis occurs, but light reflexes remain unaffected. The drug has local anaesthetic properties. It relaxes gastrointestinal smooth muscle and causes splanchnic vasoconstriction. It constricts renal blood vessels and may lead to a decrease in both renal blood flow and glomerular filtration rate. [36] The drug contracts the bladder sphincter and relaxes the detrusor muscle which may precipitate acute retention of urine. The drug also increases the rate of hepatic glycogenolysis and may increase the basal metabolic rate. The drug has been shown to stimulate oxygen uptake and thermogenesis. [34]

Uses:

Vasopressor: It is often the first choice of vasopressor. When given intravenously in a bolus dose of 5-10 mg this drug has a predominantly β adrenergic agonist effect and produces an increase in heart rate with some effect on the venous pooling but little direct effect on peripheral resistance. Hence, in pregnancy, it preserves the uterine blood flow in the presence of spinal hypotension. [32]

Diabetic protective effect: Ephedrine is considered as an oral hypoglycemic agent because it reduces glucagon and blood glucose levels mediated by increasing incretins that are responsible for inhibiting the release of glucagon and for promoting an increase in insulin secretion. The anti-hyperglycemic effects could be mediated by the elevated expression of peroxisome proliferator-activated receptor α (PPAR-α), adiponectin and the suppression of tumor necrosis factor-α (TNF-α) expression [33]

Anti-obesity activity: An induced reduction of weight gain, an epididymal fat accumulation, a visceral adipose tissue weight and that the size of adipocytes improved plasma lipids levels, associated with an upregulated expression of PPAR-α, which controls fatty acid oxidation, lipid and lipoprotein metabolism. It also suppresses appetite and stimulates thermogenesis and this effect is maintained during long-term administration though it lacks the classical dose-dependent increase in thermogenic response. [34] The success of ephedrine as a weight loss agent in combination with caffeine and or aspirin is well established

Other uses include; mild chronic bronchial asthma, nocturnal enuresis, narcolepsy, diabetic autonomic neuropathy, hiccups and, as a nasal decongestant.

Adverse effects:

Insomnia, anxiety, tremor, headache, dysrhythmias, nausea and vomiting, palpitations, tachycardia, acute myocardial infarction, cardiac arrest, sudden death and haemorrhagic and ischemic strokes can occur. Ephedrine is irritant to mucous membranes. An acute hypertensive crisis may be precipitated when the drug is administered to patients receiving MAO inhibitors, doxapram, beta-blockers, oxytocin, and ergot alkaloids.[35]

REVIEW OF LITERATURE

Propofol's favourable pharmacokinetic profile makes it ideal for induction and maintenance of anaesthesia, whether by bolus or infusion. Propofol, given as a fast IV infusion at 1.5 to 2.5 g/kg, induces unconsciousness in about 30 seconds. After anaesthesia was given with rest of the drugs used for rapid i.v induction, awakening is faster and complete. One of the most significant advantages of propofol over other medicines used for the same purpose is the faster recovery of consciousness with little lingering central nervous system (CNS) effects.[33]

The most prevalent side effect linked with i.v. propofol to awake patients is pain on injection. The pain from a propofol injection might be immediate or delayed. Immediate pain is most likely caused by a direct irritating effect, but delayed pain is most likely caused by an indirect effect through the kinin cascade. The latency of delayed pain is between 10 and 20 seconds. The source of pain after receiving a propofol injection is unknown. The osmolar content and pH of liquids that came in touch with the intimal layer of superficial vein of hand, were thought to be involved in the pain production. The amount of pain was also determined by the volume injected and the rate at which blood flowed through the vein. The unpleasant sensation from veins is thought to be caused by neural elements within the vein walls, presumably from free afferent nerve terminals between the media and intima. The pain-conducting axons are most likely myelinated A-delta axons.

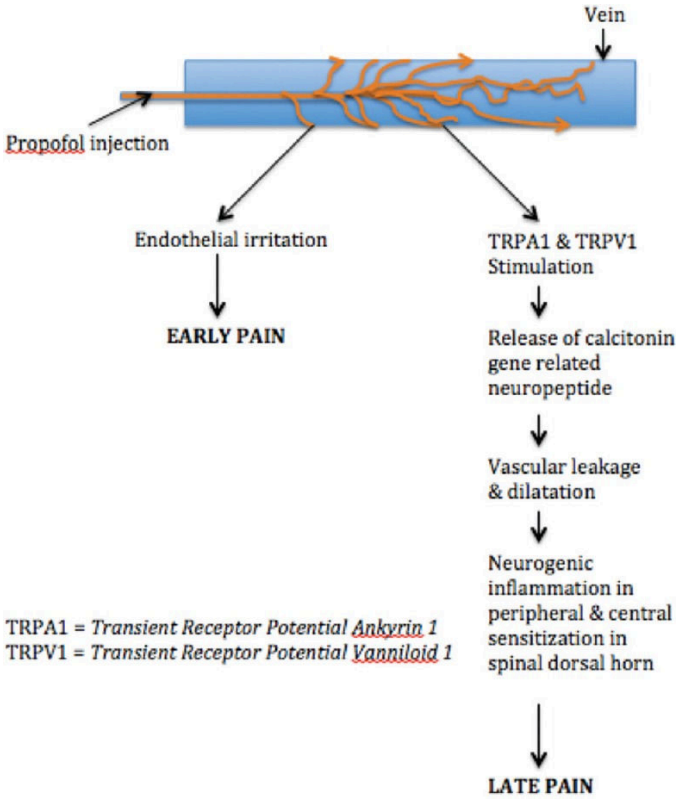

Figure5: Mechanism of Pain on Injection of Propofol

J. Brooker et al, [12] investigated 50 healthy 16-55 year old females undergoing gynaecological surgeries in 1985 and found that lignocaine alleviated discomfort induced by propofol injection. Lorazepam 2 mg was administered 2 hours prior to surgery, while papaveretum I5 mg and prochlorperazine 12.5 mg were given 1 hour before surgery. In 13 of them, 10 mg lignocaine (1%) was given before the propofol, 7.5 mg lignocaine was mixed with 142.5 mg propofol in 30 cases, and seven patients received no lignocaine. The latter group was reduced in size because three patients complained of significant pain, and it was deemed unjustifiable to continue. They came to the conclusion that adding lignocaine to the emulsified propofol is beneficial, as it reduces pain by roughly 7%.

In another study conducted in the same year by S. Helbo-Hans et al,[13] Less than 3 minutes before induction of anaesthesia, 10 mg lignocaine hydrochloride and 7 mg NaCl in 1 ml of water were mixed with 19 ml of emulsified propofol.After securing 17 G cannula into

a vein on dorsum of hand, 80 patients divided into two groups. Control group-19 ml of emulsified propofol with 1ml isotonic saline. Assessment of pain on i.v propofol injection was done after induction of anaesthesia as well as 1-2 hrs after recovery. Arterial BP and HR were measured before induction& at 5 min intervals during anaesthesia. In the control group incidence of moderate to severe pain was (7+6)/40 i.e 32.5% whereas it was just (2+0)/40 i.e 5% in the study group ($p<0.01$). they confirmed this by post- operative pain scores (<0.01). They concluded that, propofol emulsion occasionally causes severe pain on injection, unless special precautions are taken, and also that the pain is remembered very well after recovery. Also, addition of lignocaine significantly reduced the pain.

In 1991, a single blinded randomized controlled trial was conducted by P. Barker et al[14] they compared four groups namely, unmodified propofol(Group P), Propofol with 0.05% lignocaine(Group PL), Propofol at 4°C(Group CP) and 10ml of 0.9% saline at 4°C with unmodified Propofol(Group CS). Patients were premedicated with temazepam 10-20 mg 1 hr before surgery. After securing a 23-Gwide bore cannula on non-dominant large visible dorsal vein, patients were allocated randomly to one of four groups. Pain was assessed 5 seconds after administration of 50 mg propofol over 5 secs. A second pain score was assessed after 50% of calculated dose of propofol was administered. The patient was asked to rate any sensation in his or her arm or hand as 'no discomfort,' 'uncomfortable,' 'painful,' or 'very painful.' When cold saline is injected before unmodified propofol, the incidence of pain and discomfort is significantly higher (22%), as compared to unmodified propofol (75%) (p,0.005), and is similar to that after cold Propofol (33%) and Propofol with lignocaine (33%) (p,0.005). No discernible difference in treatment groups were seen.

G. Gehan et al, in 1991,[15] studied the required lignocaine dose that should be used to decrease pain after a propofol injection. Prospective, randomised, double-blinded study

was undertaken with 310 patients aged 18 to 80 years who were either ASA class I or II and were undergoing GA for diagnostic or minor surgery. Subjects did not receive any analgesic or sedative drugs in the 12 hours as premedication. All of the groups' hemodynamics were preserved. Propofol injections alone (group A) resulted in pain levels of 1, 2, and 3 in 20.7 percent, 10.3 percent, and 5.1 percent of patients, respectively. The incidence of pain was dramatically reduced in group B (lidocaine 0.1 mg/kg). The difference between group B and groups C (lidocaine 0.2 mg/kg) and D (lidoocaine 0.4 mg/kg) was not significant. As a result, they determined that a lignocaine dose of 0.1 mg/kg greatly decreased pain. Also increasing the dose had no effect.

In 1998, A. K Parmar and C. K Koay [16] tested the effectiveness of cold propofol against propofol premixed with lignocaine in reducing injection discomfort. Three study groups and one control group were assigned to patients at random. Pain was measured 15 seconds after the propofol injection began. Cold propofol (Group C) was linked with a very high incidence of injection discomfort, whereas lignocaine 0.1 mg/kg premixed with propofol (Group A) greatly reduced the incidence of pain (p 0.001).However, increasing the lignocaine dosage above 0.1 mg/kg did not significantly reduce the incidence of discomfort when the dose was increased to 0.2 mg/kg (Group B). The inclusion of lignocaine reduced the occurrence of excitatory side effects by a significant amount.

Subsequently lignocaine either as premedication or mixing with propofol solution was studied thoroughly to counter the pain on injection caused by propofol. Like, in 1999, Ho CM et al,[17] made an attempt to determine the optimum conc. of lidocaine to reduce pain on injection of propofol-lidocaine mixture. In their randomized prospective double-blinded study which

included 240 ASAI-II females, there were four groups-Group A (control),propofol with normal saline, for induction, propofol with 0.05 percent lidocaine (Group B), propofol with 0.1 percent lidocaine (Group C), and propofol with 0.2 percent lidocaine (Group D) were used. The pain scale has four categories: “no pain,” “mild pain” (soreness or slight pain when questioned), “moderate pain” (subjective complaint of a bearable uncomfortable sensation), and “severe pain” (patient flexes her arm to deny injection). Injection pain was seen in 91.7 percent of Group A, 76.7 percent of Group B, 8.3 percent of Group C, and 10.0 percent of Group D participants. According to the researchers, incidence of injection pain was considerably less in Group C than in Groups A and B ($p<0.001$). Thus, based on the findings of the study, propofol containing 0.1 percent lidocaine was more effective than propofol containing 0.05 percent lidocaine in minimising propofol injection pain. Furthermore, raising the lidocaine conc. above 0.1 percent did not further reduction in injection pain. In addition, 0.1 percent lidocaine is the most effective concentration for minimising propofol pain injection in the current study population.

After establishing that lignocaine is useful to prevent pain on propofol injection, it was then included in the control group in the future studies. Also, along with pain on injection, hypotension is another major side effect of propofol. Many drugs have been used to counter this hypotension.

