"EFFICACY OF VARYING TIME INTERVALS BETWEEN FENTANYL AND PROPOFOL ADMINISTRATION ON PROPOFOL REQUIREMENT FOR INDUCTON OF ANAESTHESIA – A ONE YEAR RANDOMIZED CONTROL TRIAL"

By

REG NO: BA0120006

Dissertation

Submitted to the

KLE Academy of Higher Education & Research

(Deemed To Be University) Belagavi, Karnataka

In Partial Fulfillment

of the requirements for the degree of

M. D.

in

ANAESTHESIOLOGY

JAWAHARLAL NEHRU MEDICAL COLLEGE,
BELAGAVI, KARNATAKA

JUNE/JULY 2023

KLE Academy of Higher Education & Research
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ABSTRACT

Background: Administration of Fentanyl prior to propofol for induction of anaesthesia should result in a significant decrease in the amount of propofol needed for induction and its side effects and maintain hemodynamic stability, aid in a steady induction of anaesthesia. This study looked at how different times between the injection of fentanyl and propofol affected the amount of the drug needed to induce anaesthesia.

Methods: Following ethical committee permission, 102 patients with ASA Grades 1 and 2, between the ages of 18 and 60, were enrolled and randomly assigned to one of three groups. Fentanyl was administered to these individuals immediately, 3 minutes, and 5 minutes before the onset of anaesthesia. Hemodynamic changes related to the medications and time periods were recorded and tabulated, as well as the overall amount of propofol needed for induction.

Results: Compared to the group that received propofol immediately after fentanyl administration, the total amount of propofol needed to induce anaesthesia was significantly reduced with a 3 minute time interval variation, and hemodynamics were tolerated better with a 5 minute group.

Conclusion: The current study contributes to the conclusion that premedicating with fentanyl for three and five minutes decreases the total amount of propofol needed for inducing anaesthesia. However, more study is needed.

Key words: Fentanyl, Propofol, Varying time intervals.

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. CMRO2 = Cerebral Metabolic Rate for Oxygen
9. ICP = Intracranial Pressure.
10. SVR = systemic vascular resistance
11. ACTH = adrenocorticotropic hormone
12. BIS = Bispectral Index
13. CHF = Congestive Heart Failure
14. ASA = American Society of Anaesthesiologists
15. N2O = Nitrous Oxide
16. yrs = years
17. Kg = kilogram
18. mg = milligrams
19. cms = centimeters
20. S.D = Standard Deviation
21. CO = Cardiac Output
22. Inj. = injection

23. IL-2 = Interleukin 2

24. NF-KB = Nuclear Factor kappa-light-chain-enhancer of activated B cells

25. BP = Blood Pressure

26. I.V = Intravenous

27. MAC = Minimum alveolar concentration

28. RCT = Randomized control trial

29. α = Alpha

30. β = Beta

31. SPO2 = Saturation percentage of oxygen

32. MPG = Mallampati Grading

33. CO2 = Carbondioxide

34. O2 = Oxygen

35. N2O = Nitrous Oxide

36. BMI = Body mass index

37. BMR = Basal metabolic rate

38. CYP = Cytochrome P

39. µg / mcg = Micrograms

40. mg = Milligrams

41. min = minutes

42. ml = Milliliters

43. & = And

44.WIC- written informed consent

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Introduction

INTRODUCTION

Propofol, which has most qualities of an unique anaesthesia induction drug, including a quicker action & hypnosis (within one arm-brain circulation time), a quick awakening, minimal excitation, etc., makes it the most widely used intravenous induction agent for inducing general anaesthesia. [1,2] The most frequent of them include a considerable fall in systemic blood pressure and systemic vascular resistance with a concurrent reduction in cardiac output[1, 2], which makes propofol lesser optimal to use as " only inducing drug".

The notion that balanced anaesthesia has been used to address this issue and involves administering opioids before injecting induction drug. This dramatically lowers dosage of propofol, preserves haemodynamic stability, and substantially reduces adverse effects [1,2] .

Fentanyl is a strong synthetized drug acting as an agonist at u receptors and is the commonly utilised IV opioid for pain intra-operatively [1,3]. Propofol and fentanyl act together synergistically to lower the dose needed to induce anaesthesia and preserve hemodynamic stability, especially when 3 and 5 minute intervals are used prior to intravenous induction.

Endotracheal intubation is one of the standard procedures to secure an airway. It aids in providing a conduit for delivery of anaesthetized gases providing positive pressure ventilation while maintaining airway pressures and helping in protecting the airway from aspiration of gastric contents. Laryngoscopy is commonly used technique for intubation. Following laryngoscopy, there is a hemodynamic response because of the noxious stimulus which results in reflex sympathetic stimulation which is caused by epi-pharyngeal and laryngo-pharyngeal stimulation [7]. Due to this, there is an increase in plasma concentrations of nor-epinephrine & other catecholamines which

results in tachycardia, hypertension, and arrhythmias [8]. These haemodynamic changes that occur due to laryngoscopy and intubation may cause a change in the balance of myocardial oxygen demand & supply and can increase the chances for myocardial ischemia in patients with known ischemic heart diseases. It is undesirable and has detrimental effects on patients with diseases like coronary artery diseases, vascular anomaly, aneurysm, etc.

Numerous drugs, including fentanyl[9], lignocaine[11], betablockers (esmolol)[9] , calcium channel blockers, or interventions like maintaining proper depth of anaesthesia, use of nerve blocks[10], have been reported to lessen the hemodynamic response during laryngoscopy and intubation.

OBJECTIVES

Primary Objective

The main goal is to determine whether different intervals between the injection of fentanyl and propofol have an impact on the amount of propofol required to induce anaesthesia.

Secondary objective

Effect on hemodynamic parameters like Heart rate, Systolic, Diastolic, Mean Arterial Blood pressure.

REVIEW OF LITERATURE

1. In a randomised controlled trial, Darlong et al. [23] divided 129 cases posted for non - emergency cases under GA in three – groups to evaluate the efficacy of different time interveining periods before the administration of inj.fentanyl & inj.propofol on amount of inj.propofol needed for inducing anaesthesia. IV Inj.fentanyl 2 microgram per kilogram is provided; group 1 patients received propofol 1-2 mg/kg right away; group 2 patients received Inj.propofol three minutes after IV inj.fentanyl & group three patients received inj.propofol five minutes later. While speaking verbally with the patient, inj.propofol has been given with flow of one millilitre every three seconds. . When verbal command loss was observed according to the Ramsay Sedation score, anaesthesia induction was deemed to be complete. Propofol dosage needed for induction was seen and recorded. Atracurium injection, 0.5 mg/kg iv, was used for tracheal intubation after establishing the patient's capacity to mask ventilate. Additional doses of 20 mg propofol boluses were ready and provided as needed when bucking, involuntary moving are observed during mask ventilation. Additionally injected drug was added to the whole dose. Compared to Groups 2 and 3, Group 1 required a considerably larger dosages of inj.propofol for every kilogram of body weight to induce anaesthesia. Between the three groups, there were substantial differences in the total amount of propofol needed, with group 1 requiring the highest dose and group 3 the lowest. Group 3 experienced much less movement during induction than the other two groups did. In comparison to the other two groups, Group 1 had much more vocalisation and bucking incidents.8.9% in 3rd Group required more propofol, comparing with 53.3% and 36.6% of patients in Group 1 and Group 2, respectively. In Groups 1 and 2, fluid bolus requirements and the incidence of

hypotension during induction were both considerably higher than in Group 3. According to the study, giving fentanyl 5 minutes before giving propofol results in a considerable reduction in the amount of propofol needed, as well as a markedly lesser low blood pressure, involuntary bucking: talking while inducing.

2. Smith et al. [25] carried out a randomised controlled research in 1994 to establish the optimal propofol concentration needed for induction of complete intravenous anaesthesia. 120 patients were randomly assigned to receive either propofol and fentanyl or only propofol at concentrations of 0.2, 0.8, 1.5, 3.0, and 4.5 ng/ml each by computer-assisted continuous infusion. Patients were assigned to groups based on goal directed propofol concentrations of 1.5–10 micrograms/ml. After seven and ten minutes, samples of arterial blood gas were obtained in order to determine the amount of propofol and fentanyl. According to the ramsay sedation score, the patient's inability to respond to a straightforward verbal order at the 10-minute mark indicated that the patient had lost consciousness. Statistics were used to determine the propofol blood concentration at which 50% or 95% of patients did not respond to verbal orders and fifty and ninetyfive percent were non responsive during skin incisions, respectively. 53 patients were available to calculate the propofol Cp50i, while 56 eligible patients were available to calculate the propofol Cp50s. The Cp50s and Cp95s were 3.3 and 5.4 microgram/ml, respectively, in the propofol alone group. Fentanyl concentrations were increased after decreasing Cp50s (P = 0.03) and increasing Cp50s (P = 0.04). The Cp50i was significantly decreased when fentanyl concentrations rose (P 0.01), and 0.63 ng/ml fentanyl caused a 50% drop in Cp50i. When 1 ng/ml of fentanyl was administered, the propofol Cp50i was decreased by 63%, and by 3 ng/ml, it was reduced by 89%. The ceiling effect was evident and the decline in Cp50i was proportionately less

with higher fentanyl doses. They found that when fentanyl is not administered, the plasma - concentrations of inj.propofol necessary to not responding the oral commands & surgical incisions were much higher, and that in patients who received fentanyl, the requirement of propofol is reduced by 63% and 89%, respectively.

3. In a computer-generated random allocation study conducted by Aynur akin et al, 40 patients were chosen and divided into 2 groups to test the effectiveness of ketamine-propofol and fentanyl-propofol combinations for sedation during endometrial biopsy. Patients in groups 1 and 2 given IV bolus doses of Inj.fentanyl one microgram per kilogram + Inj.propofol one milligram per kilogram : inj.ketamine half milligram per kilogram + Inj.propofol one milligram per kilogram. All patients underwent regular monitoring of their heart rate, systolic and diastolic blood pressure, respiration rate, and peripheral O2 saturation. The Ramsay Sedation Score was used to determine the level of sedation. One patient in group 1 and five patients in group 2 both experienced respiratory depression. When compared to group 1, group 2 experienced more frequent occurrences of nausea, dizziness, and visual abnormalities. However, group 2 had a considerably shorter time to discharge (71.2 9.7 minutes compared to 115.2 25.6 minutes in group 1). In groups 1 and 2, patient satisfaction rates were 60% and 95%, respectively. They discovered that endometrial biopsy patients can safely employ ketamine-propofol and fentanyl-propofol combinations. The combination of fentanyl and propofol was shown to be the most effective one when side effects and patient satisfaction were compared between the two groups.

4. To ascertain the hemodynamic effects of propofol, Hug CC Jr et al [32] carried out a phase IV trial with Twenty six thousand cases approximately, one thousand seven hundred hospitals, and nineteen hundred anaesthetists. Through randomization, 25 000 patients were divided into 3 groups. Propofol was the only induction agent utilised in group 1. Propofol was administered intermittently as bolus injections to group 2 patients for both induction and maintenance. In group 3, continuous infusion techniques were used for both the induction and maintenance of anaesthesia. The incidence of hypotension was 15.7% overall, with 77% of episodes occurring within 10 minutes of propofol anaesthesia induction (systolic blood pressure 90 mm Hg). 4.8% of patients experienced bradycardia, with 42% of those episodes occurring in the first 10 minutes after induction (heart rate 50 beats/min). They noticed higher incidence of lowering of blood pressure with older females having abdominal surgery and in patients who received propofol right away together with opioids or benzodiazepines with no varying time intervals in between. Bradycardia was substantially more frequent in individuals who were taking benzodiazepines, propranolol, or both during surgery when propofol was used with opioids without time intervals.
5. In a randomised controlled experiment, Hogue CW et al [38] randomly assigned 161 patients to one of two groups in order to compare the effectiveness of propofol and remifentanil for total intravenous anaesthesia (TIVA). Remifentanil is administered intravenously (i.v.) at a dose of 1 microgram/kg, and either a 0.5 or 1 microgram/kg/min infusion rate is then randomly assigned. Vecuronium I.V. 0.1 mg/kg was utilised for intubation after Propofol half to one milligram per kilogram boluses & seventy five mics-per-kilogram per minute via infusing pumps and syringes. Remifentanil infusions had 50% less following tracheal

intubation. Endpoints of ceasing infusion included tachycardia, hypertension, and responses to laryngoscopy, tracheal intubation, and surgical incisions as stressors. In both groups, anaesthesia recovery took between 3 and 7 minutes. The most frequent adverse reactions were bradycardia, lesser BP while inducing and maintaining anaesthesia. They came to the conclusion that administering remifentanil and propofol together as a bolus followed by 1.0 mics/kg/min infusions effectively regulated the stress responses to tracheal intubation. Remifentanil 0.25–4.0 mics/kg/min infusion after tracheal intubation considerably reduced intraoperative surgical response, which facilitated a speedy recovery and awakening from anaesthesia.

6. Using computer randomization, 60 patients in ASA grades 1 and 2 who were scheduled for day care urological or gynaecological procedures were divided into three groups in a randomised controlled study by Moffat et al. [31] to assess the impact of opioids as pre induction on total intravenous anaesthesia. Before delivering an induction agent, group A patients received 1 microgram/kg of fentanyl and group B patients received 5 microgram/kg of alfentanil injection. Group C had no preinduction opioid administration. Propofol intravenously was used to induce anaesthesia, and nitrous oxide mixed with oxygen at a ratio of 67% to 33% as well as further twenty milligrams boluses – inj.propofol if needed were used to maintain anaesthesia. When compared to propofol given alone, or giving with inj. fentanyl and alfentanil had no significant change in amount of propofol needed while inducing and maintaining good anaesthesia. They concluded that coadministration of fentanyl provides zero advantage while inj.propofol alone was used for small outpatient procedures under general anaesthesia.

7. At a height of approximately 2514 metres, Ramesh Bhattarai et al. [39] conducted a randomised controlled experiment to examine the effectiveness in using Keta+Propofol / Fenta+Propofol regimens for inducing & maintaining of complete TIVA anaesthesia in smaller surgeries. Two groups of 60 ASA 1 and ASA 2 patients were randomly assigned. Fentanyl 1.2mcg/kg, Propofol 1mg/kg and Ketamine 0.5mg/kg, Propofol 1mg/kg were given to group 1 and group 2, respectively. Variations in HR and MAP , the full amount of inj.Propofol needed for induction, the duration needed for achieving sedation according to the Modified Steward Score were all significantly higher in the Fentanyl-Propofol group 18 (60). Total Propofol needed for anaesthesia induction was substantially lower in the fentanyl-propofol group (1.230.16mg/kg)compared to the ketamine-propofol group (1.550.27 mg/kg) [95% CI, 0.19-0.43, P =.00].The study found that Ketamine-Propofol caused a significantly higher total consumption of Propofol during the induction and maintenance of intravenous anaesthesia at altitude elevations of 2514 metres than Fentanyl-Propofol, but less oxygen desaturation in the first 20 minutes and a requirement for PPV, with lesser reduction in HR and MAP with faster recovery.
8. In a clinical research, Claeys MA et al [37] chose 10 senior patients and gave them a single dosage of 2 mg/kg of propofol, which was then quickly changed to infusing pump at six milligramperkilogram over one hour. The goal of the study was to establish the haemodynamic efficacy of propofol. Cardiac output, systemic vascular resistance, and stroke volume were all assessed and compared across all patients. At room temperature, all of the patients were breathing on their own. According to the Ramsay Sedation Score, induction was deemed successful in all patients when unconsciousness was attained and remained for 60 minutes after the

infusion. Even throughout the infusion phase, statistically significant reductions in systolic and diastolic arterial pressures were recorded and noted in 2 minutes after induction (28% and 19%, respectively).They observed that decreased SVR (twentyone% after injection & thirty% with continuous infusing pump) were the causes of the need for positive pressure ventilation, which was at 30% and 25%, respectively. None of the patient's heart rates, stroke volumes, or cardiac outputs were significantly impacted. The study comes to the conclusion that there is no compensatory increase in heart rate or cardiac output, to the low blood pressure in arteries following propofol injection & continuous delivery was primarily caused by decreased afterload without any corresponding rise in HR or CO.