In 2002, Cheong et al,[4] conducted a randomized, placebo-controlled, double-blinded study

Where the incidence of propofol-induced pain after pre-treatment with different doses of ephedrine as compared with lidocaine were compared. No analgesics were received prior to surgery. Patients were randomly assigned to one of six groups: 0.9 percent normal saline

2 mL (Group P, n = 30), 2 percent lidocaine 2 mL (Group L,), ephedrine 30 μg/kg (Group E30), 70 μg/kg (Group E70), 110 μg/kg (Group E110), and 150 μg/kg (Group E150), The incidences of

pain were 6.6 percent in P, 43.3 percent in L, 35.6 percent in E30, 43.3 percent in E70, 40 percent in E110, and 42.8 percent in E150. MAP reduced significantly in the P and L groups compared to values before induction (P 0.05), although it remained constant in all ephedrine groups. Following intubation, the E110 and E150 groups had significantly higher MAP and heart rate characteristics than the P and L groups (P 0.05). Thus, pre-treatment with a low dose of ephedrine (30 & 70 μg/kg) decreased incidence and severity of propofol-induced pain with no significant hemodynamic change.

In 2005, Tadahiko Ishiyama et al,[18] clonidine and ephedrine on propofol-induced pain and hemodynamic alterations during the induction process were studied in 200 patients. The pain levels were graded as none, medium, or severe by each patient. The pain score was then assessed every 5 seconds by the blinded investigators, who recorded the maximum degree as the pain score. Propofol-induced pain was seen in 30% of CE patients, 68 percent of CS patients, 64 percent of DE patients, and 82 percent of DS patients. CE had a considerably lower median pain score than the other groups ($p<0.0001$). Furthermore, the medial pain scores in CS and DE were less than those in DS ($p<0.05$). The clonidine groups had lower baseline MAP than the diazepam groups ($p<0.05$), while baseline HR was similar in both groups. CE and DE had significantly increased in HR from baseline after ephedrine injection ($p<0.05$), while MAP did not change from baseline values after the ephedrine administration. Furthermore, the effects of ephedrine on MAP & HR were equivalent in CE and DE. The mean AP soon before l intubation was lower than the baseline values ($p<0.05$) and did not differ between the groups. CE and CS had

considerably lower MAP and HR following intubation than DE and DS. Clonidine and ephedrine, they said, effectively reduced propofol-induced discomfort but did not prevent propofol-induced hypotension. During the induction sequence, clonidine did

not amplify the low-dose ephedrine-induced increase in heart rate and produced stable hemodynamic conditions.

In 2008, Azim Honarmand et al,[19] compared magnesium (Group M), ketamine (Group K), lignocaine (Group L) with the control group being normal saline (Group C) in 200 patients. During i.v. propofol, 88 percent of the patients in Group C experienced pain, compared to 18 percent, 28 percent, and 34 percent in the lidocaine, ketamine, and magnesium groups (p 0.01). When compared to Group C, the incidence of mild, moderate, and severe pain was considerably lower in Groups K, L, and M (p 0.05). Heart rate and mean blood pressure were not different in the three groups at different time intervals. In the ketamine group, 32 percent experienced hypotension, compared to 64 percent, 60 percent, and 58 percent in the magnesium, lidocaine, and control groups, respectively (p = 0.005). Thus, his study showed that pretreatment with the above-mentioned drugs are equally effective in attenuating propofol-induced pain.

Kwak et al,[20,21] in his 2 studies conducted in 2007 and 2008, compared lignocaine with dexamethasone and remifentanil. In the one where he compared three groups with remifentanil alone, lignocaine and combination of remifentanil and lignocaine, Patients who received lidocaine + remifentanil (95.3 percent) had a lower overall incidence of no pain than those who received lidocaine alone (64.3 percent) [p 0.001] or remifentanil alone (57.1 percent) [p 0.001]. The incidence of discomfort was not different between the lidocaine alone group and the remifentanil alone group (p = 0.21).In the study where dexamethasone was compared in 142 patients, 1 of 35 patients (88.6%) reported pain on

injection of propofol as compared with 12 (34.3%), 13 (37.1%), and 0 (0%) who received lidocaine, dexamethasone, and a combination, respectively ($p< 0.01$). He found that a combination of lignocaine (20mg)-dexamethasone (6mg) and lignocaine (20mg)-remifentanil (0.3 g/kg) was more effective than either treatment alone in lowering the occurrence of pain after propofol injection.

James Austin et al, [6] also conducted a study in 2009 with 156 subjects allocated into Group L (10mg lidocaine), Group E15 (ephedrine-15mg), Group E30 (ephedrine-30mg). The results showed that out of the 51 patients, six patients in Group L required rescue for hypotension and no patients in the ephedrine groups required any rescue for hypo or hypertension. They said that addition of ephedrine to propofol is as effective as adding lidocaine at reducing injection pain, and its effects on hemodynamics and concluded that adding 30 μg of ephedrine to 20 mL of 1% propofol is as effective as adding lidocaine in preventing injection pain, and it results in a more stable hemodynamic profile.

In 2011, Leena Jalota et al,[22] conducted a systematic review and meta-analysis to determine the most efficacious approach for preventing pain on injection of propofol and concluded that, the two most successful options for minimising discomfort following propofol injection were the use of the antecubital vein or preparation with lidocaine in conjunction with venous occlusion when the hand vein was chosen. If independent efficacy is anticipated, pre-treatment of the hand vein with lidocaine or ketamine and use of a propofol emulsion including medium and long chain triglycerides could be a third viable approach. While not the most successful technique on its own, a modest dose of opioids before induction can help. Reduced likelihood of pain can occur from the injection by half and can thus be suggested unless contraindicated.

In 2011, the effect of lignocaine and ephedrine alone and in combination was studied by Marzieh-BeigomKhezri and Hamid Kayalha.[5] Patients in Group L had a pain rate of 39.4 percent, Group LE had a rate of 45.4 percent, Group E30 had a rate of 63.6 percent, Group E70

had a rate of 75.8%, and Group S had a rate of 72.7 percent. After propofol, the MAP in Group LE was lowered by 12.63 11.68 mmHg. Group LE and Group L (95 percent CI 5.94–16.47; p = 0.000) difference was significant, as was the difference between Group LE and Group S (95 percent CI 4.25–14.58; p = 0.001). After the propofol injection, the HR in Group L and Group S decreased significantly (p0.05), however the values in the ephedrine groups remained noticeably unchanged. Even though, HR in Group L and Group S reduced significantly (p<0.05) after the propofol injection, the values in the ephedrine groups remained noticeably unchanged. Following propofol injection, the HR was lowered by 9.30 8.88/min in Group S (95 percent CI 6.15–12.45; p = 0.000) and 6.21±11.39/min in Group L (95 percent CI 2.17–10.25; p = 0.004), but it was 1.09±14.94, 0.424±12.68, and 4.90±14.04 in Group E30, E70, and LE, respectively. The changes in HR before propofol in the ephedrine groups. Although the HR in Group L and Group S reduced significantly (p<0.05) after the propofol injection, the values in the ephedrine groups remained noticeably unchanged. Finally, they discovered that combining the two medications lowered the incidence and severity of propofol-induced pain while simultaneously improving the hemodynamic profile. However, they were unable to demonstrate that this combination is more effective in lowering additional pain.

Vida Ayatollahi et al,[23] in 2011, evaluated the ephedrine, lidocaine, and ketamine effect on injection pain, hypotension, and bradycardia caused by injection of propofol as compared to placebo in a randomised placebo-controlled clinical experiment. They came

to the conclusion that all of the test medications could significantly reduce pain when compared to a placebo. Ephedrine could also effectively regulate SBP, DBP, and MAP 1 minute after intubation for hemodynamic management. According to their findings, ephedrine could be an effective treatment for pain and hemodynamic abnormalities caused by propofol.

In the same year, Mohamed R El-Tahan,[24] said that prophylactic use of small doses of ephedrine (0.07−0.1 mg/kg) is safe to counter the hypotension response to propofol anesthesia with minimal hemodynamic changes in patients undergoing anaesthesia for valve surgery.

In 2014, Mansoor Masjedi et al,[25]assessed the Two doses of ephedrine were used as a prophylactic measure to control fall in BP and bradycardia caused by anaesthesia induced due to propofol and remifentanil in patients between the ages of 20 and 50 who were undergoing short-term elective ophthalmic and orthopaedic surgery under general anaesthesia. Patients taking 0.15 mg/kg ephedrine had significantly high mean arterial pressure than controls (p=0.017). The low dosage ephedrine group did not vary from the controls in terms of mean arterial pressure (p=0.09). The equivalent pressures in the two groups receiving ephedrine were not significantly distinct. While the mean HR between the groups was similar before induction of anaesthesia (p= 0.658), the mean HR was significant between the three groups 2 minutes after induction of anaesthesia, 1 minute after intubation, and 5 minutes after intubation. The mean HR in the high dosage ephedrine group was considerably higher than the controls, but not significantly different in the low dose ephedrine group (p= 0.263). The HR mean was not statistically significant between

the two ephedrine groups. As a result, they believe that administering a high dose of ephedrine (0.15 mg/kg) can help prevent hypotension and bradycardia.

Gilani et al,[26] in 2015, studied 120 patients randomly divided into three groups. They investigated the incidence of vascular pain following rapid (40%) and slow (52.5%) propofol injections, as well as the efficacy of ephedrine on reducing vascular pain. Pain was reported to be 27.5 percent after a rapid injection of ephedrine. Pain was statistically insignificant in the rapid injection groups than in the slow injection groups (p=0.025). With fast propofol infusion, there was no significant difference in pain between the two groups (p= 0.76). Heart rate (p=0.45) and blood pressure (p=0.58) did not differ significantly across the three groups. Hypotension was statistically significant after induction; however, it was the same in all groups (p=0.001). They found that rapid propofol administration caused less vascular pain than gradual injection, but that 10 mg ephedrine had no effect.

Pramote et al,[27] in 2016, searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 10), Ovid MEDLINE (1950 To October 2014), Ovid EMBASE (1988 to October 2014), LILACS (1992 to October 2014). This evaluation includes 85 research, with 82 of them (10,350 people) being qualified for quantitative analysis. All of the subjects, who ranged in age from 13 to 89, patients undergoing non emergent surgery. They looked into the efficacy and side effects of lidocaine in avoiding increased pain after a propofol injection in the reference lists of articles. The incidence of pain and high-intensity pain following injection of propofol was 63.7 percent (95 percent CI 60 percent to 67.9%) and 37.9 percent (95 percent CI 33.4 percent to 43.1 percent) in the control group, respectively, while the lidocaine group had 30.2 percent (95 percent CI 26.7 percent

to 33.7 percent) and 11.8 percent, respectively (95 percent CI 9.7 percent to 13.8 percent). Lidocaine admixture and pre-treatment were both beneficial in lowering discomfort after propofol injection, according to the research. There was no data on patient satisfaction in any of the studies.

Another study where causes and remedies for pain on Propofol injection (POPI) were studied by Kalindi Desousa[28] in 2016. This descriptive review included relevant papers from the Medline and Embase databases, with the following conclusions: (1) POPI is caused by venous adventitia irritation, which causes the release of mediators such as kininogen from the kinin cascade. (2) When two or more medications or measures are employed, the risk of POPI is significantly reduced. As a result, a multimodal approach to minimizing POPI is required. (3) Any regimen that combines a local anaesthetic in combination with a central sedative/analgesic and rapid injection into a big vein should significantly lower the incidence of POPI.

Agarwal et al,[8] Studied pre-injection ephedrine has a pain-relieving effect during Propofol injection. The efficacy of ephedrine 30 g/kg pretreatment to lignocaine 40 mg for avoidance of propofol-induced pain was compared in this randomised, double-blind, placebo-controlled experiment. Pain was graded on a four-point scale: 0=no pain, 1=mild pain, 2=moderate pain, and 3=severe pain at the moment of propofol injection. In the ephedrine pretreatment group, 27 patients (87%) experienced discomfort during intravenous injection of propofol, compared to 24 (77%) in the normal saline group. When compared to the other study groups, propofol-induced pain was detected in only 13 (42%) of the lignocaine group ($P<0.05$). However, pretreatment with 2% lignocaine (40 mg) was effective in attenuating propofol-associated pain.