9. McQuay et.al.,, [36] carried out a systematic investigation to assess the risk of bradycardia associated with propofol. Data were analysed quantitatively and qualitatively using various levels of support. A significant relation for propofol-induced bradycardia was explained with various strengths of evidence in 65 published studies and 187 spontaneous complaints to drug monitoring centres. 24 fatalities, 86 asystolic events, and 1444 patients with bradycardias were all reported. In comparison to other anaesthetic drugs, propofol exhibited a considerable related risk of bradycardia in 62 controlled clinical trials that assessed its effects. They also noted that one asystole was experienced by one of the 660 individuals receiving propofol induction. A death due to bradycardia under Inj. Propofol anaesthesia is found to occur in 2 out of every one lakh patients. They came to the conclusion that there was extremely little chance that bradycardia caused by propofol may cause death.

10. F.de Wit et al. [33] demonstrated a nonrandomized controlled trial to assess the effects of propofol on hemo dynamics in 17 patients scheduled for elective upper abdominal surgeries. The study included the measurement of cardiac output, systemic vascular resistance, venous return, and mean systemic filling pressures. After the induction dosage, they observed a propofol-induced substantial reduction in cardiac output. They even noted that it doesn't happen at a variety of propofol effective site concentrations that are utilised to maintain anaesthesia or sedation. In patients with intact circulation, the mean systemic filling pressure (MSFP) approach was adopted. The MSFP is the pressure that exists in a no-flow state in the systemic circulation and represents the distending pressure produced by strained volume. According to some, MSFP is the driving pressure in venous return, equal to capillary pressure, and enables the computation of the arterial and venous components of systemic vascular resistance. The difference between the MSFP and central venous pressure (CVP) multiplied by the venous resistance is the venous return. They came to the conclusion that inj.propofol causes reduced arterial blood pressure through reduction in stroke -volume with no change in cardiac output. This reduced stroke- volume linked to infusing of inj.propofol explained why individuals who are hemodynamically unstable will experience a greater drop in arterial blood pressure. The propofol-induced decrease in cardiac preload and afterload may be beneficial for patients with congestive heart failure since it will most likely increase cardiac output and result in lower cardiac and pulmonary filling pressures.

11. In order to determine the effectiveness of lignocaine airway nebulization, intravenous (IV) fentanyl, and a combination of both in reducing the hemodynamic stressor reactions to laryngoscopy and tracheal intubation, Kumar A et al. [34] undertook a randomised controlled experiment. 96 patients of either sex, ASA I and II, scheduled for elective procedures under general anaesthesia with endotracheal intubation were enrolled in this study. They were then randomly assigned to one of 3-groups. Group--F was injected with injection.fentanyl two microgram per kg, Group--FL got both three milligram per kilogram by four percent lidocaine and injection.Fenta 2 milligram for every kilogram, and L–group got nebulized at three milligram per kilogram of FOUR % lidocaine before intubation. . Prior to and immediately after induction, as well as each minute till TEN minutes post Induction, stressor responses were recorded. They observed that none of the group's hemodynamic responses to laryngoscopy and intubation were entirely diminished, but the group receiving fentanyl either by itself or in conjunction with nebulized lignocaine was the most significant and comparable. Groups F, L, and FL experienced maximum increases in mean blood pressure from baseline following intubation of 7.4%, 14.6%, and 5.4%, respectively. They came to the conclusion that there was no advantage to using the nebulized route of lignocaine to attenuate the stressor response to laryngoscopy and intubation. Instead, they recommended Injecting opiods two milligram per kilogram provided five minutes prior intubation.
12. While assessing efficacy of fentanyl on stressor response as elevated arterial BP & HR during laryngealscopy and endotracheal intubation, U M Kautto et al [5] conducted a randomised controlled experiment. Prior to anaesthesia induction with sodium thiopentone, 45 patients with normotension scheduled for elective

procedures were randomly assigned to one of three groups and given either 2,6 mics/kg of fentanyl or saline. They found that administering fentanyl at doses of 2 and 6 micrograms/kg considerably and completely reduced the stressor responses during laryngoscopy and intubation, respectively. Fentanyl administration during anaesthesia induction also lessens the need for opiods during surgery. During their post-anesthesia recovery, none of the patients had any evidence of respiratory depression.

13. In 2004, M. Kodaka, Y. Okamoto, F. Handa, J. Kawasaki, and H. Miyao conducted a study in Japan to determine the effective concentration of propofol administered via target-controlled infusion for 50% of the attempts to insert laryngeal mask airways (predicted EC50LMA) and to observe whether fentanyl affects the concentration necessary for induction, respiratory rate (RR), and bispectral index (BIS). Sixty-four patients who had been scheduled for elective surgery were divided into four groups at random (n = 16),,,,either saline or injection.fentanyl 0.5 / one or two milligram per kg were given to them. Dixon's up-and-down approach was modified to produce the desired propofol concentration. After obtaining an acceptable depth of anaesthesia for more than 10 minutes, laryngeal mask airway insertion was done without the use of neuromuscular blockers. Within 1 minute following insertion, any movements, bucking, or obvious intentional muscular action was taken into account and reported. In order to determine the EC50LMA values, the means of 16 patients from each group were determined. Results: The predicted EC50LMA of the saline, fentanyl 0.5, 1 and 2 mg/kg1 groups were correspondingly 3.25 (0.20), 2.06 (0.55), 1.69 (0.38); groups with inj.fentanyl showed lesser significance than control. But with inj.fentanyl dose of one milligram to per kilogram, RR was

reduced. In comparision with Control & half milligram per one kilogram categories, BIS values after 1 and 2 mg/kg1 of fentanyl were considerably greater. They came to the conclusion that a dose of 0.5–1 mic/kg of fentanyl is sufficient to lower projected EC50LMA with minimal respiratory depression and minor BIS value.

14. Yun Song, Jin Yu, in China studied Fifty-four patients who were posted in hysteroscopic surgery who were split to 1 of 2 groups, and Sufentanyl 0.1 / 0.2 milligram per kilogram body weight was given intravenously prior to the induction. According to Dixon and Massey's sequential up-and-down allocation rule, the induction dose of propofol was two milligram per kilogram, later with 0.1 milligram per kilogram variation. Recorded data included respiratory depression, the length of the propofol induction dose, the total amount of the medicine needed, and anaesthesia recovery time. In Group.A, propofol's ED50 was 1.6 mg/kg, while in Group.B, it was 1.9 mg/kg. Propofol's ED95 of “A” was one and a half milligram while Group.“B” was two milligram per kilogram. Propofol was administered for induction and overall in Group A at much lower doses than Group B, and Group B experienced significantly less respiratory depression (4.17%) than Group A (26.47%). Propofol's ED50 values for intravenous anaesthesia during hysteroscopy when combined via lesser dosage sufentanil are 1.71 milligram per kilogram in 0.2 gram/kilogram and 2milligramperkilogram with 0.1gram per kilogram.
15. In 2018 Uma R et.al., conducted a study in 90 cases listed for surgical procedures under GA are randomized in three categories to examine the impact of varied premedication timings with fentanyl on the stressor reaction to laryngoscopy. Fentanyl was administered to groups 1 and 2 three minutes, five minutes, and

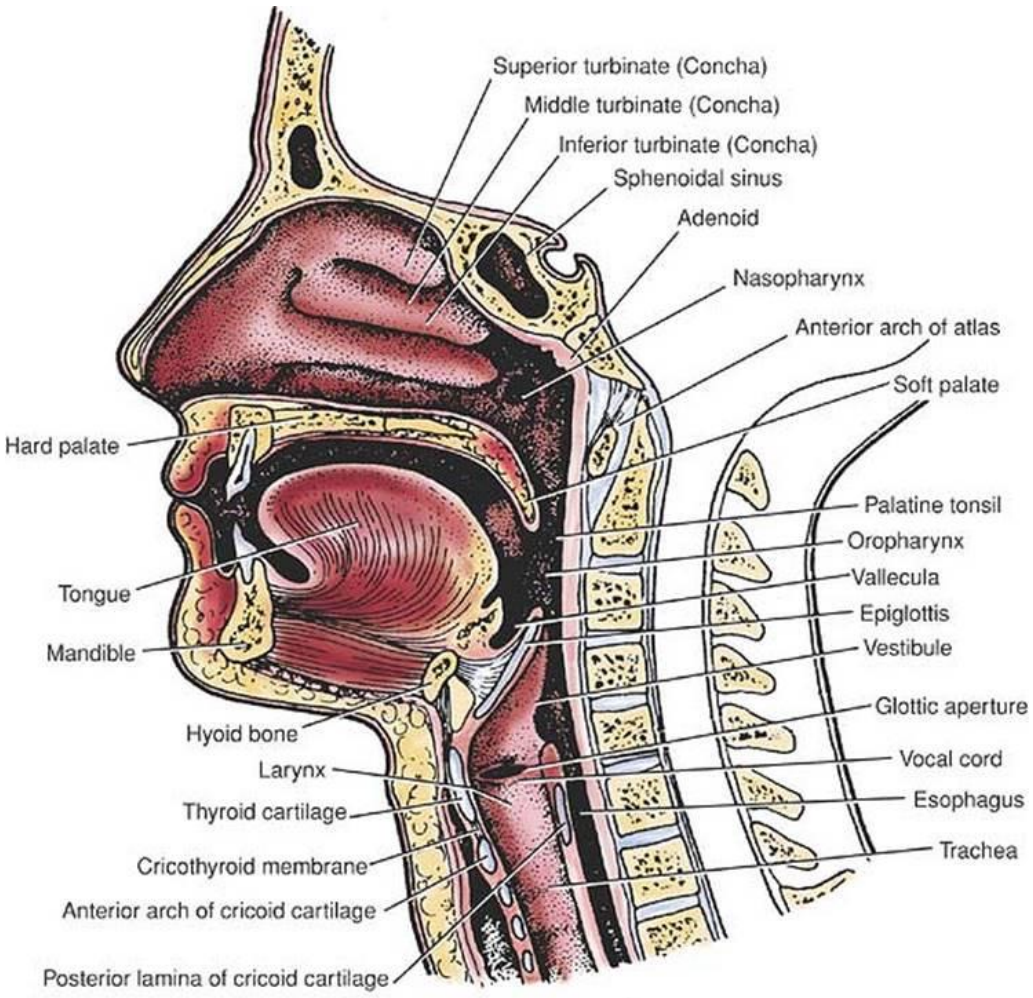
seven minutes before the induction agent, respectively. Heart rate, systolic and diastolic blood pressure, and mean arterial blood pressure were measured at baseline, during induction, during intubation, and 1 minute, 3 minutes, 5 minutes, and 10 minutes after intubation, respectively. They came to the conclusion that group 3's hemodynamic stressor response to laryngoscopy was entirely eliminated at 7 minutes of fentanyl administration prior to induction as opposed to 3 and 5 minutes, and that this helped further lower the amount of the induction agent for anaesthesia induction. In order to maintain a balanced anaesthesia, it is crucial to consider the timing and amount of opioids before induction.

16. SG Deogaonkar et al conducted a randomised controlled study in srilanka in 2018 to evaluate fentanyl effect on hemodynamic parameters, fetal well being and apgar score and cord blood pH in 45 patients undergoing elective caesarean sections under general anaesthesia belonging to ASA I and II between age 18-35 years of age. patients were divided into three groups with 15 in each group. Group S received 5 ml of saline, group F0.5 received fentanyl 0.5mics/kg, group F1 received fentanyl 1 mics /kg before induction. Hemodynamic parameters of both maternal and foetal , cord blood analysis was done and noted that there was no significant change in foetal blood parameters with fentanyl but with saline maternal Hemo dynamics were altered as they found to have higher heart rate and blood pressures. They concluded that fentanyl 0.5mics/kg can be used pre induction for safe conduct of general anaesthesia in caesarean sections without any opioid effect on foetus.

BASIC SCIENCES

ANATOMY OF THE AIRWAY

Airway is the channel through which air passes in & out the lung during respiration. The airway begins from the nose & ends at bronchioles. Airway is divided into upper airway and lower airway. Upper airway begins from the nose and extends to the glottis & lower airway begins from the glottis which includes trachea, bronchi its sub-divisions.

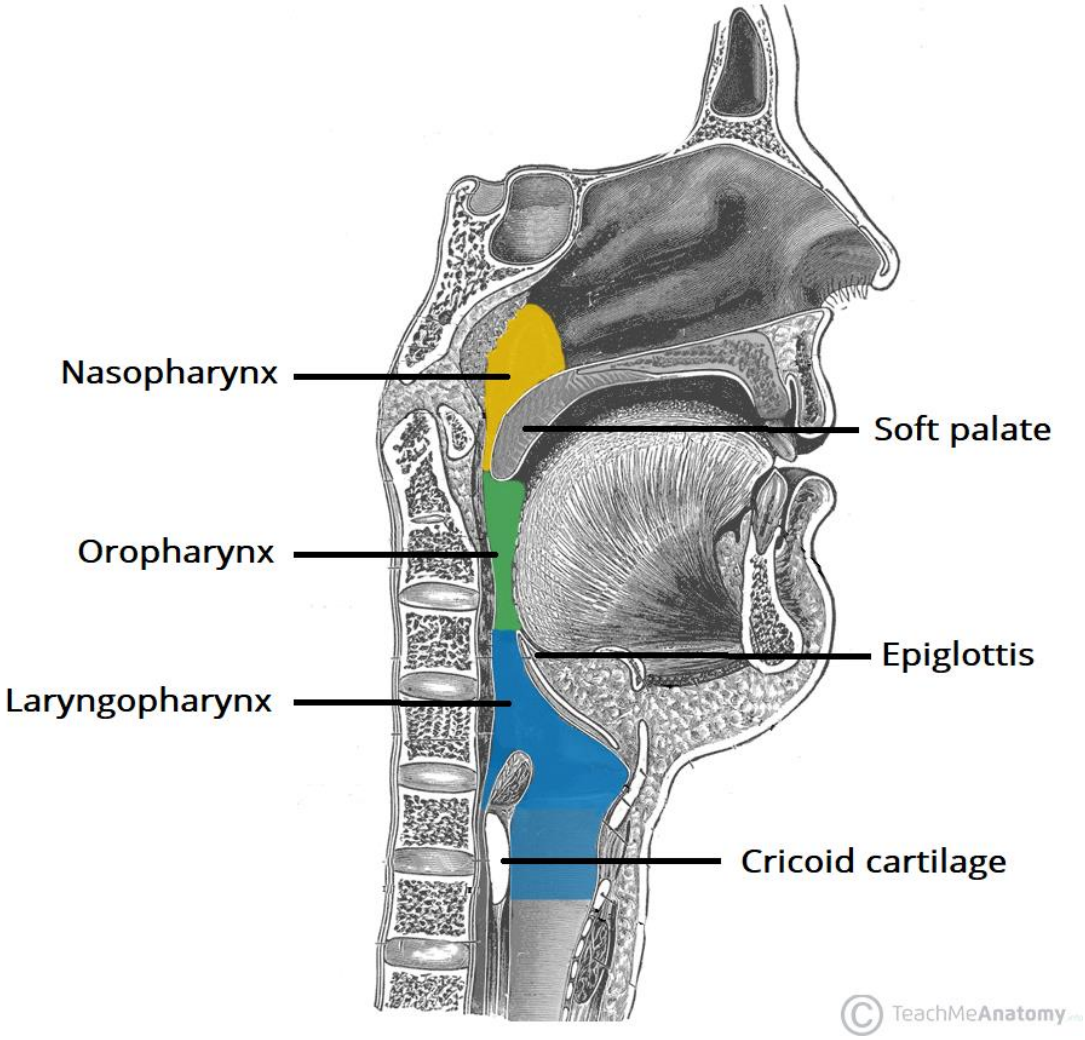


NOSE

Nose begins from nares posteriorly to the naso-pharynx for 10 to 14 centimetres & two nasal fossae are separated in the midline through the septum which is formed by cartilages and bony parts. It aids in filtration, respiration, humidification of gas, olfaction and it aids in phonation as well**.**