Ratanshi and Mandour [29] in 2021, discussed whether lidocaine should be standardised in use for prevention of pain on propofol injection for general anaesthesia induction or sedation. They concluded that pain relief and better patient satisfaction was observed, the effect on the emulsion itself, the efficacy of Propofol once mixed, and the effect on bacteria development in the syringe were all drawbacks.

Newer methods are coming up to prevent pain on Propofol injection. Like in 2021, Hwang et al,[30] a total of 100 people were randomised into two groups for elective ambulatory surgery under general anaesthesia. Patients in the control group (n = 50) got propofol infusions without vibration analgesia. Patients in a treatment group (n = 50) received propofol infusions with vibration analgesia via the Buzzy device. A 4-point pain manifestation scale score was used to assess pain. The vibration analgesia group was 0.47 times less likely than the control group to suffer any pain (95 percent confidence interval, 0.24-0.94; P = 0.03). The treatment group's median summative pain score was considerably lower than the control group's (p0.01). They came to the conclusion that propofol infusion in ambulatory surgery is a safe and effective strategy.

MATERIALS AND METHODOLOGY

The study titled "To Compare the effect of Lignocaine, Ephedrine and Combined Lignocaine and Ephedrine Pretreatment on Pain on Injection due to Propofol in Adult Patients undergoing General Anaesthesia- A One Year Hospital Based Randomized Clinical Trial" conducted in KLE's Dr. Prabhakar Kore Hospital and Medical Research Centre, Jawaharlal Nehru Medical College, Belagavi.

The inclusion and exclusion criteria were as follows:

- **Inclusion Criteria:**
  - ⇒ ASA (American Society of Anaesthesiologists) Grade I and II
  - ⇒ Age between 18 to 60 years.
  - ⇒ Patients posted for surgery under General Anaesthesia
  - ⇒ Informed consent.
- **Exclusion Criteria**:
  - ⇒ History of propofol, lignocaine or ephedrine adverse effects
  - ⇒ History of allergy, neurologic or cardiovascular disease
  - ⇒ History of intake of analgesic medication within 24 hours of surgery

Sample size calculation:[5]

Using a two-sided test with α=0.05, the sample number of subjects per group was predicted to provide an 80 percent power to detect such a difference. The formula for calculating the minimum sample size based on the mean and standard deviation:

$$n = \frac{(z_\alpha + z_\beta)^2(s_1^2 + s_2^2)}{(\bar{X}_1 - \bar{X}_2)^2}$$

Where Z_α is related to the level of significance and Z_β is related to the test's power. The significance level is set at 5%. For the test to have 80 percent power, Z_α=1.96 and Z_β =0.84.

The mean arterial pressure (MAP) was used to determine the sample size. Before intubation, X_1 is the MAP of the lignocaine group (72.29), and X_2 is the MAP of the ephedrine (70/kg) group (80.19). S_1 is the lignocaine group's standard deviation (9.28), and S_2 is the ephedrine group's standard deviation (70g/kg) (12.21). With these numbers, a sample size of 30 people was obtained in each group, for a total of 90 people. The sample size was increased to 40 in each group, for a total of 120 participants, to make the study more conclusive.

Methodology:

Randomization was done using computer generated table and patients were divided into three groups as follows:

- Group A: Intravenous lignocaine (1.5 mg/kg)
- Group B: Intravenous ephedrine (50μ/kg) alone
- Group C: Intravenous lignocaine (1.5 mg/kg) + ephedrine (30 μ/kg)

After obtaining the approval of the Institutional Review Board & Ethical Committee, registering with the Clinical Trials Registry- (CTRI/2020/09/027529) a written informed consent taken from “ASA I & II” patients posted for surgery under general anaesthesia were included in the study. A routine pre-operative assessment and routine investigation of all the patients was done.

In the recovery room adequate preoperative fasting of 8 hrs was confirmed. In the operation theatre intravenous cannula was placed. Electrocardiogram, non-invasive blood pressure, pulse oximeter monitors were attached. One minute after the administration of

the test solution, 2 mg/kg i.v propofol was given at 1 ml/s, without flow of i.v fluid. Patients were informed about a sting sensation on giving the drug before induction of anaesthesia. They were asked mean score level of their pain during the injection period before the loss of consciousness according to VRS, which was explained to patients at preoperative examination. They were asked to rate their pain on a scale of one to ten before losing consciousness during the injection phase. The following are the VRS grading criteria: 0=no pain (negative response to questioning), 1=mild pain (pain reported only in response to questioning without any behavioural signs), 2=moderate pain (pain reported in response to questioning and accompanied by a behavioural sign or pain reported spontaneously without questioning), 3=severe pain (pain reported in response to questioning and accompanied by a behavioural sign or pain reported spontaneously without questioning) (strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears).

Systolic, diastolic blood pressures, mean arterial pressures and heart rate were recorded:

- Before administration of the test solution,
- At propofol injection, and
- One minute after propofol injection.

Preoxygenation at 6 L/min was administered via facemask to all patients. Once loss of consciousness was achieved with propofol injection, midazolam 0.05 mg/kg, fentanyl 2 mg/kg, and vecuronium 0.1mg/kg were given. 3min after vecuronium injection, the tracheal intubation was done and anaesthesia maintained with 1-2% isoflurane and 50% N_2O in O_2. At the end of surgery after adequate reversal with neostigmine 0.05mg/kg tracheal extubation was done.

Statistical Analysis:

"Parametric data were analyzed using analysis of variance, independent sample t-test, and paired sample test. heart rate (HR) , blood pressures and arterial pressures (MAP) were tested for normal distribution by one sample ANOVA test and further compared with baseline values using the two tailed paired t-test. The within group comparisons in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were performed using analysis of independent sample t-test. The non-parametric data for pain scores were analyzed using the ANOVA test. Data was presented as mean±standard deviation, number (%), or median±interquartile range. A p value <0.05 was considered to be significant."

RESULTS

The present study "To compare the effect of lignocaine, ephedrine and combined lignocaine-ephedrine pretreatment on pain on injection due to propofol in adult patients undergoing general anaesthesia- A one-year hospital based randomized clinical trial" was conducted in 120 patients divided into three groups.

- Group A: Intravenous lignocaine (1.5 mg/kg)
- Group B: Intravenous ephedrine (50μ/kg)
- Group C: Intravenous lignocaine (1.5 mg/kg) + ephedrine (30 μ/kg)

The data obtained were analysed and tabulated as follows:

Table 2a: Gender Distribution in each Group

Gender	GROUP A	GROUP B	GROUP C
Female	21	20	16
Male	19	20	24
TOTAL	40	40	40

Figure 6: Gender Distribution in each Group

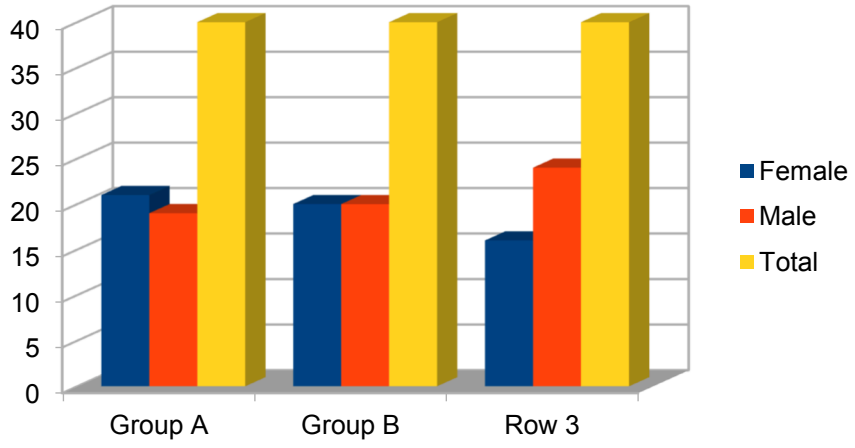

Table 2b: Distribution of Age, Height and Weight

	GROUP A		GROUP B		GROUP C	
	MEAN	**S.D.**	**MEAN**	**S.D.**	**MEAN**	**S.D.**
Age(yrs)	37.83	12.38	35.58	11.87	38.75	12.88
Height(cms)	160.15	7.60	159.80	7.09	161.00	6.92
Weight(kgs)	58.25	7.80	60.03	7.98	58.10	8.35

Figure 7: Distribution of Age, Height and Weight

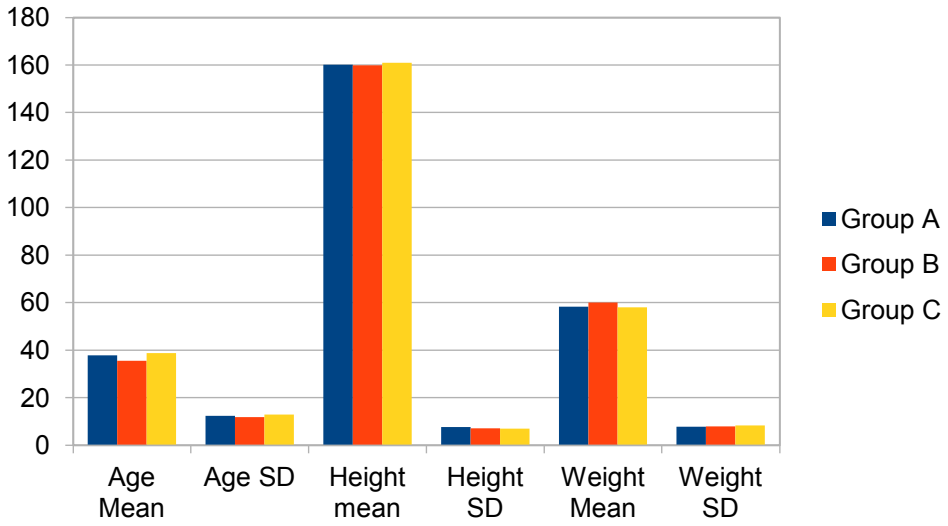

Table 2c: Distribution of ASA Grade

ASA Grade	GROUP A	GROUP B	GROUP C
	Count %	Count %	Count %
	26+14	26+14	25+15
I	65%	65%	62.5%
II	35%	35%	37.5%

Table 3a: VRS for Pain on Injection

VRS for injection of propofol	GROUP A	GROUP B	GROUP C
0	21	4	29
1	15	12	11
2	4	16	0
3	0	8	0
TOTAL	40	40	40

- Using CHI-SQUARE test the value of p is less than 0.0001 (highly significant)
- There is a significant association between the levels of VRS and the three groups

Figure 8 :VRS for Pain on Injection

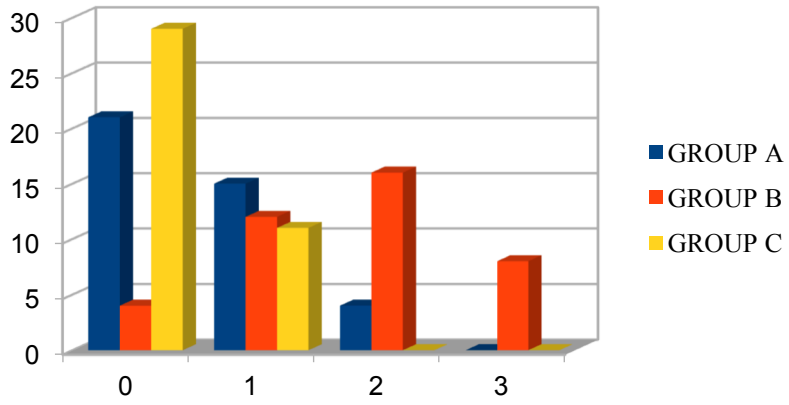

Table 3b: Median and interquartile range for VRS on Injection of Propofol

	Median	Inter quartile range
Group A	0	0,1
Group B	2	1,1
Group C	0	0,1

- Using the non-parametric, KRUSKAL-WALLIS test the value of p is less than 0.0001 (highly significant)
- GROUP B significantly differs from the other two groups.

Table 4a: Comparison of Systolic Blood Pressure (SBP) & Diastolic Blood Pressure (DBP) between the three Groups

SBP											
before Injection of test solution (BI)	**Mean**	**SD**	**p value**	**At Propofol injection (PI)**	**Mean**	**S. D**	**p value**	**one minute after Propofol injection (AP)**	**Mean**	**S. D**	**p value**
Group A	130.60	16.97	**0.1197**	**Group A**	128.13	15.67	**0.1446**	**Group A**	115.53	15.35	**<0.0001**
Group B	125.18	10.55		**Group B**	130.18	8.12		**Group B**	128.40	8.24	
Group C	125.25	11.75		**Group C**	124.98	10.35		**Group C**	121.95	10.05	
DBP											
before Injection of test solution (BI)	**Mean**	**SD**	**p value**	**At Propofol injection (PI)**	**Mean**	**S. D**	**p value**	**one minute after Propofol injection (AP)**	**Mean**	**S. D**	**p value**
Group A	83.30	8.92	**0.0255**	**Group A**	80.63	9.14	**0.0640**	**Group A**	72.05	10.33	**0.0004**
Group B	78.30	9.96		**Group B**	81.68	7.21		**Group B**	80.53	7.64	
Group C	78.38	9.02		**Group C**	77.58	7.60		**Group C**	75.43	9.64	

For SBP, by observing the above table since p-value is less than 0.0001 at propofol injection, therefore there is significant difference of means between the groups A, B & C in AP.

For DBP, by observing the above table since p-value is equal to 0.0004 after propofol injection, therefore there is significant difference of means between the groups A, B & C in AP.

- **Comparison between Group A and Group B for SBP:**
- **P value < 0.0001**
- **Inference:** Highly Significant
- There is non-Homogeneity in the means of AP between Group A and Group B.
- Using Students unpaired t-test, Group A significantly differs from Group B (AP).
- **Comparison between Group A and Group B for DBP:**
- **P value = 0.0001**
- **Inference:** Highly Significant
- There is non-Homogeneity in the means of AP between Group A and Group B.
- Using Students unpaired t-test, Group A significantly differs from Group B (AP).
- **Comparison between Group B and Group C for SBP:**
- **P value = 0.002**
- **Inference:** Very Significant
- There is non-Homogeneity in the means of AP of the two groups.
- Using Students unpaired t-test, Group B significantly differs from Group C (AP).
- **Comparison between Group B and Group C for DBP:**
- **P value = 0.011**
- **Inference:** Significant
- There is non-Homogeneity in the means of AP of the two groups.

- Using Students unpaired t-test, Group B significantly differs from Group C (AP).

➢ **Comparison between Group A and Group C for SBP:**

- **P value = 0.0297**
- **Inference:** Significant
- There is non-Homogeneity in the means of AP of the two groups.
- Using Students unpaired t-test, Group A does not significantly differ from Group C (AP).

➢ **Comparison between Group A and Group C for DBP:**

- **P value = 0.1349**
- **Inference:** Not Significant
- There is non-Homogeneity in the means of AP of the two groups.
- Using Students unpaired t-test, Group A does not significantly differ from Group C (AP).

Table 4b: Comparison of Mean Arterial Pressure (MAP) between the three Groups

before Injection of test solution (BI)	Mean	SD	p value	At Propofol injection (PI)	Mean	S. D	p value	one minute after Propofol injection (AP)	Mean	S. D	p value
Group A	99.16	11.45	**0.0356**	**Group A**	96.52	11.07	**0.0702**	**Group A**	86.61	11.29	**< 0.0001**
Group B	93.93	9.83		**Group B**	97.84	6.95		**Group B**	96.48	7.05	
Group C	94	9.33		**Group C**	93.38	7.84		**Group C**	90.93	9.07	

By observing the above table since p-value is less than 0.0001 after propofol injection, therefore there is significant difference of means between the groups A, B & C in AP.

- **Comparison between Group A and Group B:**

- **P value < 0.0001**
- **Inference:** Highly Significant
- There is non-Homogeneity in the means of AP between Group A and Group B.
- Using Students unpaired t-test, Group A significantly differs from Group B (AP).

- **Comparison between Group B and Group C:**

- **P value = 0.003**
- **Inference:** Very Significant
- There is non-Homogeneity in the means of AP of the two groups.
- Using Students unpaired t-test, Group B significantly differs from Group C (AP).

- **Comparison between Group A and Group C:**

- **P value = 0.0627**
- **Inference:** Not Significant
- There is non-Homogeneity in the means of AP of the two groups.
- Using Students unpaired t-test, Group A does not significantly differ from Group C (AP).