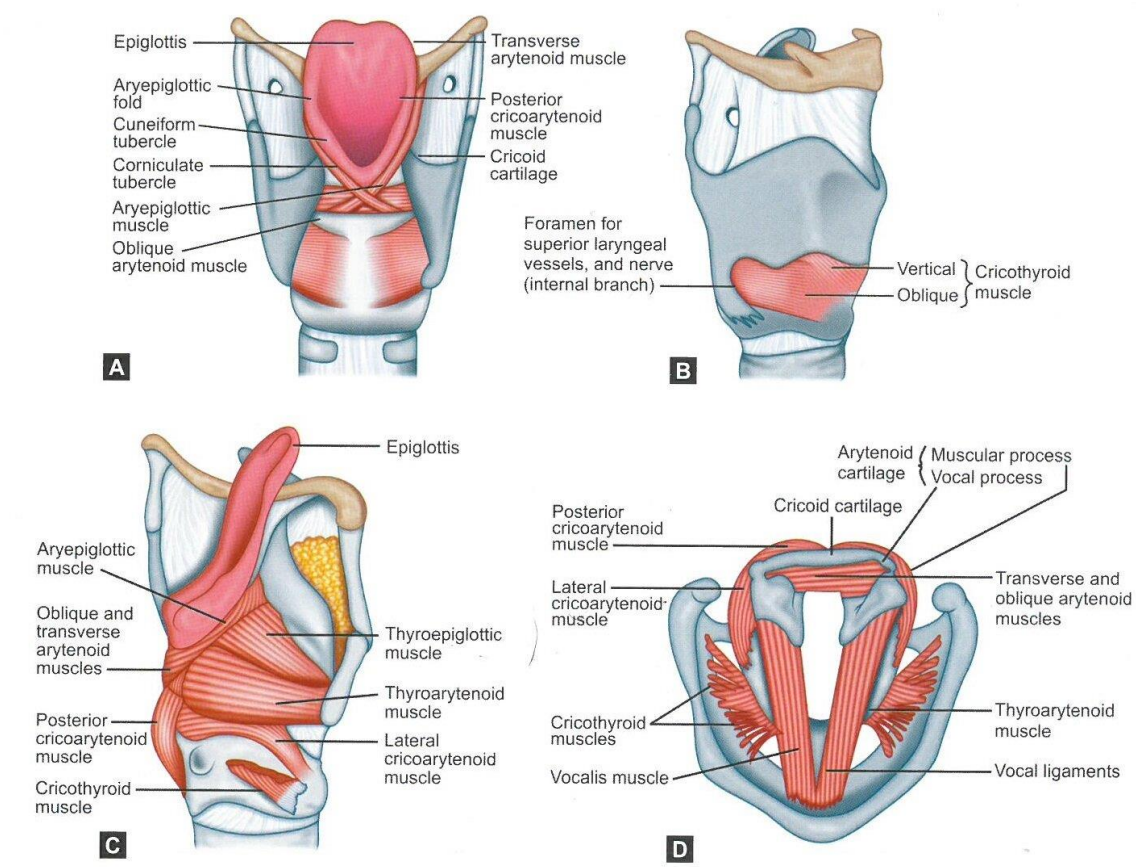
PHARYNX

Pharynx begins from base of skull it measures at 12- 15 centimetres. It ends anteriorly to cricoid cartilage and posteriorly to inferior border of 6th cervical vertebra.



LARYNX

Larynx is made of cartilage. It is present opposite to the cervical vertebrae where it begins from 3rd and extends to 6th in adults.



It is made of cartilages, ligaments & muscles where every structure has an important role.

The larynx is made of 9 cartilages, 3 paired & 3 unpaired cartilages.

There are 3 unpaired cartilages which are

1. Thyroid
2. cricoid
3. epiglottis.

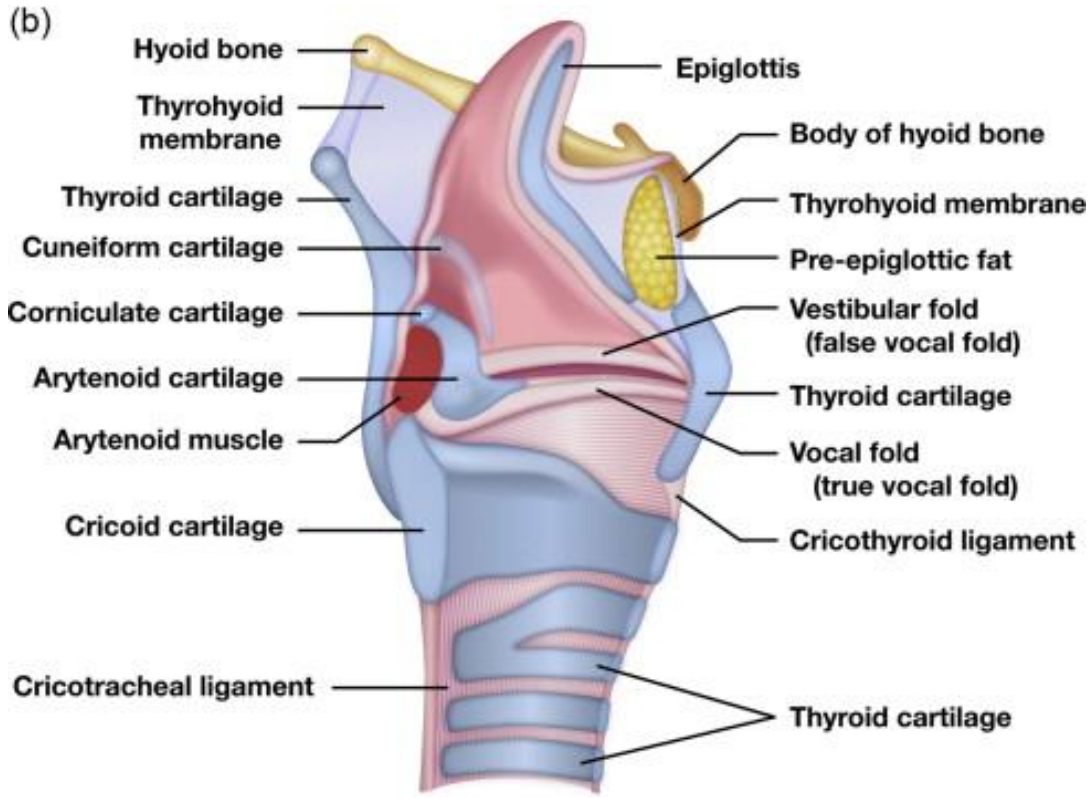
There are 3 paired cartilages

1. arytenoids,

2. corniculate

3. cuneiform.

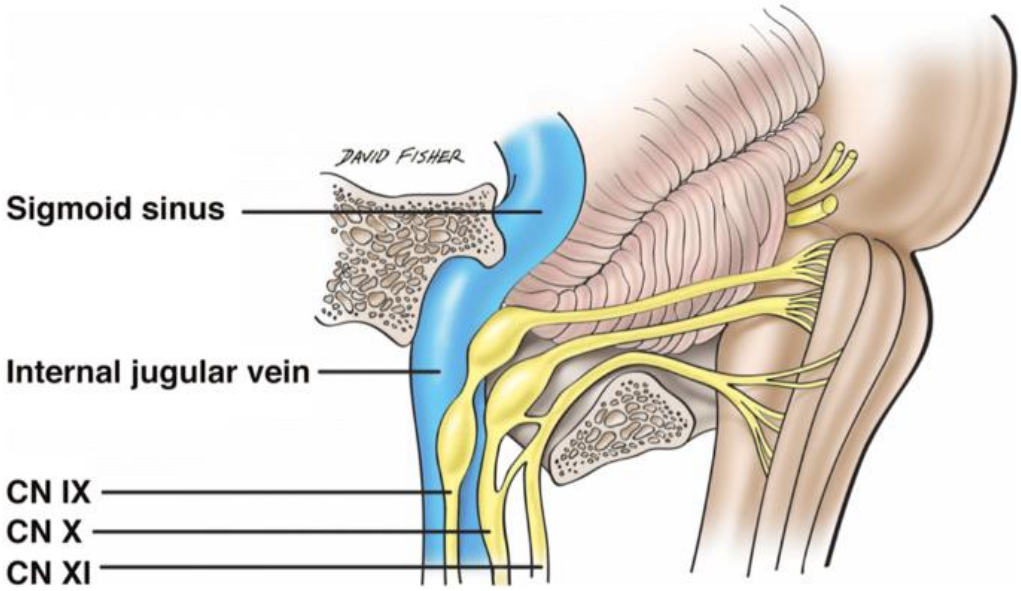
Laryngeal cavity begins from epiglottis and extends to sub glottis.



NERVE INNERVATIONS

Pharynx

The pharynx is innervated by cranial nerves 7th, 9th, 10th, and 12th. The motor & sensory innervation to most of the pharynx other than nasopharynx is innervated by the pharyngeal plexus. Pharyngeal plexus, are present above the middle pharyngeal constrictor which is made by:



1. The Pharyngeal branches which arise from the glossopharyngeal nerve i.e. 9th cranial nerve.

2. The Pharyngeal branches which arise from the vagus nerve i.e. 10th cranial nerve.

3. Branches which arise from the external laryngeal nerve

4. There are Sympathetic nerve fibres which arise from the superior cervical ganglion.

Sensory Innervations:

Pharynx is supplied with sensory innervation from the glossopharyngeal nerve. The superior & anterior part of naso-pharynx is supplied by the maxillary nerve whereas the inferior aspect of the laryngo-pharynx is supplied by internal branch of the vagus nerve.

Motor Innervations:

In pharynx all the muscles are supplied by the vagus nerve, apart from the stylopharyngeus muscle, which is supplied by the glossopharyngeal nerve**.**

Larynx:

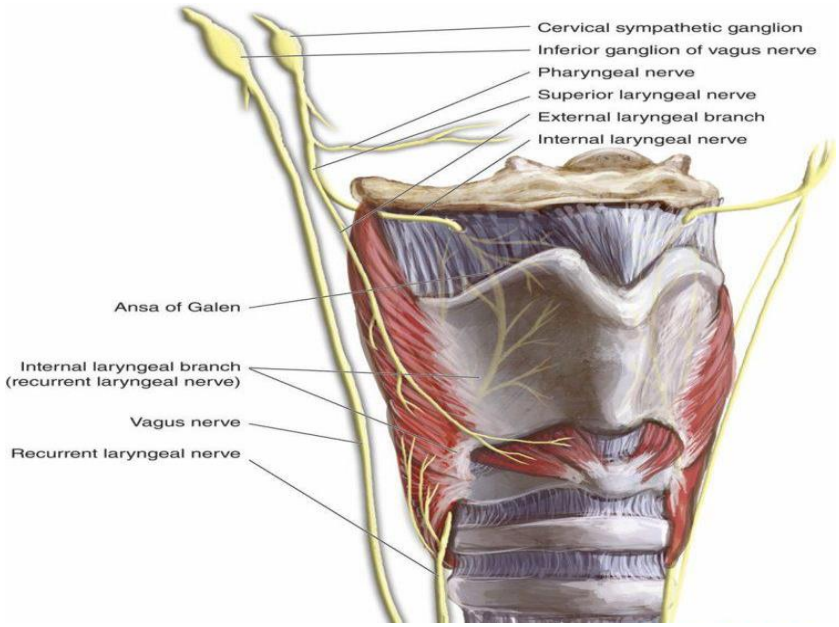
Larynx is innervated by the vagus 10th cranial nerve where it gives branches as

1. Superior laryngeal nerve branch.

2. Recurrent laryngeal nerve branch**.**

Superior laryngeal nerve:

The internal division of superior laryngeal nerve supplies the epiglottis, the base of tongue, supra-glottic mucosa, thyro-epiglottic joint & crico-thyroid joint.



The external division of superior laryngeal nerve gives sensory innervations to anterior subglottic mucosa and motor innervations to crico-thyroid muscle which is adductor, tensor.

The Recurrent laryngeal nerve provides sensory supply to the sub-glottic mucosa & muscle spindles. It also provides motor supply to thyro-arytenoid, lateral crico-arytenoid, inter arytenoids & posterior crico-arytenoid.

HEART RATE

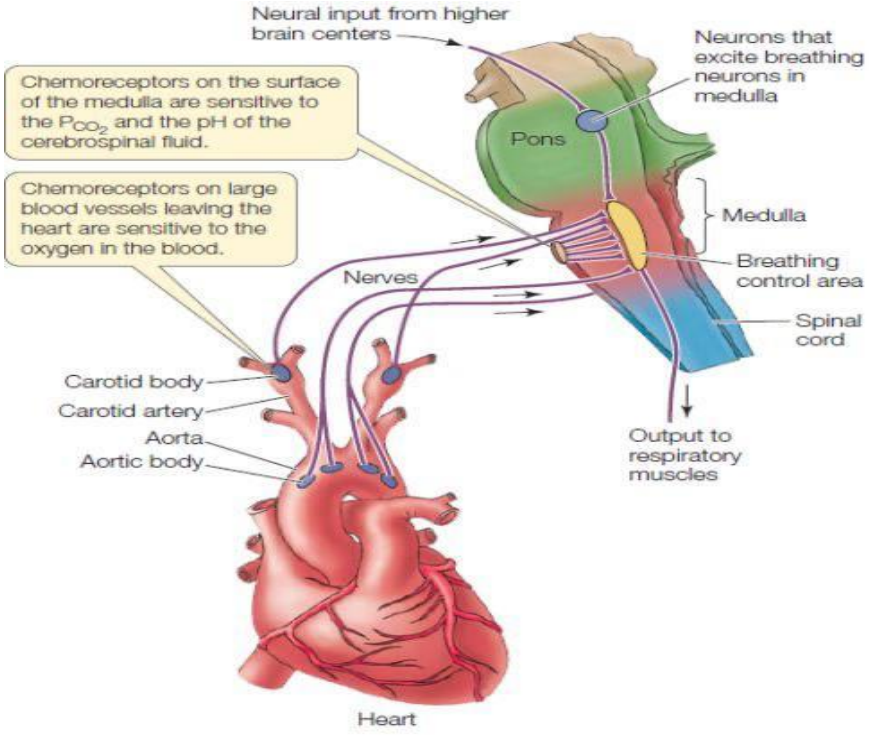
INTRODUCTION

Heart rate can vary during normal physiological condition such as exercise, emotion etc. however under physiological conditions, the altered heart rate is quickly brought to normal by various regulatory mechanisms.

REGULATION OF HEART RATE:

Heart rate is regulated by nervous mechanisms such as:

Vasomotor center, Efferent nerve fibers to the heart, Afferent nerve fibers from the heart



VASOMOTOR CENTRE: it is situated in the reticular formation of medulla oblongata and the lower part of pons consisting of three areas,

The Vasoconstrictor area, Vasodilator area and Sensory area Vasoconstrictor area increases the heart rate by sending impulses through sympathetic nerves. This is under the control of hypothalamus and cerebral cortex. Vasodilator area decreases the

heart rate by sending impulses through vagus, which is under the control of hypothalamus. It is also controlled by baroreceptors and chemoreceptors.