Figure 9 :Comparison of Mean Arterial Pressure (MAP) between the three Groups

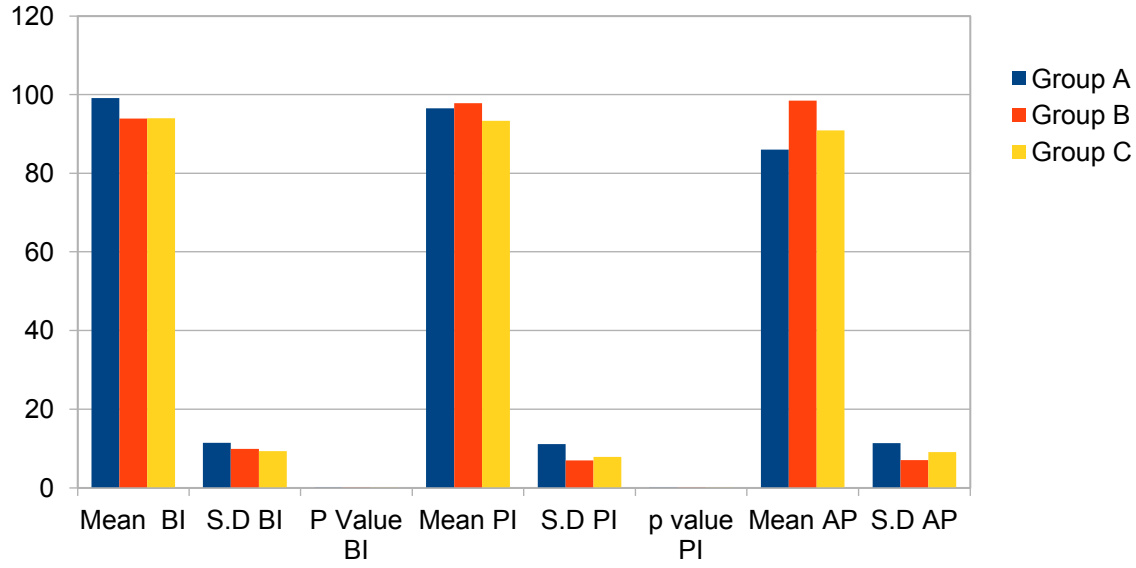

Figure 10 : Comparison of Mean Arterial Pressure (MAP) between Group A & Group B

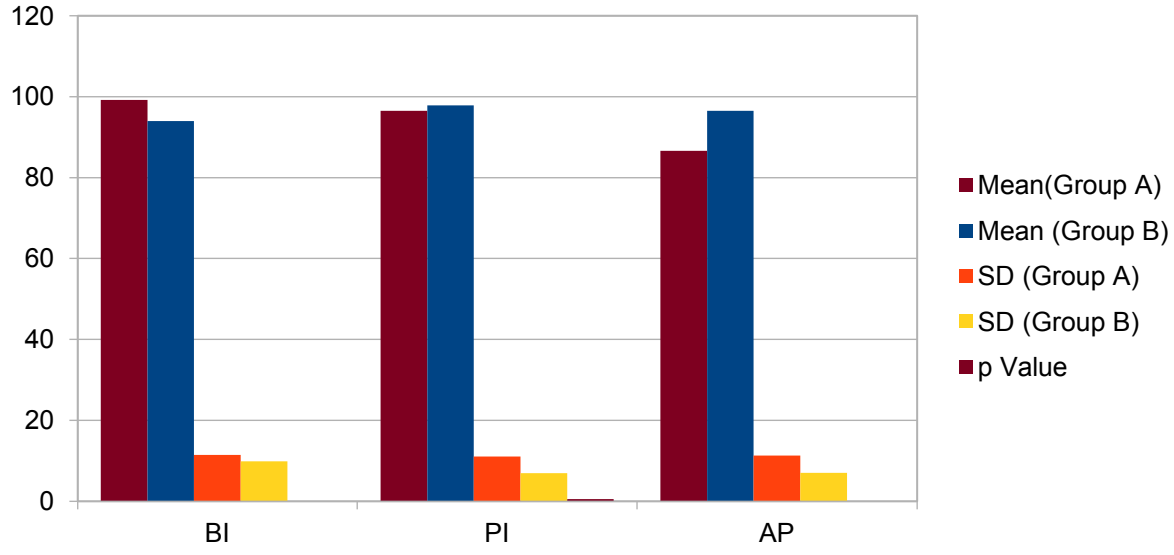

Figure 11: Comparison of Mean Arterial Pressure (MAP) between Group B & Group C

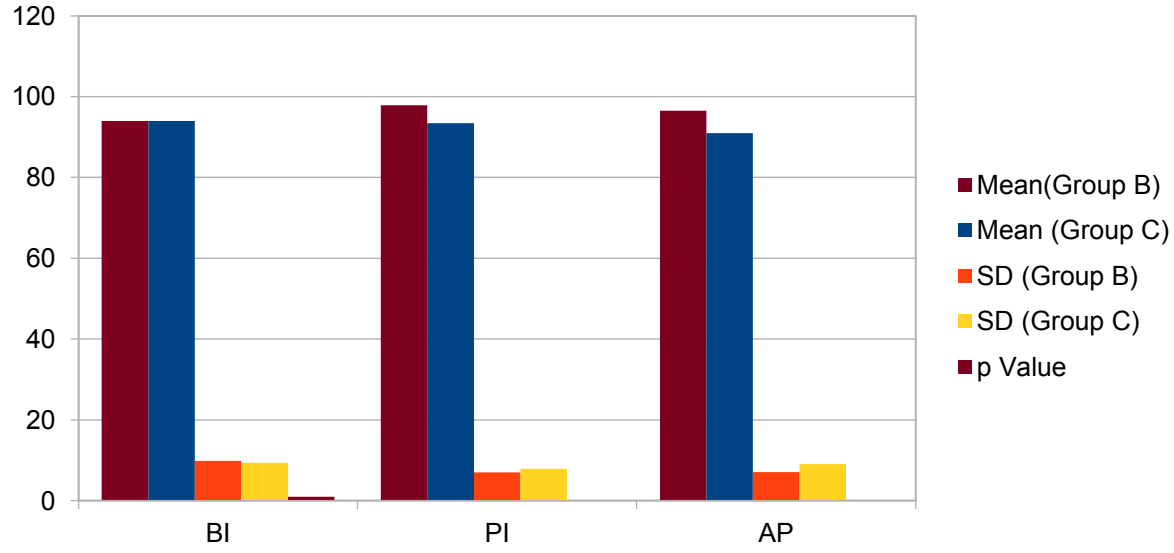

Figure 12: Comparison of Mean Arterial Pressure (MAP) between Group A & Group C

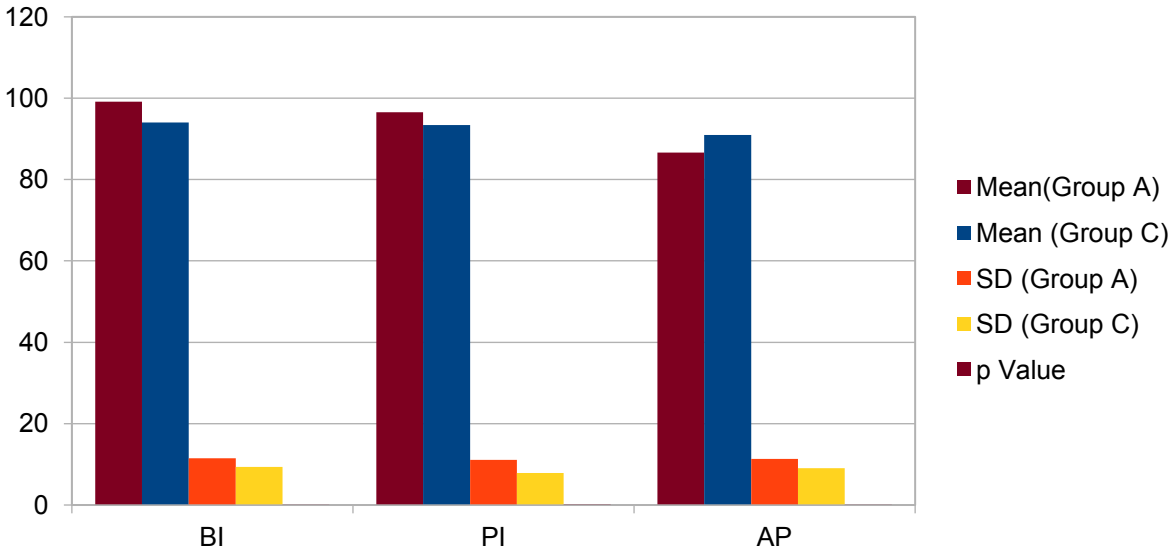

Table 4c: Mean Arterial Pressure (MAP) comparison within Group A

BI		PI			
MEAN	**S.D.**	**MEAN**	**S.D.**	p VALUE	INFERENCE
99.16	11.45	96.52	11.07	0.2973	NS
BI		**AP**			
MEAN	**S.D.**	**MEAN**	**S.D.**	**p VALUE**	**INFERENCE**
99.16	11.45	86.61	11.29	< 0.0001	HS

- There Is Non-homogeneity in the means of BI and AP and also PI and AP.
- Using Students unpaired t-test, MAP significantly differs before injection of test solution (BI) and after propofol injection (AP).

Table 4d: Comparison of Mean Arterial Pressure (MAP) within Group B

BI		PI			
MEAN	**S.D.**	**MEAN**	**S.D.**	**p VALUE**	**INFERENCE**
93.93	9.83	97.84	6.95	0.0430	S
BI		AP			
MEAN	**S.D.**	**MEAN**	**S.D.**	**p VALUE**	**INFERENCE**
93.93	9.83	96.48	7.05	0.1849	NS

- There Is Homogeneity in the means of BI, PI and AP.
- Using Students unpaired t-test, MAP does not significantly differ before injection of test solution (BI) and after propofol injection (AP)

Table 4e: Comparison of Mean Arterial Pressure (MAP) within Group C

BI		PI			
MEAN	**S.D.**	**MEAN**	**S.D.**	**p VALUE**	**INFERENCE**
94.00	9.33	93.38	7.84	0.7466	S
BI		AP			
MEAN	**S.D.**	**MEAN**	**S.D.**	**p VALUE**	**INFERENCE**
94.00	9.33	90.93	9.07	0.1402	NS

- There Is Homogeneity in the means of BI, PI & AP.
- Using Students unpaired t-test, MAP does not significantly differ before injection of test solution (BI) and after propofol injection (AP).

Table 5a: Comparison of Heart Rate (HR) between the three groups

Before Injection of test solution (BI)	**Mean**	**S. D**	**p value**	**at Propofol injection (PI)**	**Mean**	**S. D**	**p value**	**One minute after Propofol injection (AP)**	**Mean**	**S. D**	**p value**
Group A	79.68	12.70		**Group A**	80.38	11.90		**Group A**	75.43	11.84	
Group B	79.15	11.21	**0.9748**	**Group B**	85.70	11.37	**0.1494**	**Group B**	85.15	11.98	**0.0007**
Group C	79.10	13.79		**Group C**	84.25	14.13		**Group C**	84.53	13.25	

- Before injection there is no statistical significance between the three Groups.
- At propofol injection at 85% confidence level there is significant difference between Groups A, B & C.
- One minute after injection at 99% confidence level, there is significant difference between Groups A, B & C

➢ **Comparison between Group A and Group B:**

- **P value = 0.0005**
- **Inference:** Highly Significant
- There is non-Homogeneity in the means of AP of the two groups.
- Using Students unpaired t-test, Group A significantly differs from Group B (AP).

➢ **Comparison between Group B and Group C:**

- **P value = 0.825**
- **Inference:** Not Significant
- There is Homogeneity in the means of AP of the two groups
- Using Students unpaired t-test, Group B does not significantly differ from Group C (AP).

➢ **Comparison between Group A and Group C:**

- **P value = 0.0018**
- **Inference:** Very Significant
- There is non-Homogeneity in the means of AP of the two groups.
- Using Students unpaired t-test, Group A significantly differs from Group C (AP).

Figure 13 :Comparison of Heart Rate (HR) between Groups A,B & C

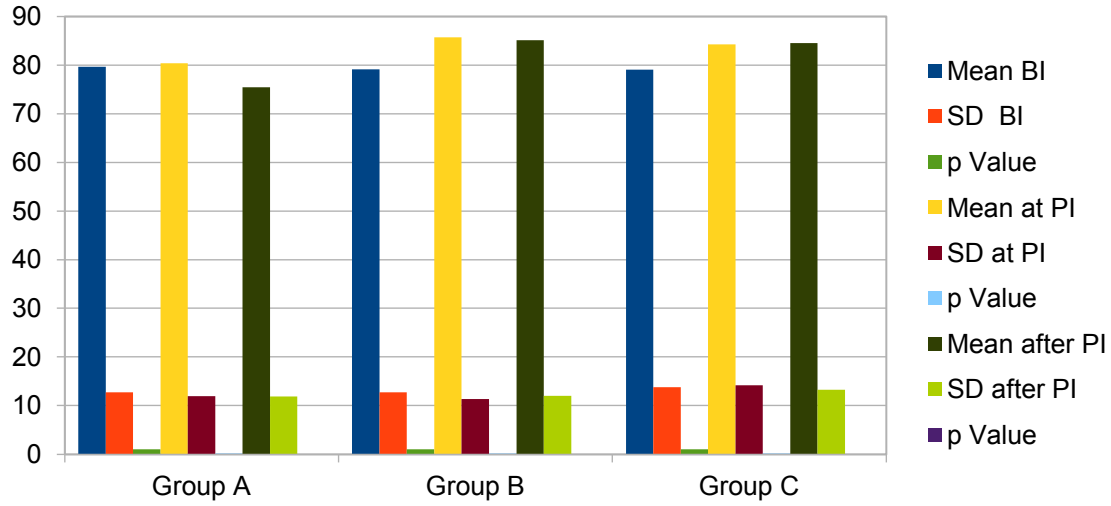

Figure 14 : Comparison of Heart Rate (HR) between Group A & Group B

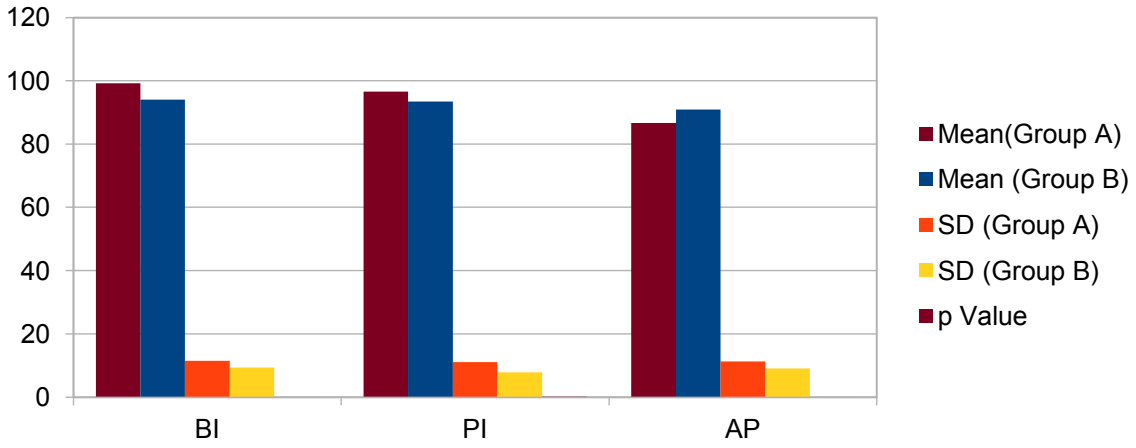

Figure 15 : Comparison of Heart Rate (HR) between Group B and Group C

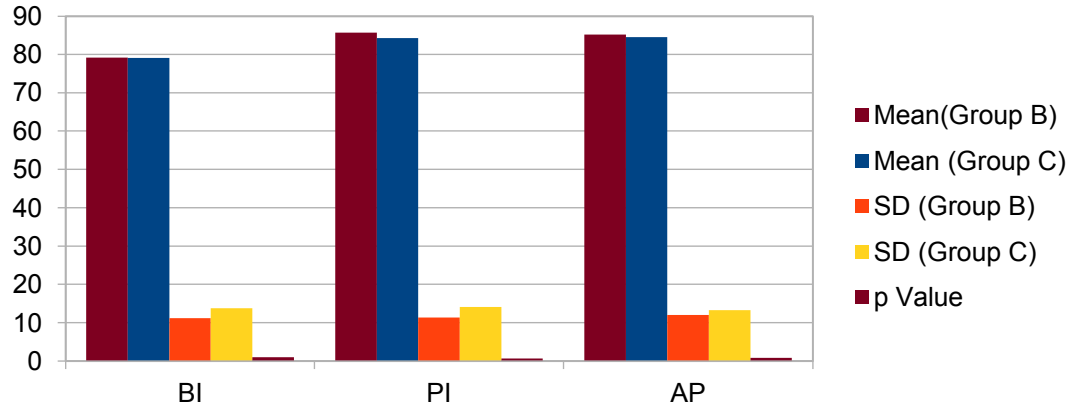

Figure 16 : Comparison of Heart Rate (HR) between Group A and Group C

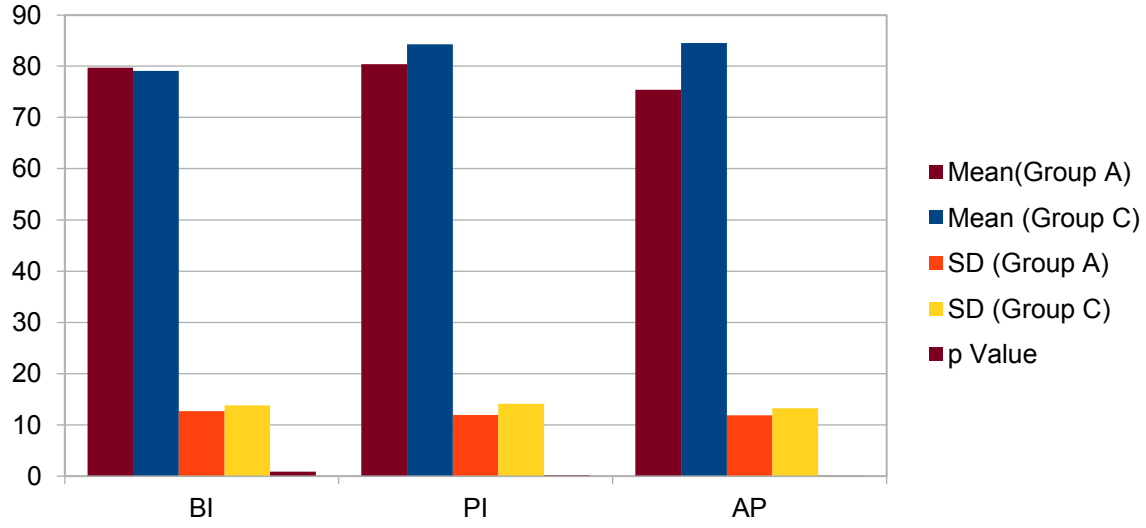

Table 5b: Comparison of Heart Rate (HR) within Group A

BI		PI			
MEAN	**S.D.**	**MEAN**	**S.D.**	**p VALUE**	**INFERENCE**
79.68	12.70	80.38	11.90	0.7999	NS
BI		AP			
MEAN	**S.D.**	**MEAN**	**S.D.**	**p VALUE**	**INFERENCE**
79.68	12.70	75.43	11.84	0.1256	NS

- There Is Homogeneity in the means of BI, PI and AP.
- Using Students unpaired t-test, HR does not significantly differ before injection of test solution (BI) and after propofol injection (AP).