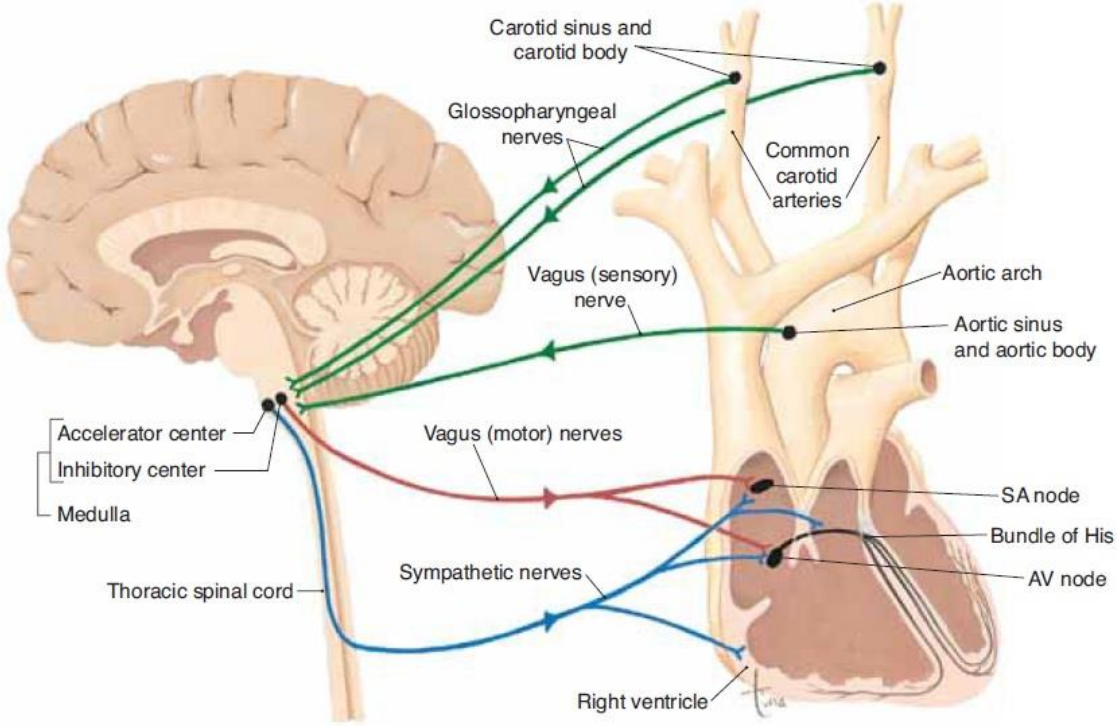


Figure 12–7. Nervous regulation of the heart. The brain and spinal cord are shown on the left. The heart and major blood vessels are shown on the right.
QUESTION: Sympathetic impulses to the ventricles will have what effect?

Sensory area lies in the nucleus tractus solitarius in medulla and pons. This area receives sensory impulses via glossopharyngeal and vagus nerves. Efferent nerve fibers are Parasympathetic arising from dorsal nucleus of vagus. They innervate the heart by cardiac branch of vagus, terminating in sinoatrial node (SAN) and atrioventricular node (AVN) causing decrease in heart rate. Factors affecting vasomotor center: Impulses from higher center:

 Cerebral cortex area 13 is concerned with emotional reactions of the body. It causes cardiac acceleration with emotions.

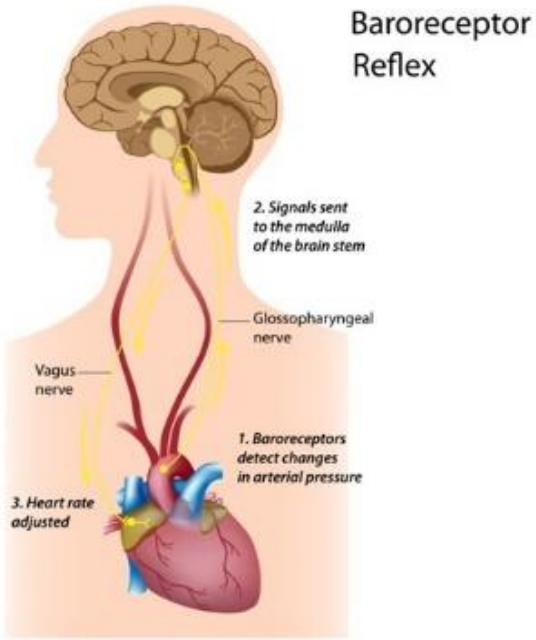
 Hypothalamus: stimulation of posterior and lateral hypothalamic nuclei causes tachycardia, whereas stimulation of preoptic and anterior nuclei causes bradycardia.

Impulses from respiratory center:

In forced breathing heart rate increases during inspiration and decreases during expiration. This variation is called respiratory sinus arrhythmia.

Impulses from baroreceptors (marey's reflex)

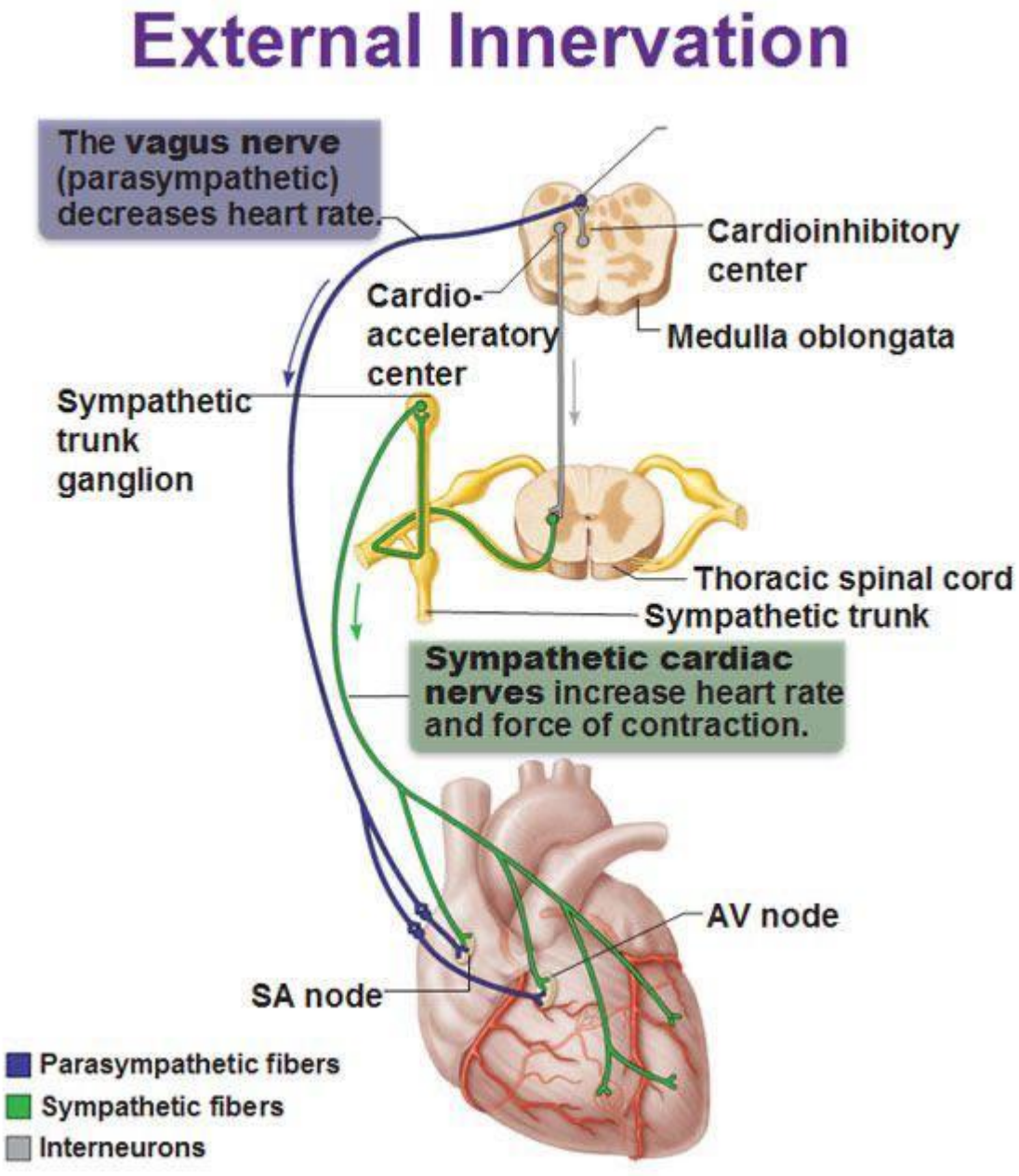
Baroreceptors respond to change in blood pressure, Carotid baroreceptors are situated in the carotid sinus, which is present in the internal carotid artery near bifurcation of common carotid artery. The aortic baroreceptors are situated in the arch of aorta.Afferent from carotid sinus passes through herings branch of glossopharyngeal nerve, Afferent from aortic sinus passes through vagus nerve. The nerve fibers reach the nucleus of tractus solitarius situated adjacent to vasomotor center.



Marey's law: The heart rate is inversely proportional to blood pressure. The baroreceptor produces the marey's reflex only during resting conditions.

Impulse from chemoreceptors:

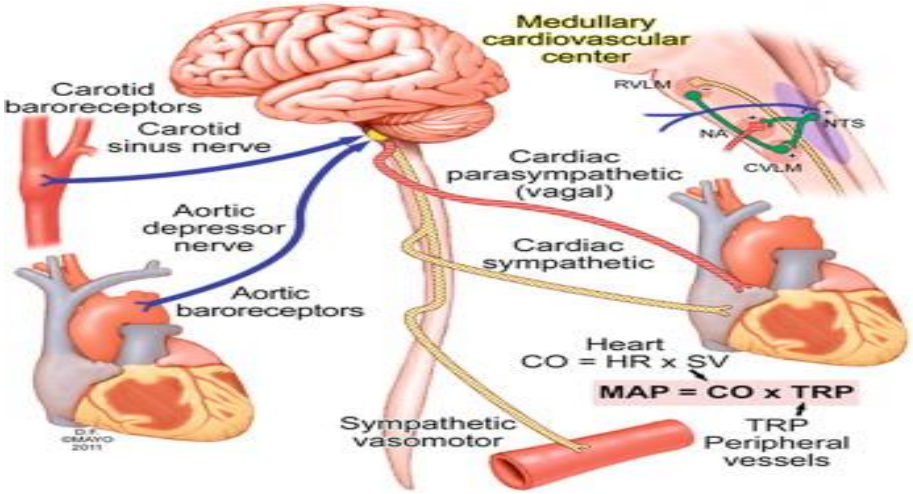
Chemoreceptors respond to change in chemical constituents of blood, particularly oxygen, carbon di oxide and hydrogen ion concentration. These are adjacent to baroreceptors.



ARTERIAL BLOOD PRESSURE

Arterial blood pressure is defined as the lateral pressure exerted by the column of blood on the wall of arteries. Mean arterial pressure is the average pressure existing in the arteries. It is diastolic pressure plus one third of pulse pressure. Since the diastolic period (0.53s) is longer than the systolic period (0.27s).

Normal mean arterial pressure is 93



Regulation of arterial blood pressure:

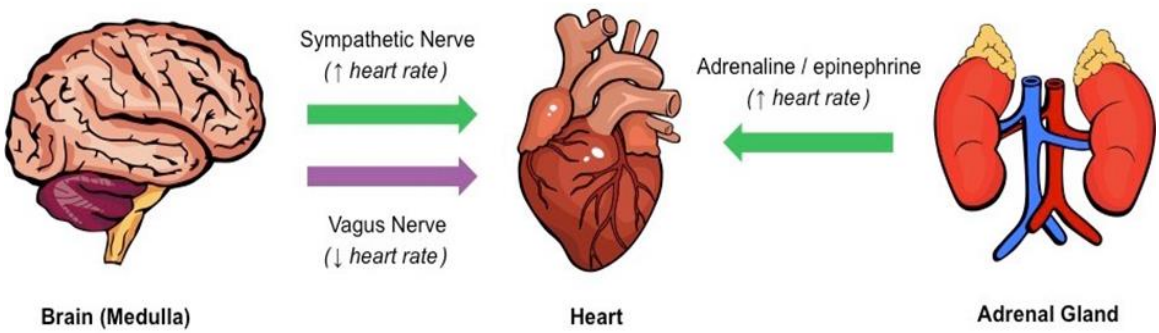
Regulatory mechanisms:

1) Nervous mechanism or short-term regulatory mechanism.

2) Renal mechanisms or long-term regulatory mechanism.

3) Hormonal mechanisms

4) Local mechanisms.



Haemodynamic responses to laryngoscopy and intubation

The hemodynamic response to laryngoscopy and endotracheal intubation have been recognised as early as 1951 by various studies. The induction of anaesthesia, laryngoscopy, endotracheal intubation and the surgical stimuli evoke cardiovascular responses that is manifested as alteration in systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate and cardiac rhythm. This occurs mainly due to catecholamine release in response to sympathetic stimulation that occurs during tracheal intubation.

The response following laryngoscopy and intubation peaks at about 1 to 2minutesutes and return to baseline within 5 to 10minutes. Although the sympatho-adrenal responses probably causes little consequences in healthy patients, it is hazardous in patients with comorbid illness such as systemic hypertension, coronary artery disease (CAD), cerebrovascular disease (CVA), intracranial pathology and hyperactive airways.

In such cases, reflex circulatory response to tracheal intubation such as an increase in heart rate, blood pressure and disturbances in cardiac rhythm should be suppressed Prof.

King et al (1951) documented myocardial ischemic changes due to reflex sympatho-adrenal changes immediately following laryngoscopy and endotracheal intubation with a mean increase in systolic pressure of 40mmHg even in normotensive individuals.

The hemodynamic responses during laryngoscopy and endotracheal intubation should be abolished to balance the myocardial oxygen supply demand which is a key note in the safe conduct of anaesthesia. Attempts to reduce these untoward

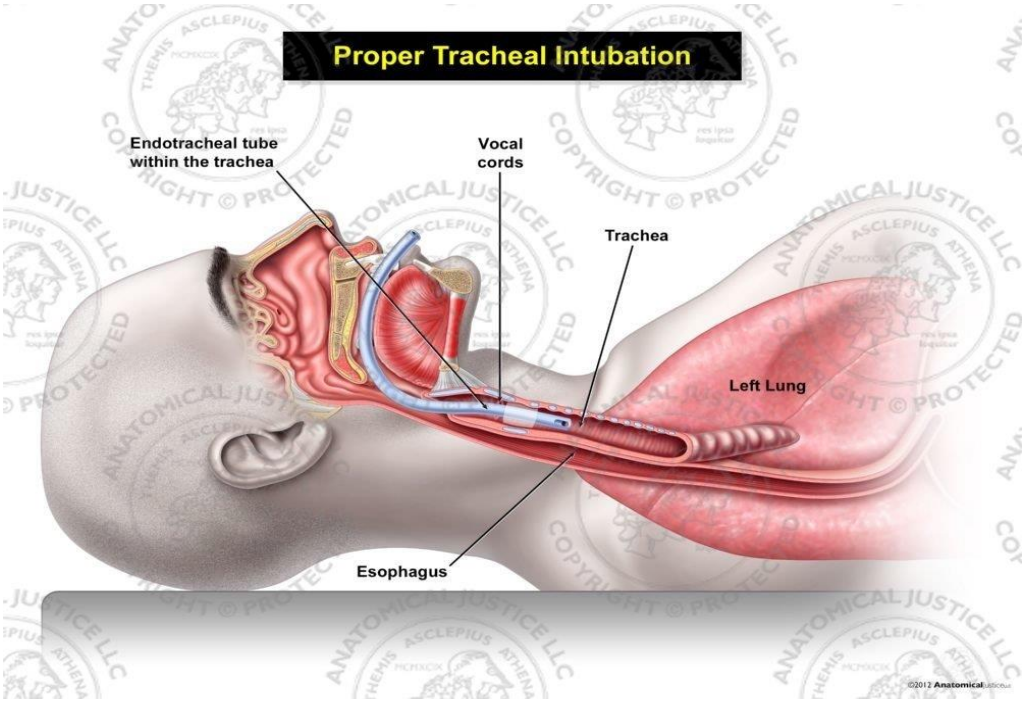
cardiovascular responses during laryngoscopy and endotracheal intubation lead to the trial of various systemic as well as topical agents.