Table 5c: Comparison of Heart Rate (HR) within Group B

BI		PI			
MEAN	**S.D.**	**MEAN**	**S.D.**	**p VALUE**	**INFERENCE**
79.15	11.21	85.70	11.37	0.0113	S
BI		AP			
MEAN	**S.D.**	**MEAN**	**S.D.**	**p VALUE**	**INFERENCE**
79.15	11.21	85.15	11.98	0.0234	S

- There Is Non-Homogeneity in the means of BI, PI and AP.
- Using Students unpaired t-test, HR significantly differs before injection of test solution (BI) and after propofol injection (AP).

Table 5d: Comparison of Heart Rate (HR) within Group C

BI		PI			
MEAN	**S.D.**	**MEAN**	**S.D.**	**p VALUE**	**INFERENCE**
79.10	13.79	84.25	14.13	0.1030	NS
BI		AP			
MEAN	**S.D.**	**MEAN**	**S.D.**	**p VALUE**	**INFERENCE**
79.10	13.79	84.53	13.25	0.0767	NS

- There Is Homogeneity in the means of BI and PI.
- Using Students unpaired t-test, HR does not significantly differ before injection of test solution (BI) and after propofol injection (AP).

DISCUSSION

Propofol injection pain (PIP) is ranked seventh among the most important 33 low-morbidity clinical anaesthesia problems by a panel of expert anaesthesiologists.[41] It is postulated that, the osmolarity and pH of solutions when comes into contact with the intima of a vein on the hand, determines pain production.[40] Other factors influencing the degree of pain include, volume injected& flow of blood through vein. Endothelial irritation causes early pain while vascular leakage and dilatation caused by TRPA1 and TRPV1 stimulation leading to neurogenic inflammation in peripheral and central sensitisation in spinal dorsal horn leads to late pain. decreases sympathetic activity and leads to indirect arterial vasodilation and venodilation. Heart rate does not change significantly despite the fall in aortic pressure. This effect is enhanced by direct effects on smooth muscle and depressant effects on the myocardium, affecting intracellular calcium balance and influx. The decreased sympathetic tone is also coupled with direct inhibition of the baroreceptor response, leading to a diminished reflex increase in heart rate and a more pronounced hemodynamic effect.

In our study titled "To compare the effect of lignocaine, ephedrine and combined lignocaine and combined lignocaine and ephedrine pretreatment on pain on injection due to propofol in adult patients undergoing general anaesthesia- A one year hospital based randomized clinical trial", with comparable demographic data, we found that the incidence of pain on injection due to propofol was 55%.

In this study, pain on propofol injection was maximally seen in ephedrine group than in lignocaine group than in combined lignocaine & ephedrine group. Among the 40 study individuals in lignocaine group 52.5% of patients had no pain while 37.5% had mild pain,

10% had moderate pain, none of them had severe pain. In ephedrine group 10% had no pain, 30% had mild pain, 40% had moderate pain and 20% severe pain. In combined lignocaine and ephedrine group, 27.5% had mild pain, while rest of the patients experienced no pain.

Though ephedrine showed some reduction in pain when used alone, it is more effective when used along with lignocaine.

In a similar study conducted by Khezri et al,[5] they compared five groups as opposed to ours which was only three groups. When the incidence of pain in patients taking ephedrine (E30-63.6 percent, E70-75.8%) was compared to saline (72.7 percent), they found no statistically significant difference. In contrast, lignocaine (39.4%) and combined lignocaine-ephedrine (45.4%) had lower pain scores.

In another study by Agarwal et al,[8] which is contradicting ours, where they studied ninety-three patients, they said pretreatment with ephedrine 30 μg/kg did not appear to significantly decrease the incidence of propofol-induced pain, nor did it improve haemodynamic stability during induction with propofol. However, it reduced the severity of propofol-induced pain. Pretreatment with 2% lignocaine (40 mg) was effective in decreasing both the incidence and severity of propofol-associated pain.

This was probably because they used only one dose of ephedrine 30 μg/kg rather than two used in our study i.e. 30 μg/kg & 50 μg/kg. Thus, lignocaine being the most commonly used drug to counter this pain has a direct effect on vascular smooth muscle and thus reduces the pain.[42] Also, endogenous noradrenaline released by ephedrine might reduce the effect of bradykinin and thus result in attenuation in propofol associated pain.[8]

We also observed hemodynamic changes at various intervals. The change in MAP in the three groups was a decrease from 99.16±11.45 to 86.61±11.29 in lignocaine group, an increase from 93.93±9.83 to 98.48±7.05 in ephedrine group and a decrease from 94±9.33 to 90.93±9.07 in combined lignocaine & ephedrine group. And the HR changes were as follows, in lignocaine group a decrease from 79.68±12.70 to 75.43±11.21, in ephedrine group it increased from 79.15±11.21 to 85.15±11.98 and in combined lignocaine & ephedrine group it increased from 79.10±13.79 to 84.53±13.25 .We also compared MAP and HR within the groups wherin only lignocaine group showed statistical significance ($p< 0.0001$) in MAP and ephedrine group showed significance in HR. A comparison was also done between the groups. Though most of the parameters were not statistically significant, they can be considered clinically significant. Overall, it can be concluded that combined lignocaine-ephedrine group is better for both pain on injection and hemodynamic stability of propofol injection during induction of general anaesthesia.

Khezri et al,[5] suggested that pretreatment with a combination of small-dose ephedrine and lidocaine resulted in a more stable hemodynamic profile. However, due to lack of synergistic effect between lidocaine and ephedrine, pretreatment with combination of these two drugs failed to work better in further reduction of pain. They also said that further studies are needed to evaluate the analgesic efficacy of combination of lidocaine-ephedrine admixture with propofol for minimizing its injection pain with more stable hemodynamic profile.

Cheong et al,[4] did not find adverse hemodynamic effects after tracheal intubation with pretreatment of ephedrine, such as severe hypertension, tachycardia, and arrhythmias. They said that larger doses of ephedrine (110 and 150 μg/kg) could produce these adverse

effects and concluded that a small dose of ephedrine (30 and 70 μg/kg) reduced the incidence and intensity of propofol-induced pain without significant adverse hemodynamic effects.

Limitations:

- Patients can have allergeric reactions to either propofol, lignocaine or ephedrine.
- In patients with cardiovascular disease, ephedrine cannot be administered.
- Patients taking any analgesic medication within 24 hours of surgery will have altered results.

Future Scope:

- Since the mechanism of action by which ephedrine reduces pain on propofol injection and there is very little literature on the same, further research needs to be done on the effects of ephedrine to reduce pain on injection of propofol.

CONCLUSION

In conclusion,

Pretreatment with lignocaine-ephedrine combination had reduced pain, better hemodynamic stability due to i.v. propofol injection during induction of general anaesthesia and is superior compared to either lignocaine or ephedrine alone.

SUMMARY

This randomized control study titled “To Compare the Effect of Lignocaine, Ephedrine and Combined Lignocaine and Ephedrine Pretreatment on Pain on Injection due to Propofol in Adult Patients undergoing General Anaesthesia”- A One Year Hospital based Randomized Clinical Trial, included 120 patients in KLE’s Dr. Prabhakar Kore Charitable Hospital and MRC for a period if one year, compared different drugs and their combination to combat the side effects of propofol injection which is a widely used drug for the induction of General Anaesthesia. Pain on propofol injection being a major adverse effect needs to be given attention.

The objectives of the study were comparison of effect of lignocaine, ephedrine and combined lignocaine and ephedrine on pain on injection and hemodynamic changes namely systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) and heart rate (HR), in patients receiving propofol for General Anaesthesia. Patients were divided into three groups of 40 each. Group A received i.v. lignocaine, Group B received i.v ephedrine and Group C received a combination of i.v. lignocaine & i.v ephedrine. In lignocaine group, 52.5% of patients had no pain while 37.5% had mild pain, 10% had moderate pain, none of them had severe pain. In ephedrine group 10% had no pain, 30% had mild pain, 40% had moderate pain and 20% severe pain. In combined lignocaine and ephedrine group, no patients had moderate or severe pain, while 27.5% had mild pain. MAP changes before and after propofol in the three groups were as follows, there was 12.55±16.08 increase in lignocaine group, while in ephedrine group, the increase was only 4.55±12.09 and the decrease was 3.07±13.01 in combined lignocaine-ephedrine group. Similarly, HR changes were as follows: 4.25±16.94 decrease in the lignocaine group, 6±16.41 increase in ephedrine group and 5.43±19.12 increase in

combined lignocaine and ephedrine group. Therefore, to conclude, though individually they can be effective, their combination has better results in reduction of injection pain and for maintenance of hemodynamics.

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ANNEXURE-I

INFORMED CONSENT FORPARTICIPATION IN RESEARCH TRIAL

- **Objective/ Purpose of the study:**

We are requesting you to enrol in study titled **"TO COMPARE THE EFFECT OF LIGNOCAINE, EPHEDRINE AND COMBINED LIGNOCAINE AND EPHEDRINE PRETREATMENT ON PAIN ON INJECTION DUE TO PROPOFOL IN ADULT PATIENTS UNDERGOING GENERAL ANAESTHESIA–A ONE YEAR HOSPITAL BASED RANDOMIZED CLINICAL TRIAL"**

This study will be conducted by DR. NEHA SANJEEV ADHYAPAK, Post Graduate in M.D. Anaesthesiology under the guidance of DR. RAJESH S. MANE$_{M.D.}$ Professor and Head, Department of Anaesthesiology, J.N. Medical College, Belagavi under KAHER, Belagavi.

Respected Sir/Madam, we request you to enrol yourself to participate in our study as you are eligible for the same. Your participation in this research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with J. N. Medical College or KLEH. If you decide not to participate you are free to withdraw at any time.

- **Procedure Involved:**

If the participant gives consent, a pre-anaesthetic evaluation will be done. On the day of the study, he/she will be brought to the operation theatre and placed in supine position on the

operating table. Patient will be again explained about the procedure. Intravenous cannula will be placed. Electrocardiogram, non-invasive blood pressure, pulse oximeter will be applied. The drug will be injected. One minute after the administration of the test solution, the 1% solution of propofol at 2 mg/kg will be given through the IV catheter at 1 mL/s, while the running of IV infusion will be temporarily ceased. After the injection of propofol the crystalloids will be administered at maximal gravity flow at uniform height. Patients will be informed regarding the possible stinging sensation on administration of a drug at the start of the anaesthesia and they would be asked the mean level score of their pain during the injection period before the loss of consciousness according to the verbal rating scale (VRS) explained to patients at the preoperative visit. The grading criteria of VRS will be as follows: 0= no pain experienced (negative response to questioning), 1=mild pain (pain reported only in response to questioning without any behavioral signs), 2= moderate pain (pain reported in response to questioning and accompanied by a behavioral sign or pain reported spontaneously without questioning), 3=severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears). The systolic and diastolic blood pressures and heart rate will be recorded before administration of the test solution, at propofol injection, and one minute after propofol injection. At the end of surgery after adequate reversal with neostigmine 0.05mg/kg patient will be extubated. After propofol injection and the loss of consciousness, midazolam 0.05 mg/kg, fentanyl 2 mg/kg, and vecuronium 0.1mg/kg will be administered. Supplemental oxygen at a rate of 6 L/min will be delivered by means of a face mask to all patients. Three minutes after vecuronium injection, the trachea will be intubated and anaesthesia will be maintained with 1.0-2.0% isoflurane and 50% N_2O in oxygen.

- **Risks:**

Lignocaine and ephedrine have no risks involved when given in small doses.

Though lignocaine can cause dizziness and ephedrine can cause mild hyperglycemia.

- **Benefits:**

Reduced incidence and intensity of pain caused by propofol injection and hemodynamic stability

- **Alternatives:**

Even if you decline your participation in the study, the course of your treatment will not be affected. You are free to withdraw from the study at any point of time. Everything about the study will be explained in detail to you before giving consent for the same.

- **Privacy and Confidentiality:**

The only people to know that you are a research subject are members of the research team. No information about you or information provided by you during the research will be disclosed to other without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

- **Institutional policy:**

In the event of injury related to the study, treatment will be made available through KLES' Hospital & MRC, Belagavi. There is no compensation or payment for such medical treatment by law.

- **Financial Incentives for participation:**

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and all the cost of the study will be borne by the investigator.

- **Authorization to Publish Results:**

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with your identity remaining confidential.

Consent statement:

- Mode of communication of consent form: Verbal / Written
- Contents: Self-Read/ Read out by Investigator
- Participant's awareness regarding voluntary withdrawal from study: Yes / No
- Investigators decision to remove participants from study: Yes / No
- Awareness regarding voluntary participation: Yes/No
- Adequate time given to clarify any doubts about the study or rights a study participant: Yes/ No

In case they have any questions related to the study, in future or in case of study related injury or illness, they can contact **DR. NEHA SANJEEV ADHYAPAK**, Department of Anaesthesiology, KLES Hospital and MRC, Belagavi, Phone number-9483272179 or **DR. RAJESH S. MANE**M.D., Professor & Head of Deptartment of Anaesthesiology, KLE'S Hospital and MRC, Belagavi Phone number: 9844131062

If they have any queries about their rights as a study subject, they may call **DR. ROOPA BELLAD**M.D., Chairman, and Ethical Committee for Human Subjects Research.Professor, Department of Paediatrics, J. N. Medical College, Belagavi, Phone number-9448113403.

Signature or left thumb print of participant or legally authorized representative

_____Participant's name. _____Participant's signature/thumb print

_____Experimenters' name _____Experimenters' signature

_____ Witness' name _____Witness' signature

ANNEXURE-II

PROFORMA

Name of the Patient: _____

Address of the Patient: _____

Age: _____yrs Sex: _____M/F

IP. No. _____ Date: _____

Anaesthesiologist: _____ Surgeon: _____

PREANAESTHETIC EVALUATION:

Chief Complaints:

Past History:

- H/O Diabetes Mellitus/Hypertension/Asthma/Tuberculosis/Thyroid disease/Cardiac illness/ Neurological disease /Any other illness
- H/O Previous Anaesthetic procedure/Previous surgeries
- H/O Allergy to lignocaine, ephedrine, propofol or any other drug
- H/O intake of analgesic medication within 24 hours of surgery

Family History:

General Physical Examination:

Height: Weight: Temperature:

Pallor: Cyanosis: Pedal Oedema: Clubbing:

Pulse : B.P: RR:

Systemic Examination:

Cardiovascular System: Per Abdomen:

Respiratory System: Central Nervous system:

Airway Assessment:

Teeth: Jaw Movements:

MP Grading:

Spine assessment:

ASA STATUS: Grade I II III IV

Diagnosis:

Proposed Surgery:

Observations:

Readings will be recorded in the following manner:

Group: _____

Preoperative baseline values:

HR: SBP: DBP: MAP:

Monitors attached:

Pulse oximetry: NIBP:

ECG:

Characteristics of the patient:

Group	**A**	**B**	**C**
Age			
Weight(kg)			
Sex			
Height(cm)			

Verbal Rating Scale (VRS) on injection of propofol:

Group	**A**	**B**	**C**
0=no pain			
1=Mild pain			
2=Moderate pain			
3=Severe pain			

Hemodynamic variables data:

Group	SBP		
	BI	BT	AT
A			
B			
C			
Group	DBP		
	BI	PI	AP
A			
B			
C			
Group	MAP		
	BI	PI	AP
A			
B			
C			

BI= before injection of test solution; PI= At propofol injection; AP= one minute after propofol injection; L= lignocaine (1mg/kg); E= ephedrine (30 microgram/kg); HR= Heart Rate (bpm); SBP= Systolic Blood Pressure (mmHg); DBP= Diastolic Blood Pressure (mmHg); MAP= Mean Arterial Pressure (mmHg)

Group	HR		
	BI	PI	AP
A			
B			
C			

Signature of Principal Investigator: _____

ANNEXURE-III

ETHICAL CLEARANCE LETTER

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed – to- be- University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu
Phone: (+ 91-(0)831 Office : 2472550
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Ref: MDC/DOME/ 179. **Date: 24/12/2019**

To,

Dr. Neha Sanjeev Adhyapak
PG student in Anaesthesiology,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"tO COMPARE THE EFFECT OF LIGNOCAINE, EPHEDRINE AND COMBINED LIGNOCAINE AND EPHEDRINE PRETREATMENT ON PAIN ON INJECTION DUE TO PROPOFOL IN ADULT PATIENTS UNDERGOING GENERAL ANAESTHESIA – A ONE YEAR HOSPITAL BASED RANDOMIZED CLINICAL TRIAL"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Anita Dalal)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

ANNEXURE-IV

KEY TO MASTER CHART

1. yrs = Years
2. mg = Milligram
3. kg = Kilogram
4. mmHg = Millimetres of Mercury
5. bpm = Beats per minute
6. BI = Before injection of test solution
7. PI = At propofol injection
8. AP = One minute after propofol injection

ANNEXURE-V MASTER CHART

Group A (1.5 mg/kg Lignocaine)

Sl no	Name	Age (yrs)	Sex	ASA Grade	Weight (kgs)	Height (cm)	VRS on injection of propofol	Systolic Blood Pressure(mmHg)			Diastolic Blood Pressure(mmHg)			Mean Arterial Pressure(mmHg)			Heart Rate(bpm)		
								BI	PI	AP	BI	PI	AP	BI	PI	AP	BI	PI	AP
1	Sunita Kanbarkar	46	F	II	50	155	1	180	170	130	100	100	100	130	126	113	75	84	84
2	Leela Sanadi	38	F	II	70	156	1	156	157	153	100	99	107	119	118	122	81	85	73
3	Siddesh Kulkarni	31	M	I	68	175	0	116	124	108	76	76	68	89.3	92	81.3	68	70	65
4	Hoovappa	40	M	I	72	168	0	150	150	140	96	92	88	114	111	105	62	72	62
5	Bharati Jolad	28	F	I	55	157	0	106	104	90	70	70	60	82	81.3	70	88	94	72
6	Ashok G	38	M	II	65	166	0	134	126	124	86	80	80	102	95.3	94.7	76	80	74
7	Vanita	53	F	II	62	150	1	134	130	116	92	90	76	106	103	89.3	64	68	64
8	Vijay Kitale	37	M	I	65	169	0	124	124	114	76	74	68	92	90.7	83.3	86	82	80
9	Laxman Savant	60	M	II	67	166	0	160	160	146	97	97	80	118	118	102	66	70	65
10	Chandrappa	60	M	II	66	166	0	136	120	112	88	80	76	104	93.3	88	68	69	62
11	Meeramma K	50	F	II	58	154	0	125	125	116	83	81	73	97	95.7	87.3	83	80	70
12	Jayashree T	60	F	II	54	157	0	130	136	120	90	90	76	103	105	90.7	62	64	60
13	Yallappa D P	51	M	I	64	170	1	124	130	116	78	70	66	93.3	90	82.7	82	82	82
14	Shivangouda B N	20	M	I	45	165	1	120	120	100	70	70	60	86.7	86.7	73.3	90	90	86
15	Maria S	27	F	I	54	148	0	116	120	105	72	70	64	86.7	86.7	77.7	85	84	82
16	Nadeem Bagwan	27	M	I	50	160	0	115	113	102	73	72	66	87	85.7	78	88	86	80
17	Shivanand	27	M	I	46	164	0	120	120	108	80	80	76	93.3	93.3	86.7	88	90	85
18	Pratipala Nari	19	F	I	45	154	0	125	120	104	90	86	74	102	97.3	84	98	100	90
19	Prakash Maratha	37	M	I	62	173	0	140	138	120	90	87	78	107	104	92	67	64	60
20	Indrayani Ghumate	31	F	I	58	158	1	128	125	120	85	83	72	99.3	97	88	90	90	88
21	Priyanka Buchalkar	23	F	I	51	152	1	116	116	100	72	74	68	86.7	88	78.7	95	90	86
22	Lakhan Jadhav	30	M	I	60	164	1	120	124	102	76	75	64	90.7	91.3	76.7	74	76	74
23	Sagar Ghodke	32	M	I	64	168	1	130	135	126	90	92	88	103	106	101	78	80	76
24	Mahanda Kadarwadkar	55	F	II	68	154	0	150	140	128	88	84	76	109	103	93.3	70	74	72
25	Yallappa Vagga	30	M	I	67	160	0	126	120	105	80	76	70	95.3	90.7	81.7	64	64	60
26	Lata Goral	41	F	II	57	154	0	150	150	138	93	95	80	112	113	99.3	64	68	60
27	Ajit	37	M	I	66	170	0	124	123	108	80	82	70	94.7	95.7	82.7	69	62	64
28	Aminsab	25	F	I	53	155	0	116	110	90	76	74	62	89.3	86	71.3	89	90	86
29	Aslam	40	M	I	58	175	0	130	120	110	82	74	63	98	89.3	78.7	70	75	71
30	Balasaheb	44	M	II	64	167	0	136	130	122	88	76	70	104	94	87.3	85	80	78
31	Geeta	56	F	II	63	155	0	160	150	133	90	88	72	113	109	92.3	80	82	80
32	Hasina	28	F	I	52	150	0	110	130	121	70	74	60	83.3	92.7	80.3	100	98	90
33	Jamal	60	M	II	65	163	0	154	150	140	89	88	70	111	109	93.3	56	56	50
34	Jyotiba	23	M	I	53	164	0	123	116	100	74	74	64	90.3	88	76	78	78	72
35	Kavita	32	F	I	55	158	1	124	120	105	75	70	60	91.3	86.7	75	88	85	81
36	Lakavva	55	F	II	63	154	0	130	130	120	90	85	72	103	100	88	72	70	64
37	Vijaylami	31	F	I	50	160	0	114	101	100	81	72	72	92	81.7	81.3	100	105	99
38	Prema	28	F	I	45	148	1	152	132	130	96	88	71	115	103	90.7	111	104	102
39	Lalitha	25	F	I	45	150	0	120	114	107	78	69	60	92	84	75.7	95	96	92
40	Mala Asodi	38	F	I	55	154	0	100	102	92	72	68	62	81.3	79.3	72	82	78	76