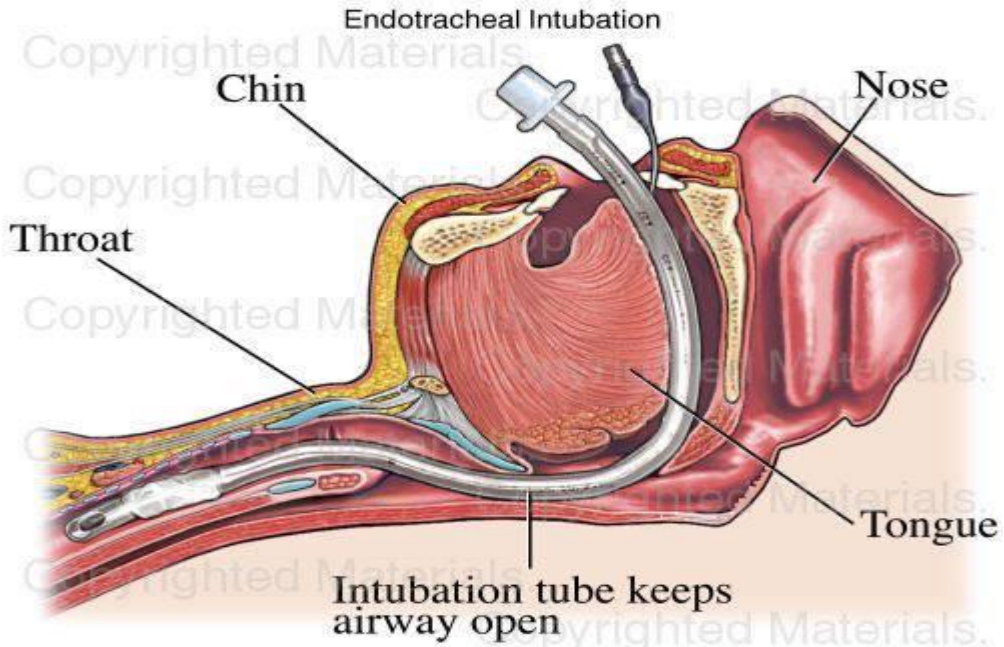
Pyrs Roberts et al (1971) showed exaggerated form of this response in hypertensive patients. Various systemic and topical agents have been used to reduce these adverse hemodynamic responses during laryngoscopy.

The present concept of a definitive sympathetic over activity during laryngeal intubation clearly shows that a more protection against vagal over activity and the use of anticholinergic drugs alone may not be sufficient.

Compared to systemic agents, administration of local anaesthetic solutions are likely to be of limited value in reducing these responses. The commonest strategies adopted are narcotics, vasodilator agents, β-blockers, calcium channel blockers, lignocaine, alpha 2 agonists and other sympatholytic agents.

In our study we have used fentanyl as premedication for attenuating stress response to intubation.



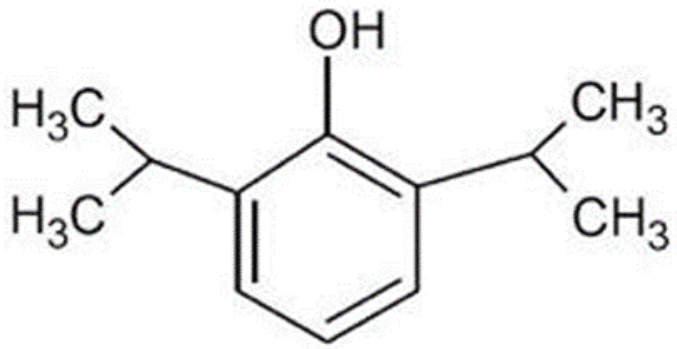


PHARMACOLOGY OF PROPOFOL

Aminobutyric Acid Agonists Propofol

 Propofol is a substituted isopropyl phenol (2,6-dilsopro- pylphenol) that is administered intravenously as 1% solution in an aqueous solution of 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide.

Figure 3: Chemical structure of propofol



Administration of propofol, 1.5 to 2.5 mg/kg IV (equivalent to thiopental, 4 to 5 mg/kg IV, or methohexital, 1.5 mg/kg IV) as a rapid IV injection (15 seconds), produces unconsciousness within about 30 seconds. Awakening is more rapid and complete when compared with all other drugs used for rapid IV induction of anaesthesia The more rapid return of consciousness with minimal residual central nervous system (CNS) effects is one of the most important advantages of propofol.

Commercial Preparations

Propofol is an insoluble drug that requires a lipid vehicle for emulsification. Current formulations of propofol use soybean oil as the oil phase and egg lecithin as the emulsifying agent that is composed of long chain triglycerides.

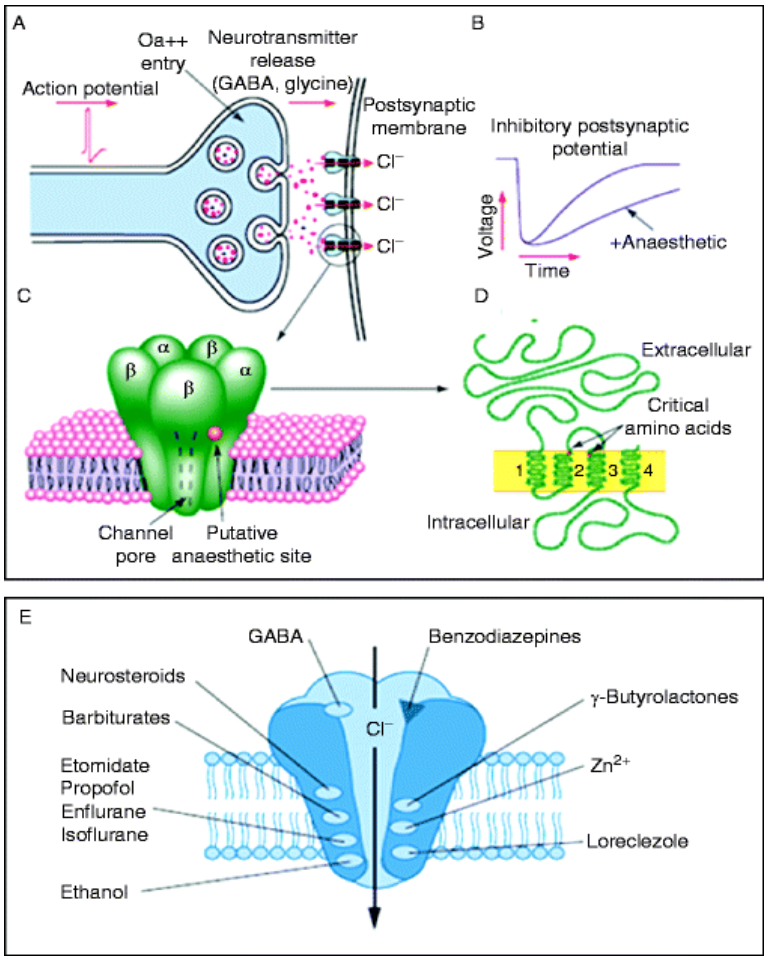
This formulation supports bacterial growth and causes increased plasma triglyceride concentrations when prolonged IV Infusions are used. Compared with propofol, the prodrug has a slower onset, larger volume of distribution, and higher potency. Another nonlipid formulation of propofol uses cyclodextrins as a solubilizing agent.

Mechanism of Action

Propofol is presumed to exert its sedative-hypnotic effects through a GABA-A receptor interaction. GABA is the principal inhibitory neurotransmitter in the brain. When GABA-A receptors are activated, transinembrane chloride conductance increases, resulting in hyperpolarization of the postsynaptic cell membrane and functional inhibition of the postsynaptic neuron.

The interaction of propofol (also etomidate and barbiturates) with specific components of GABA-A receptors appears to decrease the rate of dissociation of the inhibitory neurotransmitter, GABA from the receptor, thereby increasing the duration

of the GABA-activated opening of the chloride channel with resulting hyperpolarization of cell membranes.



Pharmacokinetics

Clearance of propofol from the plasma exceeds hepatic blood flow, emphasizing that tissue uptake (possibly into the lungs), as well as hepatic oxidative metabolism by cytochrome P450, is important in removal of this drug from the plasma.

Hepatic metabolism is rapid and extensive, resulting in inactive, water soluble sulfate and glucuronic acid metabolites that are excreted by the kidneys.

Propofol may also undergo ring hydroxylation by cytochrome P450 to form 4-hydroxypropofol which is then glucorinated or sulfated. Although the glucuronide and

sulfate conjugates of propofol appear to be pharmacologically inactive, 4-hydroxypropofol has about one-third the hypnotic activity of propofol.

Less than 0.3% of a dose is excreted unchanged in urine. The elimination halftime is 0.5 to 1.5 hours, but more important, the context-sensitive half-time for propofol infusions lasting up to 8 hours is less than 40minutes.

The context-sensitive half-time of propofol is only minimally influenced by the duration of the infusion at times relevant for surgery because of slow return of the drug from tissue storage sites to the circulation.

When the infusion is discontinued, this influx from tissues is not sufficient to retard the decrease in plasma concentrations of the drug.Propofol, like thiopental and alfentanil, has a short effect-site equilibration time such that effects on the brain occur promptly after IV administration.

Comparative Characteristics of Common Induction Drugs

The fact that total body clearance of propofol exceeds hepatic blood flow is consistent with extrahepatic clearance (pulmonary uptake and first-pass elimination, renal excretion) of propofol. Pulmonary uptake of propofol is significant and influences the initial availability of propofol.

Although propofol can be transformed in the lungs to 2,6-diisopropy1-1,4-quiniol, most of the drug that undergoes pulmonary uptake during the first pass is released back into the circulation. Glucuronidation is the major metabolic pathway for propofol and uridine 5‘- diphospho-glucuronosyl transferase isoforms are expressed in the kidneys and brain. Plasma concentrations of propofol at the time of awakening are similar in alcoholic and normal patients.

Renal dysfunction does not influence the clearance of propofol despite the observation that nearly three-fourths of propofol metabolites are eliminated in urine in the first 24 hours.

Patients older than 60 years of age exhibit a decreased rate of plasma clearance of propofol compared with younger adults. The rapid clearance of propofol confirms this drug can be administered as a continuous infusion during surgery without an excessive cumulative effect. Propofol readily crosses the placenta but is rapidly cleared from the neonatal circulation.

Clinical Uses

Propofol has become the induction drug of choice for many forms of anaestheisa, especially when rapid and complete awakening is considered desirable. Continuous IV infusion of propofol, with or without other anesthetic drugs, has become a commonly used method for producing “conscious” sedation or as part of a balanced or total IV anesthetic.’

Administration of propofol as a continuous infusion may be used for sedation of patients in the ICU.In this regard; a 2% solution may be useful to decrease the volume of lipid emulsion administered with long-term sedation.

Induction of Anesthesia

The induction dose of propofol in healthy adults is 1.5 to 2.5 mg/kg IV, with blood levels of 2 to 6 µg/mL producing unconsciousness depending on associated medications and the patient’s age. As with barbiturates, children require higher induction doses of propofol on a milligram per kilogram basis, presumably reflecting a larger central distribution volume and higher clearance rate.

Elderly patients require a lower induction dose (25% to 50% decrease) as a result of a smaller central distribution volume and decreased clearance rate and

increased pharmacodynamic activity. Awakening typically occurs at plasma propofol concentrations of 1.0 to 1.5 µg/mL.

The complete awakening without residual CNS effects that is characteristic of propofol is the principal reason that this drug has replaced thiopental for induction of anaestheisa in many clinical situations.

Intravenous Sedation

The short context-sensitive half-time of propofol, combined with the short effect-site equilibration time, make this a readily titratable drug for production of IV sedation. The prompt recovery without residual sedation and low incidence of nausea and vomiting make propofol particularly well suited to ambulatory conscious sedation techniques.

The typical conscious sedation dose of 25 to 100 µg/kg/minute IV producesminutesimal analgesic but marked animistic effects.

In selected patients, midazolam or an upload may be added to propofol for continuous IV sedation. A sense of well-being may accompany recovery from conscious sedation with propofol.

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.

Propofol has emerged as the agent of choice for sedation for brief gastrointestinal endoscopy procedures. A computer-assisted personalized sedation for upper endoscopy and colonoscopy, called SEDASYS.

Propofol also provides control of stress responses and has anticonvulsant and amnesic properties. After cardiac surgery, propofol sedation appears to modulate

postoperative hemodynamic responses by decreasing the incidence and severity of tachycardia and hypertension.

Increasing metabolic acidosis, lipemic plasma, bradycardia, and progressive myocardial failure has been described, particularly in children who were sedated with propofol during management of acute respiratory failure in the ICU.

Maintenance of Anaestheisa

The typical dose of propofol for maintenance of anaestheisa is 100 to 300 µg/kg/minute, doses that are often lowered by combination with a short acting opioid.

Nonhypnotic Therapeutic Applications

In addition to its clinical application as an IV induction drug, propofol has been shown to have beneficial effects that were not anticipated when the drug was initially introduced in 1989.

Antiemetic Effects

The incidence of postoperative nausea and vomiting is decreased when propofol is administered, regardless of the anesthetic technique. Subhypnotic doses of propofol (10 to 15 mg IV) may be used in the postanaestheisa care unit to treat nausea and vomiting, particularly if it is not of vagal origin.

Propofol is generally efficacious in treating postoperative nausea and vomiting at plasma concentrations that do not produce significant sedation. Antiemetic plasma concentrations of propofol are achieved by a single IV dose of 10 mg followed by 10 µg/kg/minute Propofol in subhypnotic doses is effective against chemotherapy-induced nausea and vomiting. It is almost as effective as ondansetron in preventing postoperative nausea and vomiting.

Anticonvulsant Activity

Propofol possesses antiepileptic properties, presumably reflecting GABA mediated presynaptic and postsynaptic inhibition of chloride ion channels. In this regard, propofol in doses of greater than 1 mg/kg IV decreases seizure duration 35% to 45% in patients undergoing electroconvulsive therapy.

Analgesia

Propofol does not relieve acute nociceptive pain. However in animal models, low-dose propofol equivalent to antiemetic concentrations earlier was highly effective in relieving nociceptive responses to neuropathic pain.

Effects on Organ Systems

Central Nervous System

Propofol decreases cerebral metabolic rate for oxygen (CMRO2), cerebral blood flow, and intracranial pressure (ICP). Administration of propofol to produce hypnosis in patients with intracranial space-occupying lesions does not increase 1CP. 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 PaCO2 are not affected by propofol.

Cerebral blood flow velocity changes in parallel with changes in Paco2 in the presence of propofol and midazolam (Fig. 5-3). Propofol produces cortical electroencephalographic (EEG) changes that are similar to those of thiopental, including the ability of high doses to produce burst suppression.

Cardiovascular System

Propofol produces decreases in systemic blood pressure, which are greater than those evoked by comparable doses of thiopental. These decreases in blood

pressure are often accompanied by corresponding changes in cardiac output and systemic vascular resistance.

The relaxation of vascular smooth muscle produced by propofol is primarily due to inhibition of sympathetic vasoconstrictor nerve activity. A negative inotropic effect of propofol may result from a decrease in intracellular calcium availability secondary to inhibition of trans sarcolemmal calcium influx.

Stimulation produced by direct laryngoscopy and intubation of the trachea reverses the blood pressure effects of propofol.Propofol also effectively blunts the hypertensive response to placement of a laryngeal mask airway.

The blood pressure effects of propofol may be exaggerated in hypovolemic patients, elderly patients, and patients with compromised left ventricular function. Adequate hydration before rapid IV administration of propofol is recommended to minimize the blood pressure reduction.

Despite decreases in systemic blood pressure, heart rate typically remains unchanged. Baroreceptor reflex control of heart rate may be depressed by propofol. Bradycardia and asystole have been observed after induction of anaesthesia with propofol.