Group B (0.7 mg/kg Ephedrine)																				
Sl no	Name	Age (yrs)	Sex	ASA Grade	Weight(kgs)	Height (cm)	VRS on injection of propofol	Systolic Blood Pressure			Diastolic Blood Pressure			Mean Arterial Pressure			Heart Rate		
								BI	PI	AP	BI	PI	AP	BI	PI	AP	BI	PI	AP
1	Maruti Mandalik	50	M	II	55	146	1	140	140	146	90	90	90	106.7	106.7	108.7	96	98	100
2	Ashok Kargutkar	29	M	I	62	160	2	134	136	140	90	86	94	104.7	102.7	109.3	86	90	86
3	Rangnath	28	M	I	66	168	3	124	124	124	76	76	80	92	92	94.67	85	95	90
4	Mahadevi Patil	36	F	I	56	146	2	132	140	136	82	82	80	98.67	101.3	98.67	84	86	86
5	Vasant Honnappa	50	M	II	70	165	1	123	150	146	72	90	85	89	110	105.3	66	70	66
6	Aarti Sambrekar	49	F	I	62	156	0	139	140	145	90	90	90	106.3	106.7	108.3	67	67	67
7	Sarita Patil	21	F	I	46	158	3	115	124	130	68	72	68	83.67	89.33	88.67	78	80	80
8	Dhanamma	20	F	I	48	154	2	108	120	120	62	70	70	77.33	86.67	86.67	90	94	95
9	Pooja Bhangari	35	F	II	58	160	1	118	118	126	72	76	82	87.33	90	96.67	79	80	76
10	Lagmavva	37	F	I	60	164	2	128	130	124	84	88	82	98.67	102	96	76	80	80
11	Mallamma Raju	55	F	II	53	152	1	125	125	125	73	76	74	90.33	92.33	91	68	74	70
12	Sumitra Medar	38	F	I	64	154	0	130	130	120	92	90	84	104.7	103.3	96	80	88	84
13	Shahid Mulla	20	M	I	64	167	3	110	120	120	75	70	70	86.67	86.67	86.67	90	90	90
14	Bharati Tambali	36	F	I	52	156	0	123	130	126	64	78	80	83.67	95.33	95.33	83	88	88
15	Shwetha	56	F	II	50	150	1	138	140	134	94	96	96	108.7	110.7	108.7	62	72	72
16	Priyanka	21	F	I	42	160	2	104	130	125	61	82	75	75.33	98	91.67	79	85	80
17	Sunita Kanbarkar	46	F	I	56	156	1	120	126	124	80	86	84	93.33	99.33	97.33	72	76	76
18	Ajay Hampannavvar	21	M	I	62	160	2	120	122	120	70	76	72	86.67	91.33	88	68	80	76
19	Nandini Naik	42	F	I	60	152	3	130	130	126	90	90	84	103.3	103.3	98	92	100	106
20	Ramjanshah Makandar	33	M	II	68	165	2	122	126	130	65	70	66	84	88.67	87.33	82	90	92
21	Rachanna Karabasappa	34	M	I	68	168	2	130	140	130	70	80	80	90	100	96.67	96	102	110
22	Veena Kangralkar	23	F	I	56	156	1	130	130	130	80	90	80	96.67	103.3	96.67	86	96	94
23	Afsar Mulla	37	M	II	60	164	2	140	130	130	90	80	84	106.7	96.67	99.33	90	96	90
24	Sanjeev Prasad	23	M	I	66	165	3	140	140	134	90	90	90	106.7	106.7	104.7	86	92	96
25	Manjunath	54	M	II	68	164	2	118	126	124	76	80	74	90	95.33	90.67	90	96	94
26	Sandeep Jarmule	40	M	II	74	168	2	140	140	140	90	90	90	106.7	106.7	106.7	72	86	92
27	Raghavendra	49	M	II	70	168	1	120	126	130	70	78	72	86.67	94	91.33	92	100	106
28	Malappa Darur	26	M	I	68	165	2	122	130	126	72	76	70	88.67	94	88.67	66	72	76
29	Laxmi	49	F	II	58	155	1	135	134	135	86	86	86	102.3	102	102.3	76	89	89
30	Manavva	45	F	II	62	154	1	137	140	130	90	85	92	105.7	103.3	104.7	56	64	64
31	Mubarak	41	M	I	74	170	1	126	126	126	84	90	86	98	102	99.33	65	69	70
32	Mukund	22	M	I	64	168	2	114	123	120	70	70	70	84.67	87.67	86.67	87	90	87
33	Ningappa	44	M	II	69	175	3	108	110	104	64	70	72	78.67	83.33	82.67	71	76	80
34	Parasappa	39	M	I	62	165	2	142	142	136	90	80	80	107.3	100.7	98.67	67	80	78
35	Prabhavati	43	F	I	57	150	3	127	130	130	85	89	86	99	102.7	100.7	59	70	68
36	Prajwal	18	M	I	63	166	0	118	120	120	72	76	75	87.33	90.67	90	91	90	88
37	Preethi	19	F	I	46	150	2	122	130	124	74	80	83	90	96.67	96.67	89	96	90
38	Pushpa	49	F	II	61	160	1	131	134	130	88	85	85	102.3	101.3	100	65	76	75
39	Sunita F	27	F	I	45	154	3	102	125	120	66	78	80	78	93.67	93.33	83	89	89
40	Pramod Patil	18	M	I	56	158	2	122	130	130	75	80	80	90.67	96.67	96.67	96	116	110

Group C (1.5 mg/kg Lignocaine+0.5mg/kg ephedrine)																						
Sl no	Name	IP number	Age (yrs)	Sex	ASA Grade	Weight(kgs)	Height (cm)	VRS on injection of propofol	Systolic Blood Pressure			Diastolic Blood Pressure			Mean Arterial Pressure			Heart Rate		
									BI	PI	AP	BI	PI	AP	BI	PI	AP	BI	PI	AP
1	Chetanaraddi Hampiholi	1017306	18	M	I	45	168	1	132	121	120	82	82	80	98.67	95	93.33	74	114	110
2	Sumit Chachadi	1029371	27	M	I	66	162	1	124	126	122	74	76	78	90.67	92.67	92.67	64	76	74
3	Rakesh Ghatage	1028373	40	M	I	74	168	2	150	150	148	100	100	92	116.7	116.7	110.7	90	80	86
4	Naseemabanu Sanadi	1028488	34	F	I	55	165	1	123	126	110	82	86	72	95.67	99.33	84.67	76	72	86
5	K Babasaheb Jajjundin	1003679	21	M	I	45	166	0	130	130	126	76	70	68	94	90	87.33	100	90	80
6	Shantamaruti Mattikoppa	1001989	60	F	II	45	140	2	130	120	116	90	90	80	103.3	100	92	80	90	86
7	Akshay Shivapur	1005906	24	M	I	65	170	1	118	120	116	76	78	60	90	92	78.67	60	80	86
8	Nagavva Doddannavar	15459	44	F	II	50	150	0	130	124	120	80	76	74	96.67	92	89.33	70	80	80
9	Deepak Jakkannavar	15566	41	M	II	56	167	1	106	120	110	64	70	60	78	86.67	76.67	76	86	70
10	Anand Dodamani	1024984	18	M	I	60	160	0	130	122	124	90	82	78	103.3	95.33	93.33	94	90	92
11	Samarth Rahul	1022716	18	M	I	52	152	0	126	120	122	86	76	82	99.33	90.67	95.33	96	102	98
12	Bhavana	1024398	18	F	I	40	150	1	110	120	110	70	76	72	83.33	90.67	84.67	92	98	96
13	Kamalavva Shirgur	15524	43	F	II	45	152	0	120	118	114	70	72	70	86.67	87.33	84.67	70	76	72
14	Shankar Tondale	15518	40	M	I	68	170	1	140	130	130	90	80	80	106.7	96.67	96.67	90	94	96
15	Mayappa Kusabi	15288	55	M	II	64	164	0	118	120	116	72	76	68	87.33	90.67	84	82	86	82
16	Palak Patil	1023564	60	M	II	56	162	1	116	122	120	76	82	78	89.33	95.33	92	64	72	78
17	Badruddin Talikhot	1023692	40	M	I	72	166	1	130	120	120	70	70	60	90	86.67	80	88	96	100
18	Rudrappa Deyannavar	1005007	52	M	II	60	162	0	140	140	134	86	84	84	104	102.7	100.7	68	72	74
19	Sahebi Desai	1028521	31	F	I	52	160	0	110	108	108	69	67	64	82.67	80.67	78.67	106	104	96
20	Rohini Chougule	1028613	22	F	I	60	160	0	140	138	128	80	78	76	100	98	93.33	86	89	85
21	Sitaram	1023758	59	M	II	55	162	0	140	140	140	100	90	90	113.3	106.7	106.7	62	72	78
22	Vijaya Mallaya Allanavarmath	1000254	31	M	I	50	166	1	116	114	114	72	70	68	86.67	84.67	83.33	60	56	54
23	Fakiravva Halagi	15614	52	F	I	64	156	0	120	110	110	80	70	70	93.33	83.33	83.33	68	72	76
24	Mahantesh Banavannavar	1028476	24	M	I	56	167	0	122	115	127	64	68	70	83.33	83.67	89	64	72	76
25	Anasuya Angadi	15543	60	F	II	52	160	2	140	136	120	80	76	70	100	96	86.67	76	80	80
26	Chennavva Kenchanagoudar	1037235	60	F	II	56	156	0	140	140	144	90	90	112	106.7	106.7	122.7	106	117	116
27	Nandini	1028674	30	F	I	56	156	0	110	108	106	80	80	80	90	89.33	88.67	86	80	80
28	Nikita Mathapati	1030425	30	F	I	62	156	1	110	108	108	70	68	68	83.33	81.33	81.33	78	86	84
29	Shankunta Chavan	1030866	42	F	II	64	160	1	140	130	126	80	76	74	100	94	91.33	72	76	74
30	Mohammed Rafi	1027355	39	M	I	70	160	0	120	130	120	80	80	80	93.33	96.67	93.33	82	80	80
31	Rayappa Adin	1040126	39	M	II	62	164	1	124	130	130	72	72	72	89.33	91.33	91.33	88	88	90
32	Shakul	1040605	43	M	I	67	170	1	135	138	126	88	84	82	103.7	102	96.67	68	72	75
33	Manisha	1040208	37	F	I	56	154	0	106	118	114	65	68	70	78.67	84.67	84.67	75	80	89
34	Vittal Maddimani	1040945	40	M	I	60	165	0	127	130	130	78	80	82	94.33	96.67	98	56	60	65
35	Mahantesh Lagashetti	1040901	50	M	II	65	165	0	134	134	134	75	76	76	94.67	95.33	95.33	63	63	64
36	Lata Mirashi	1040824	38	F	II	48	150	1	109	116	120	70	72	70	83	86.67	86.67	89	96	100
37	Rinki Kerkar	1040736	47	F	I	52	156	0	140	140	134	82	88	83	101.3	105.3	100	98	106	105
38	Ram Nagina	1040174	47	M	I	66	172	0	126	131	125	86	84	84	99.33	99.67	97.67	62	68	68
39	Mahdevgouda Y M	1039658	31	M	I	65	166	0	122	126	126	74	70	70	90	88.67	88.67	86	99	100
40	Krishna Sagare	1041085	45	M	II	68	165	2	106	110	110	66	70	70	79.33	83.33	83.33	99	100	100