Propofol may decrease sympathetic nervous system activity to a greater extent than parasympathetic nervous system activity1, resulting in a predominance of parasympathetic activity). Propofol does not alter sinoatrial or atrioventricular node function in patients with Wolff- Parkinson White syndrome, for ablative procedures.

Nevertheless, there is a case report of a patient with Wolff- parkinson-White syndrome in whom 6 waves on the electrocardiogram disappeared during infusion of propofol. Unlike sevoflurane, propofol does not prolong the QTc interval on the electrocardiogram.

Lungs

Propofol produces dose-dependent depression of ventilation, with apnea occurring in least of patients after induction of anaestheisa with propofol. Opioids enhance this ventilatory depression. A maintenance infusion of propofol decreases tidal volume and frequency of breathing. The ventilatory response to arterial hypoxemia are also decreased by propofol due to an effect at the central chemoreceptors. Hypoxic pulmonary vasoconstriction remains intact in patients receiving propofol.

Hepatic and Renal Function

Propofol does not normally affect hepatic or renal function as reflected by measurements of liver transaminase enzymes or creatinine concentrations. Prolonged infusions of propofol have been associated with hepatocellular injury accompanied by lactic acidosis, bradydysrhythmias, and rhabdomyolysis as part of the propofol infusion syndrome.

Prolonged infusions of propofol may also result in excretion of green urine, reflecting the presence of phenols in the urine. This discoloration does not alter renal function. Urinary uric acid excretion is increased after administration of propofol and may manifest as cloudy urine when the uric acid crystallizes in the urine under conditions of low pH and temperature. Thus cloudy urine is not considered to be detrimental or indicative of adverse renal effects of propofol.

Intraocular Pressure

In this regard, propofol is associated with significant decreases in intraocular pressure that occur immediately after induction of anaestheisa and are sustained during tracheal intubation. Total IV anaestheisa with propofol for laparoscopic surgery was associated with lower intraocular pressures than in patients undergoing similar surgery with isoflurane anaestheisa .

Coagulation

Propofol does not alter tests of coagulation or platelet function. However, propofol inhibits platelet aggregation that is induced by proinflammatory lipid mediators including thromboxane A2 and platelet activating factor.

Other Side Effects

Side effects of propofol may reflect the parent drug or actions attributed to the oil-in-water emulsion formulation.

For example, some of the side effects of propofol (bradycardia, risk of infection, pain on injection, hypertriglyceridemia with prolonged administration, potential for pulmonary embolism) are believed to be due in large part to the lipid emulsion formulation.

Allergic Reactions

Allergenic components of propofol include the phenyl nucleus and di isopropyl side chain. Patients who develop evidence of anaphylaxis on first exposure to propofol may have been previously sensitized to the di isopropyl radical, which is present in many dermatologic preparations. Indeed, anaphylaxis to propofol during the first exposure to this drug has been observed, especially in patients with a history of other drug allergies, often to neuromuscular blocking drugs.

Lactic Acidosis

Lactic acidosis (“propofol infusion syndrome”) has been described in pediatric and adult patients receiving prolonged high-dose infusions of propofol (>75 µg/kg/minute) for longer than 24 hours.

Even short-term infusions of propofol (Diprivan) for surgical anaestheisa have been associated with development of metabolic acidosis dysrhythmias. 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 in a patient receiving a prolonged propofol infusion (Diprivan) for a craniotomy.

The differential diagnosis when propofol-induced lactic acidosis is suspected includes hyperchloremic metabolic acidosis associated with large volume infusions of 0.9% saline and metabolic acidosis associated with excessive generation of organic acids, such as lactate and ketones (diabetic acidosis, release of a tourniquet). Measurement of the anion gap and individual measurements of anions and organic acids will differentiate hyperchioremic metabolic acidosis from lactic acidosis.

Proconvulsant Activity

The majority of reported propofol-induced “seizures” during induction of anaestheisa or emergence from anaestheisa 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 propofol administration. The incidence of excitatory movements and associated ECG changes are low after the administration of propofol.

Abuse Potential

Intense dreaming activity, amorous behaviour, and hallucinations have been reported during recovery from low-dose infusions of propofol.

Bacterial Growth

Propofol strongly supports the growth of Escherisia coli and Pseudomonas aeruginosa.An aseptic technique be used in handling propofol as reflected by disinfecting the ampule neck surface or vial rubber stopper with 70% isopropyl alcohol;

The contents of the ampule containing propofol should be withdrawn into a sterile syringe immediately after opening and administered promptly. The contents of an opened ampule must be discarded if they are not used within 6 hours. In the ICU, the tubing and any unused portion of propofol must be discarded after 12 hours.
Propofol is aseptically drawn into an uncapped syringe, it will remain Sterile at room temperature for several days.

Antioxidant Properties

Propofol has potent antioxidant properties that resemble those of the endogenous antioxidant vitamin E. Like vitamin E, propofol contains a phenolic hydroxyl group that scavenges free radicals and inhibits lipid peroxidation. A neuroprotective effect of propofol is due to the antioxidant potential of propofol's phenol ring structure.

Propofol reacts with lipid peroxyl radicals and thus inhibits lipid peroxidation by forming relatively stable propofol phenoxyl radicals. Propofol also scavenges peroxynitrite, A potent reactive metabolites for the initiation of lipid peroxidation. Propofol strongly attenuates lipid peroxide-tion during coronary artery bypass graft surgery CABG.

Pain on injection

Pain on injection is the most commonly reported adverse event associated with propofol administration to awake patients. This unpleasant side effect of propofol occurs in fewer than 10% of patients when the drug is injected into a large vein rather than a dorsum vein on the hand.

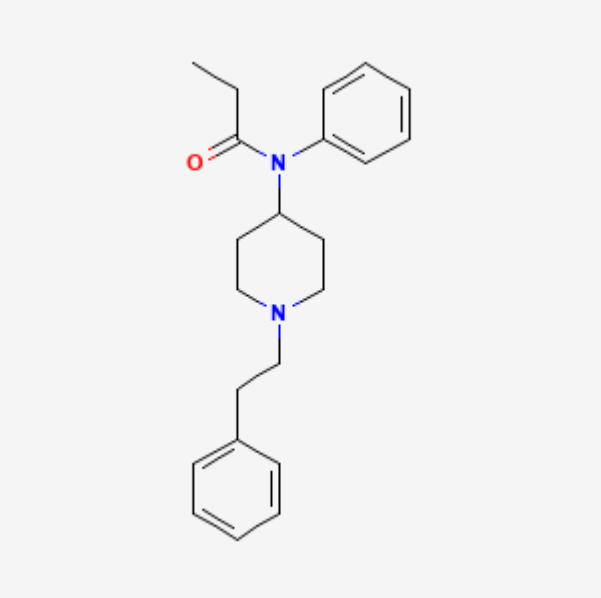
Preceding the propofol with 2% lidocaine, using the same injection site, or by prior administration of a potent short- acting opioid decreases the incidence of discomfort experienced by the patient. The incidence of thrombosis or phlebitis is usually less than 1%. Changing the composition of the carrier fat emulsion for propofol to long and medium chain triglycerides decreases the incidence of pain on injection.

PHARMACOLOGY OF FENTANYL

Fentanyl is a phenylpiperidine-derivative synthetic opioid agonist that is structurally related to meperidine.

As an analgesic, fentanyl is 75 to 125 times more potent than morphine.

It was first synthesized by Janssen Pharmaceutica in 1960 during an assay on meperidine derivatives and subsequently released as the citrate salt under the trade name Sublimaze .



Pharmacokinetics

A single dose of fentanyl administered IV has a more rapid onset and shorter duration of action than morphine. This delay reflects the effect-site equilibration time between blood and the brain for fentanyl, which is 6.4minutes. The greater potency and more rapid onset of action reflect the greater lipid solubility of fentanyl compared with that of morphine, which facilitates its passage across the blood– brain barrier.

The short duration of action of a single dose of fentanyl reflects its rapid redistribution to inactive tissue sites such as fat and skeletal muscles, with an associated decrease in the plasma concentration of the drug. The lungs serve are a large inactive storage site, with an estimated 75% of the initial fentanyl dose undergoing first-pass pulmonary uptake.

This non respiratory function of the lungs limits the initial amount of drug that reaches the systemic circulation and may play an important role in determining the pharmacokinetic profile of fentanyl. When multiple IV doses of fentanyl are administered or when there is continuous infusion of the drug, progressive saturation of these inactive tissue sites occurs.

Metabolism

Fentanyl is extensively metabolized by N-demethylation, producing norfentanyl, hydroxyproprionyl -fentanyl, and hydroxyproprionyl norfentanyl. Norfentanyl is structurally similar to normeperidine and is the principal metabolite of fentanyl.

It is excreted by the kidneys and can be detected in the urine for 72 hours after a single IV dose of fentanyl. Less than 10% of fentanyl is excreted unchanged in the urine. Fentanyl is a substrate for hepatic P450 enzymes (CYP3A) and is susceptible to drug interactions that reflect interference with enzyme activity.

Elimination Half-Time

Despite the clinical impression that fentanyl has a short duration of action, its elimination half-time is longer than that for morphine. This longer elimination half-time reflects a larger Vd of fentanyl because clearance of both opioids is similar.

The larger Vd of fentanyl is due to its greater lipid solubility and thus more rapid passage into tissues compared with the less lipid- soluble morphine. After an IV bolus, fentanyl distributes rapidly from the plasma to highly vascular tissues (brain, lungs, heart).

More than 80% of the injected dose leaves the plasma in 5minutesutes. The plasma concentrations of fentanyl are maintained by slow reuptake from inactive tissue sites, which accounts for persistent drug effects that parallel the prolonged elimination half-time.

A prolonged elimination half-time for fentanyl in elderly patients is due to decreased clearance of the opioid because Vd is not changed in comparison with younger adults. This change may reflect age-related decreases in hepatic blood flow, microsomal enzyme activity, or albumin production, as fentanyl is highly bound (79% to 87%) to protein.

Context-Sensitive Half-Time

As the duration of continuous infusion of fentanyl increases beyond about 2 hours, the context-sensitive half-time of this opioid becomes greater than sufentanil. It is due to saturation of inactive tissue sites with fentanyl during prolonged infusions and return of the opioid from peripheral compartments to the plasma. Thus tissue reservoir of fentanyl replaces fentanyl eliminated by hepatic metabolism to slow the rate of decrease in the plasma concentration of fentanyl when the infusion is discontinued.

Clinical Uses

Fentanyl is administered clinically in a wide range of doses. For example, low doses of fentanyl, 1 to 2 mcg/kg IV, are injected to provide analgesia.

Fentanyl, 2 to 20 mcg/kg IV, may be administered as an adjuvant to inhaled anesthetics in an attempt to blunt circulatory responses to direct laryngoscopy for intubation of the trachea, or sudden changes in the level of surgical stimulation. Timing of the IV injection of fentanyl to prevent responses should consider the effectsite equilibration time, which for fentanyl is prolonged compared with alfentanil and remifentanil.

Injection of an opioid such as fentanyl before painful surgical stimulation may decrease the subsequent amount of opioid required in the postoperative period to provide analgesia. Administration of fentanyl 1.5 or 3 mcg/kg IV 5minutesutes before induction of anaestheisa decreases the subsequent doses of isoflurane or desflurane with 60% nitrous oxide needed to block the sympathetic nervous system response to surgical stimulation (Fig. 7-14).92

Large doses of fentanyl, 50 to 150 mcg/kg IV, have been used alone to produce surgical anaestheisa.

Large doses of fentanyl as the sole anaesthetic have the advantage of stable hemodynamics due principally to the lack of direct myocardial depressant effects, absence of histamine release, and suppression of the stress responses to surgery.

Disadvantages of using fentanyl as the sole anesthetic include failure to prevent sympathetic nervous system responses to painful surgical stimulation, especially in patients with good left ventricular function; unpredictable amnestic effects potentially leading to recall; and postoperative depression of ventilation.

Fentanyl may be administered as a transmucosal preparation (oral transmucosal fentanyl) in a delivery device (several formulations are available, including a lozenge mounted on a handle or a film or rapid-dissolving preparation applied to the buccal mucosa) designed to deliver 5 to 20 mcg/kg of fentanyl.

In children 2 to 8 years of age, the preoperative administration of oral transmucosal fentanyl, 15 to 20 mcg/kg 45minutesutes before the induction of anaesthesia, reliably induces preoperative sedation and facilitates induction of inhalation anaestheisa. Decreases in breathing frequency and arterial oxygenation and an increased incidence of postoperative nausea and vomiting that is not influenced by prophylactic administration of droperidol.

Transdermal fentanyl preparations delivering 75 to 100 mcg per hour result in peak plasma fentanyl concentrations in about 18 hours that tend to remain stable during the presence of the patch, followed by a decreasing plasma concentration for several hours after removal of the delivery system, reflecting continued absorption from the cutaneous depot.

These transdermal delivery systems were designed to produce stable, long-term fentanyl plasma concentrations in efforts to provide adequate, sustained analgesia for chronic, cancer-related pain.

Transdermal fentanyl systems applied before the induction of anaestheisa and left in place for 24 hours decrease the amount of parenteral opioid required for postoperative analgesia.

Side Effects

The side effects of fentanyl resemble those described for morphine. Persistent or recurrent depression of ventilation due to fentanyl is a potential postoperative problem

Sequestered fentanyl could then be absorbed from the more alkaline small intestine back into the circulation to increase the plasma concentration of opioid and cause depression of ventilation to recur.

The secondary peak of fentanyl can be due to the washout of opioid from the lungs as ventilation to perfusion relationships are reestablished in the postoperative period.

Cardiovascular Effects

Carotid sinus baroreceptor reflex control of heart rate is markedly depressed by fentanyl, 10 mcg/kg IV, administered to neonates. Therefore, changes in systemic blood pressure occurring during fentanyl anaestheisa have to be carefully considered because cardiac output is principally rate dependent in neonates. Bradycardia is more prominent with fentanyl than morphine and may lead to occasional decreases in blood pressure and cardiac output.

Seizure Activity

Seizure-like activity has been described to follow rapid IV administration of fentanyl, sufentanil, and alfentanil In the absence of EEG evidence of seizure activity, how- ever, it is difficult to distinguish opioid-induced skeletal muscle rigidity or myoclonus from seizure activity.

Conversely, opioids might produce a form of myoclonus secondary to depression of inhibitory neurons that would produce a clinical picture of seizure activity in the absence of EEG changes. Somatosensory Evoked Potentials and

Electroencephalogram Fentanyl in doses exceeding 30 mcg/kg IV produces changes in somatosensory evoked potentials.

Opioids, including fentanyl, attenuate skeletal muscle movement at doses that have little effect on the EEG. This suggests that movement in response to surgical skin incision (used to measureminutesimum alveolar concentration [MAC]) primarily reflects the ability of a drug to obtund noxious reflexes and may not be the most appropriate measure for assessing consciousness or loss of consciousness.

Intracranial Pressure

Administration of fentanyl to head injury patients has been associated with modest increases (6 t o 9 mm Hg) in ICP despite maintenance of an unchanged Paco 2. These increases in ICP are typically accompanied by decreases in mean arterial pressure and cerebral perfusion pressure. Opioid-induced increases in ICP are similar in the presence of intact or impaired autoregulation.

MATERIAL AND METHODS

Type of study: Hospital based randomized control trial

Data Collection-12 Months

Duration of study and study population:

102 ASA I & II Adult patients posted for surgery under general anaesthesia between January 2021-December 2021 at KLE'S Dr. Prabhakar Kore's Hospital & MRC, Nehru Nagar, Belagavi-590010. were included who satisfied both "inclusion & exclusion criterias".

Inclusion Criteria:

1.ASA grades I & II

2.Age 18-60 years

3.Patients willing to give informed consent

4. Patients undergoing elective surgeries under GA with endotracheal intubations.

Exclusion Criteria:

1.Hypersensitivity to propofol and fentanyl.

2.Pre-existing respiratory, cardiovascular, neurological, renal disorders etc.

3.Alcohol or drug abuse.

Sample Size Calculation:

Sample size overall: 102

Determining the sample size:

The calculation for the minimum sample size depending 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 is associated with the test's power and z is associated with the test's level of significance. Z values of 1.96 and 0.84 at 5% level of significance and 80% power of the test, respectively.

Referring to: X1 was the first group's mean (86.8) and X2 was the second group's mean (71.67).

The first group's standard deviation was s1 (21.12), while the second group's standard deviation was s2 (21.68).

With these settings, a sample size of 34 was obtained.

There are three groups, each containing a minimum of 34 cases.

Statistics Analytical focus:

The study compared three groups that were randomly assigned using the ENVELOPE method. We computed the mean and standard deviation for the continuous quantitative data. Suitable statistical procedures, such as one group ANOVA, was used to compare the continuous variables between groups. The student's paired t test was used to compare two quantitative variables within a group.

Rates, ratios, and percentages were used to express the categorical data. Using the Chi-square test or Fisher's exact test, the relationship between the result, clinical, and demographic factors were examined.

Median was used to represent discrete variables. Discrete variable comparisons were made using nonparametric testing.

The comparison will be shown using the appropriate graphs. The value of p less than 5% (0.05) was regarded as significant for all tests.

Methodology:

- Following approval from the ethical clearance committee of our institute. pre-anesthesia check-up was done, Written informed consent was obtained. The night before surgery, all patients were pre-medicated in accordance with institutional practise, with the exception of sedatives. All patients were secured with 18 gauge intravenous access and routine monitoring (ECG, SpO2, NIBP) were established. Preoxygenation for three minutes was completed and then general anaesthesia was induced with Inj. Glycopyrrolate 0.005mg/kg, Inj. Midazolam 0.05mg/kg and then INJ.Fentanyl two microgram per kilogram was given to patients in Group I and inj. propofol was administered without any time interval. Group. II patients got inj. propofol three minutes after Inj.fentanyl, and Group.III patients were given inj. propofol five minutes after Inj.fentanyl. Inj.Propofol was administered while communicating verbally to the patient through an infusion pump at a rate of
  1 ml/10seconds till patient was induced.
- A ramsay sedation score RSS of six was used to determine when the induction was complete. Scale of RSS Response:
  1.Anxious and Agitated or restless or both
  2.Cooperative, oriented and tranquil
  3.Responds to commands only
  4.brink response to light
  5.Sluggidh response to light
  6.NO response
- INJ. Propofol dosage required for induction was noted. After confirmation of mask ventilation, Inj. Succinylcholine 1-2mg/kg was administered to facilitate tracheal intubation. Hemodynamic responses like blood pressure, pulse rate, heart

rate, respiratory rate were monitored and recorded throughout the procedure. once the surgical procedure was completed, reversal was achieved with Inj. Glycopyrrolate 0.01 mg/kg and Inj. Neostigmine 0.05mg/kg after thorough oral suctioning and patient extubated and monitored in PACU for four hours.

RESULTS

TABLE 1: Comparison of gender between three groups

	GROUP 1		GROUP 2		GROUP 3	
GENDER	**NUMBER**	**%**	**NUMBER**	**%**	**NUMBER**	**%**
FEMALE	17	50.00	21	53.85	16	40.00
MALE	17	50.00	18	46.15	24	60.00
TOTAL	34	100.00	39	100.00	40	100.00

GRAPH 1:

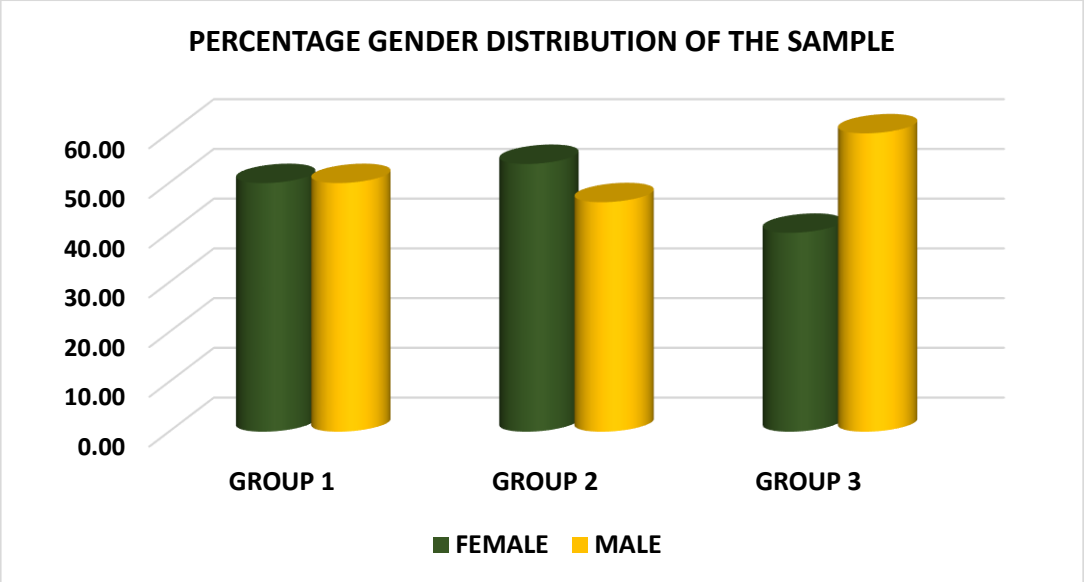
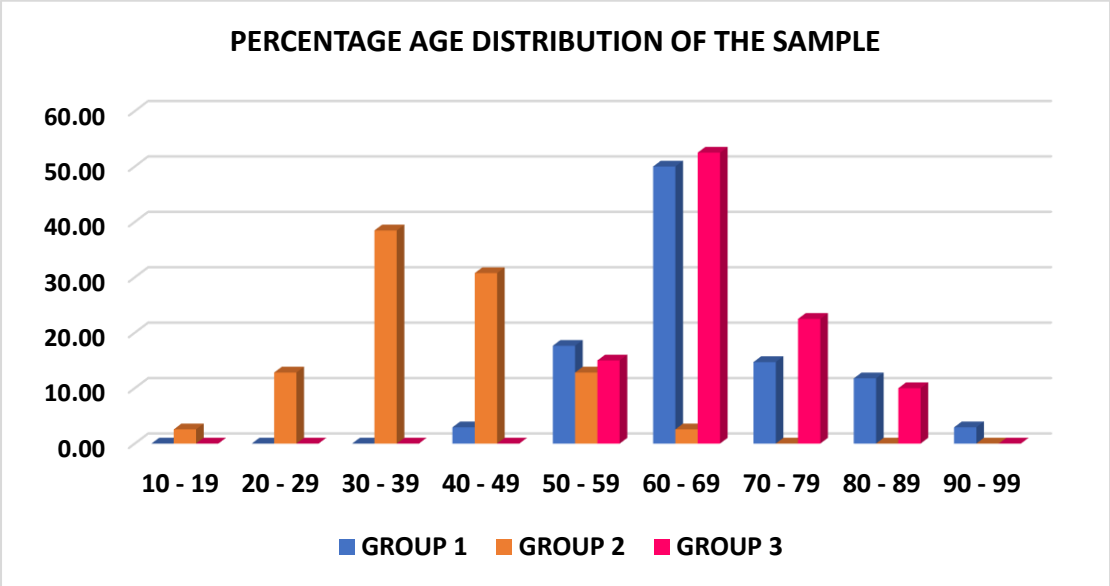


TABLE 2: Age comparison between three groups

	GROUP 1	GROUP 2	GROUP 3			
AGE	**NUMBER**	**%**	**NUMBER**	**%**	**NUMBER**	**%**
10 - 19	0	0.00	1	2.56	0	0.00
20 - 29	0	0.00	5	12.82	0	0.00
30 - 39	0	0.00	15	38.46	0	0.00
40 - 49	1	2.94	12	30.77	0	0.00
50 - 59	6	17.65	5	12.82	6	15.00
60 - 69	17	50.00	1	2.56	21	52.50
70 - 79	5	14.71	0	0.00	9	22.50
80 - 89	4	11.76	0	0.00	4	10.00
90 - 99	1	2.94	0	0.00	0	0.00
TOTAL	34	100.00	39	100.00	40	100.00

GRAPH 2:



IN THE FOLLOWING TABLES p VALUES ARE CALCULATED USING ONE WAY ANALYSIS OF VAIANCE

ABBREVIATIONS: NS -NOT SIGNIFICANT S - SIGNIFICANT VS - VERY SIGNIFICANT HS - HIGHLY SIGNIFICANT

IF p<0.05, THEN TO FIND BETWEEN WHAT GROUPS THERE IS SIGNIFICNT DIFFERENCE, SCHEFFE'S TEST IS USED

	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	p VALUE
AGE	42.06	14.64	18	60	39.41	10.33	19	60	42.70	12.18	19	60	0.4656

THE MEAN AGE OF THE THREE GROUPS DO NOT DIFFER SIGNIFICANTLY WITH EACH OTHER

	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	p VALUE
WEIGHT	65.03	10.38	40	90	64.05	9.14	50	80	65.43	7.71	50	85	0.7885

THE MEAN WEIGHT OF THE THREE GROUPS DO NOT DIFFER SIGNIFICANTLY WITH EACH OTHER

	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	p VALUE
HEIGHT	162.88	8.85	150	178	163.95	5.83	154	176	164.60	6.85	150	180	0.5917

THE MEAN HEIGHT OF THE THREE GROUPS DO NOT DIFFER SIGNIFICANTLY WITH EACH OTHER

	GROUP 1		GROUP 2		GROUP 3	
ASA	**NUMBER**	**%**	**NUMBER**	**%**	**NUMBER**	**%**
1	28	82.35	28	71.79	19	47.50
2	6	17.65	11	28.21	21	52.50
TOTAL	34	100.00	39	100.00	40	100.00

THE p VALUE, FOR THE ABOVE TABLE, USING CHI-SQUARE TEST IS 0.0045

THE VALUES OF ASA ARE NOT UNIFORMLY DISTRIBUTED AMONG THE THREE GROUPS.

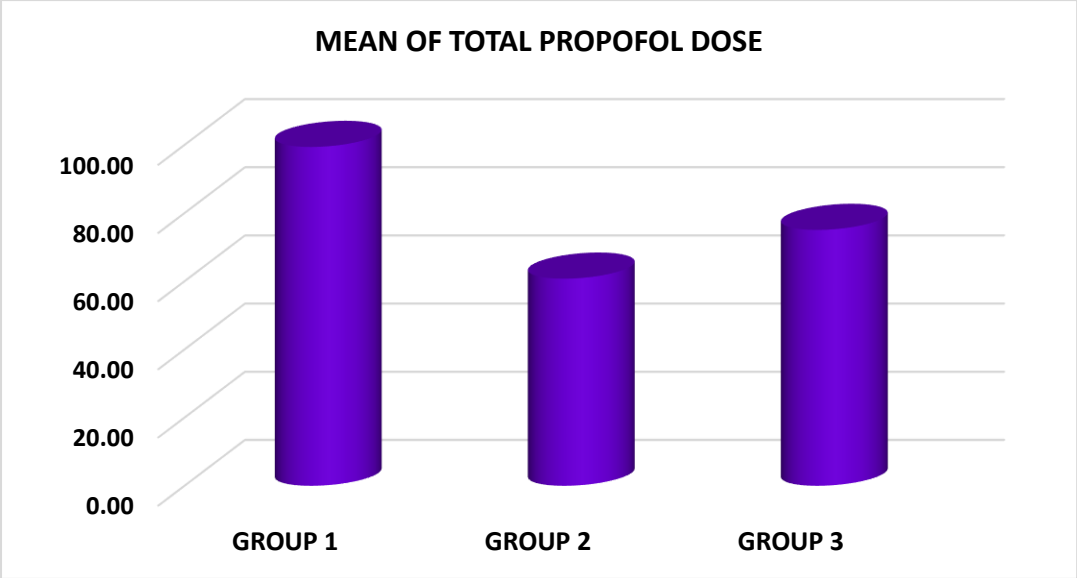
ASA 1 ARE MORE IN GROUPS 1 AND 2. ASA2 ARE MORE IN GROUP 3.

	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	p VALUE
TOTAL PROPOFOL DOSE	99.41	3.43	80	100	60.77	10.23	40	80	75.08	12.56	40	100	< 0.0001

THE MEANS OF TOTAL PROPOFOL DOSE ARE NOT HOMOGENEOUS IN THE THREE GROUPS.

THE MEAN TOTAL PROPOFOL DOSE OF EACH GROUP SIGNIFICANTLY DIFFERES WITH THE MEANS OF OTHER TWO GROUPS.

GRAPH 3:



THE PERCENTAGE OF MOVEMENT, VOCALIZATION, BUCKING AND ADDITIONAL PROPOFOL REQUIREMENT ARE ZERO FOR EACH CASE IN EACH OF THE THREE GROUPS

Table Comparison of heart rate

	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	p VALUE
HEART RATE	86.62	6.99	68	100	79.38	8.67	60	92	85.38	5.74	72	98	0.0001

THE MEANS OF HEART RATE ARE NOT HOMOGENEOUS IN THE THREE GROUPS.

THE MEAN HEART RATE OF GROUP 2 IS SIGNIFICANTLY SMALLER THAN THE MEAN HEART RATES OF OTHER TWO GROUPS.

GRAPH 4:

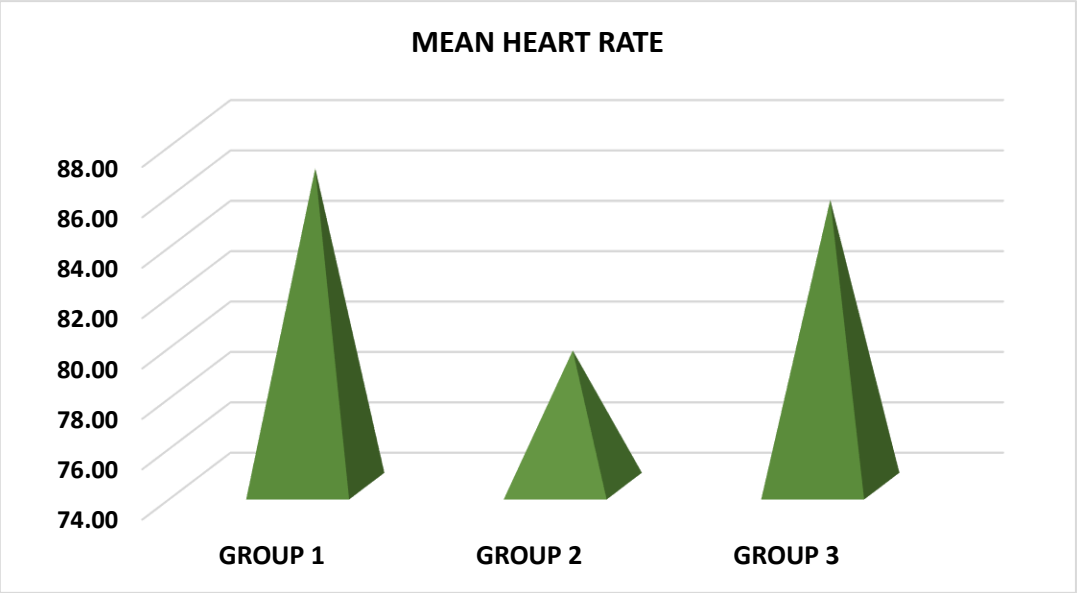


Table Comparison of: systolic arterial pressure

	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX
SYSTOLIC BLOOD PRESSURE	**130.15**	**8.61**	**116**	**166**	**121.64**	**10.57**	**100**	**140**	**126.28**	**11.48**	**96**	**152**

THE MEANS OF SYSTOLIC BLOOD PRESSURE ARE NOT HOMOGENEOUS IN THE THREE GROUPS.

THE MEAN SYSTOLIC BLOOD PRESSURE OF GROUP 2 IS SIGNIFICANTLY SMALLER THAN THE SYSTOLIC BLOOD PRESSURES OF OTHER TWO GROUPS.

GRAPH 5:

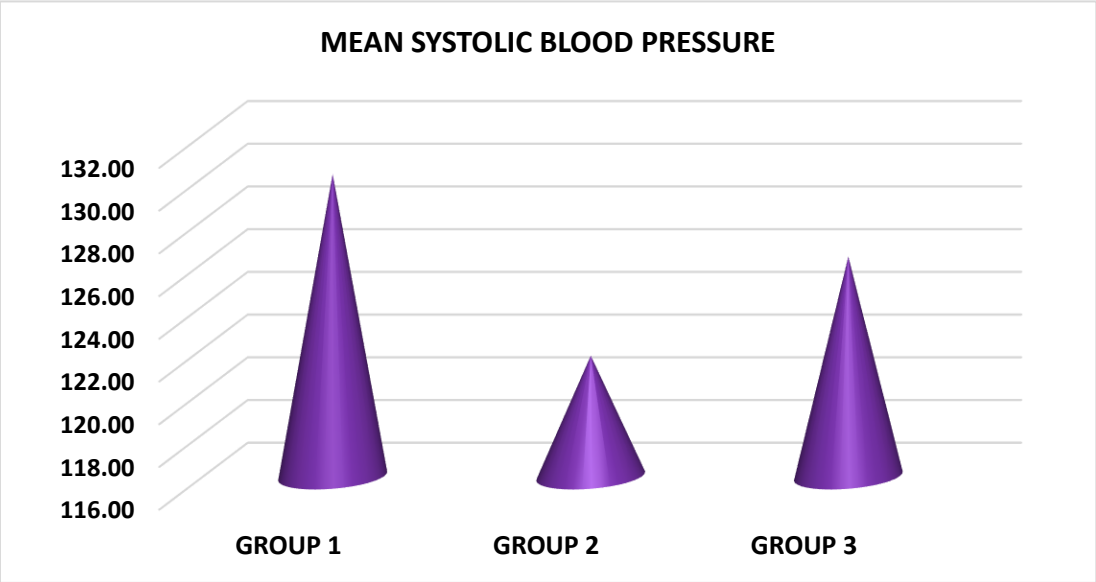


Table Comparison of: Diastolic arterial pressure

	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	p VALUE
DIASTOLIC BLOOD PRESSURE	85.59	5.57	74	98	79.31	7.72	62	95	82.85	6.42	70	90	0.0005

THE MEANS OF DIOSTOLIC BLOOD PRESSURE ARE NOT HOMOGENEOUS IN THE THREE GROUPS.

THE MEAN DIASTOLIC BLOOD PRESSURE OF GROUP 2 IS SIGNIFICANTLY SMALLER THAN THE DIASTOLIC BLOOD PRESSURE OF OTHER TWO GROUPS.

GRAPH 6:

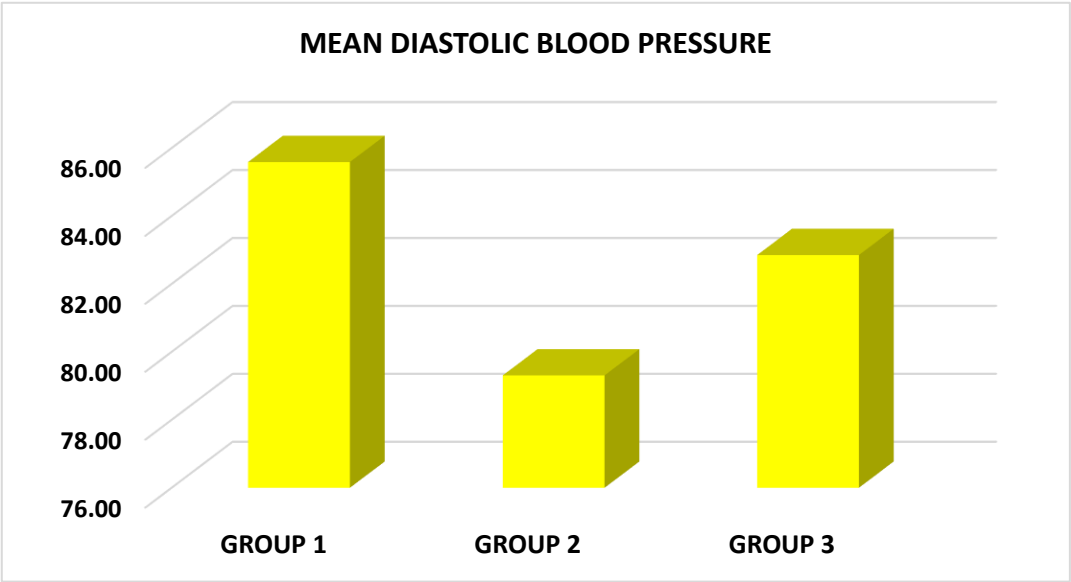


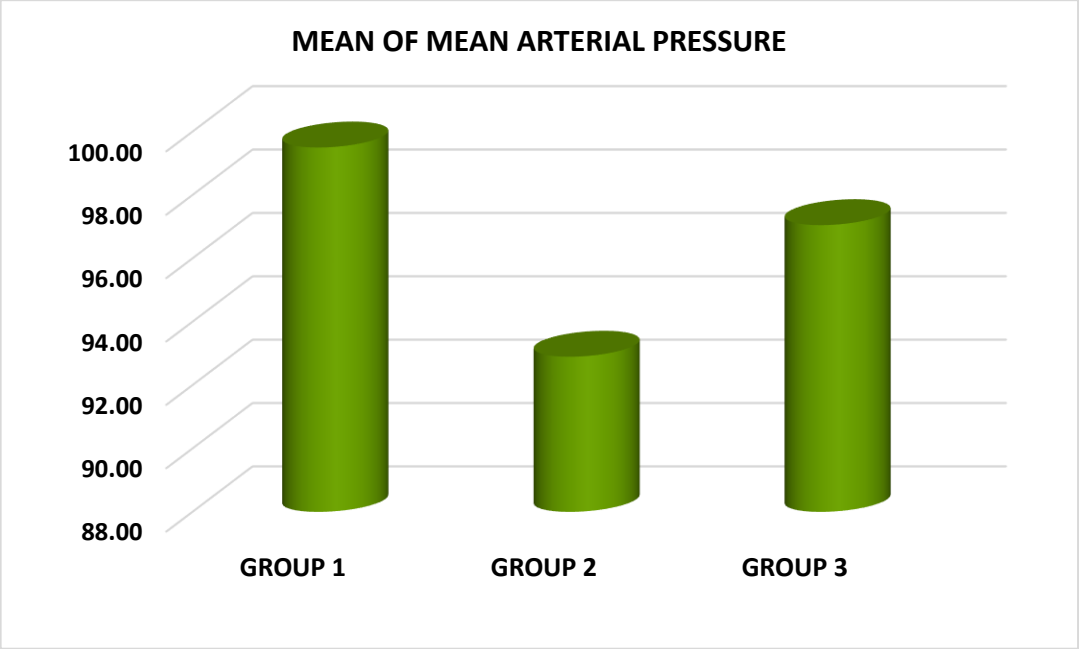
Table Comparison of: mean arterial pressure

	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	p VALUE
MEAN ARTERIAL PRESSURE	99.50	6.14	88	120	92.90	7.95	78	106	97.05	7.62	78	110	0.0008

THE MEANS OF MEAN ARTERIAL PRESSURE ARE NOT HOMOGENEOUS IN THE THREE GROUPS.

THE MEAN OF MEAN ARTERIAL PRESSURE OF GROUP 2 IS SIGNIFICANTLY SMALLER THAN THE MEANS OF MEAN ARTERIAL PRESSURE OF THE OTHER TWO GROUPS.

GRAPH 7:



DISCUSSION

Propofol, an aminobutyric agonist cpmmonly used induction agent, offers several perfect properties, including a faster onset of action, rapid hypnosis via “One Arm Brain Circulation”, with early awakening and minimal excitement.

Propofol should be used cautiously in patients with CVS disorders, hypovolemia because it has significant cardiovascular effects, which include a marked fall in SBP [Twenty–forty five percent fall in Systolic Blood Pressure], reduction in cardiac index of about 15%, and reduction in systemic vascular resistance of 15–25%. Additionally, propofol decreases laryngeopharyngeal reflexes, lowers ICP, it even has both proconvulsant and anticonvulsant effects.

As part of a balanced anaesthesia induction method, it has been demonstrated that co-administration of opioids with or before propofol administration significantly decreases inj. propofol dosage needed to induce the patient, enhances & preserves equilibrium of the vitals. Numerous studies have been done on the synergistic interactions between propofol and fentanyl.

In the current research, Inj.fentanyl given 3 and 5 minutes before inj.propofol leads in a significant decrease in inj.propofol dosage in comparison with inj.propofol administered right after Inj. Fentanyl. Although the three group's overall hemodynamic characteristics were equal, those who received propofol just after fentanyl experienced much more severe hypotension. Smitha.ett.al., demonstrated that when propofol is administered alone, plasma concentrations are considerably higher than necessary to achieve no response for oral communication, stressor response to surgical incisions, but that this is not the case when fentanyl is administered either before or along with propofol [sixty three percent & eighty nine percent fall with Inj.Propofol. fentanyl at the rate of one & three nanogram per millilitre].

Lysakowski et al. used a target-controlled infusion device to obtain an appropriate concentration required for several intravenous opiods to act at effective sites, and they evaluated whether propofol was required to induce no response to oral communication with opioids using sedation score systems and the bispectral index. This implies that opioid doses required for analgesia might help to induce unconsciousness earlier.

Similar to this, we discovered that administering fentanyl reduces the total amount required for propofol to induce anaesthesia, preventing the needless usage of highly significant dosage of drug inj. propofol & hazards that go along with it.

Fentanyl and propofol should be administered at different times, but this has not yet been determined. Fentanyl has either been delivered immediately after propofol administration in several studies, or there has been a 3–5-minute varying intervals between the two medications.

In patients hospitalised for daycare surgeries either fentanyl 1 mcg/kg with a 3 minute interval or alfentanil 5 mcg/kg with a 1 minute interval was administered before the induction of anaesthesia, Moffat.et.al., analyzed impact with opioids on dose of inj.propofol needed for inducing the patient. In comparison to cases who were not administered fentanyl during induction, have not seen the decreased amount in the dosage of the drug inj.propofol following opioid delivery. In all three groups, the hemodynamic alterations were equivalent. The lower fentanyl dose and the short alfentanil half-life may be the reason for the lack of any discernible effects.

According to Aken et al., patients receiving fentanyl experience a significant decrease in BP , C.O, HR after given 3 mcg/kg of fentanyl immediately after taking propofol. The prompt administration of Inj. propofol after fentanyl administration as well as the effects of larger dosages of fentanyl and lormetazepam premedication may

have played a role in these outcomes. Therefore, we investigated the impact of fentanyl (2 mcg/kg) on the requirement for propofol, which is frequently used in clinical settings, and we observed a significant decrease in propofol dose after observing 3-to-5-minute time intervals between fentanyl and propofol. In our study, however, administering propofol just after fentanyl caused a considerable haemodynamic disruption (hypotension).

In a study by Thomas et al, patients undergoing daycare gynecological procedures at the induction time, propofol dosage and mean blood pressure significantly decreased when 100 mcg of fentanyl was administered 1-5 minutes prior to the administration of propofol for induction. However, the authors did not think the modifications were clinically significant. This is because of the standard dosage of 100 micrograms, in many patients may be less than 2 mcg/kg, and the variable time intervals. A more clinically meaningful outcome, like in our trial, may have been achieved by using 2 mcg/kg of fentanyl with a minimum 3-min time interval.

The lag time between change in fentanyl plasma concentration and its effects has been found to range from 3 to 5 minutes, or as 6.4minutes, in pharmacokinetic and pharmacodynamic studies. This timing is consistent with our current study's findings, which show that giving fentanyl 3 minutes before propofol reduces the dose needed and that giving it 5 minutes before propofol lowers the risk of hypotension and aids in maintaining hemodynamic stability.

While the incidence of hypotension was substantially lower in the other two groups, over one-third of the patients in Group I experienced severe hypotension and needed fluid boluses.

None of the trial participants however" experienced any bradycardia necessitating atropine or substantial hypotension requiring a vasopressor

(phenylephrine/ephedrine). No group was found to have experienced movement, vocalization at start of ventilation via facemask, necessitating the administration in further dose of inj.propofol. This demonstrates that administering fentanyl before propofol early also makes it easier to regulate airways. Prior to the administration of propofol, no patient experienced any instances of apnea or desaturation throughout the 3- to 5-min window. A face mask was used to constantly administer oxygen during the procedure.

CONCLUSION

1. In this randomised controlled experiment, the effectiveness of different times between the administration of fentanyl and propofol was examined. When compared to patients who got fentanyl immediately or at a 5-minute interval, the mean propofol dose needed for induction was lower in patients who received fentanyl as premedication three minutes prior to induction.
2. There was higher significant incidence of hypotension in patients receiving propofol immediately and even higher induction dose is required.
3. None of the groups had any undesired movements, bucking during induction.
4. Hemodynamics were well maintained in 3minutes and 5 minutes groups varying time intervals in all the patients

SUMMARY

In our study, 102 patients were separated into 3 groups to compare the effects of different times between the administration of fentanyl and propofol on the dosage of propofol needed to induce anaesthesia.

Propofol was administered to

Group I patients immediately following the administration of fentanyl,

Group II patients 3 minutes later,

Group III patients 5 minutes later.

Groups I, II, and III had respective mean ages of **42.06, 39.4**, and **42.77** years. The three groups' mean ages did not significantly differ from one another. The age of the patients involved in the study did not significantly affect the results, as indicated by the insignificant value of p0.5.,

It did not show discernible variations between all three groups when it came to gender participation in the study. With 0.882 of p, result achieved is insignificant. As a result, patient gender discrepancies did not affect the study's findings.

Differences in mean weights of patients in I, II, and III groups, with p values of 0.7665 , 0.7885 and 0.7885, respectively, indicating that the difference was not statistically significant. There was a significant difference between the three groups in terms of the mean propofol dose, with p values 0.001 for each of the three groups' respective mean propofol doses of **99.41, 60.77,** and **75.08** mgs. Important research revealed that patients who got fentanyl as a premedication 3 minutes before induction needed less of the drug in patients who had received fentanyl at 1- and 5-minute intervals were given propofol in comparison to those patients.

For the three groups, the mean dose per kilogramme was **1.72, 0.89,** and **1.39** milligrams per kilogram. This concludes that induction propofol dosage for patients is

higher if they had received fentanyl soon prior to induction without a suitable time interval was validated by the substantial differences between Groups I, II, and III. While comparing the blood pressure readings of three groups for five minutes, one can determine the prevalence of hypotension. Blood pressure readings at 1 and 3 minutes showed a significant difference, particularly in group 1 patients, indicating a higher incidence of hypotension in patients receiving higher induction doses of propofol.

After 5 minutes, the mean systolic blood pressures for groups I, II, and III were **130.15, 121.64-, and 126.28-mm** Hg, respectively. This is statistically significant, and the p value is 0.001. This indicated that patients who got propofol right after fentanyl had a higher prevalence of hypotension. This finding was corroborated by a research by Darlong et al.[23] that revealed a higher incidence of hypotension in patients who got propofol right after receiving fentanyl.

After 5 minutes, the mean diastolic blood pressures of groups I, II, and III were **85.59, 79.31,** and **82.85** mmHg, respectively. This is statistically significant because the p value was 0.0005. study indicated that individuals who received propofol right after receiving fentanyl had a greater frequency of hypotension. This outcome was consistent with a research by Darlong et al. [23] that revealed a higher incidence of hypotension in patients who took propofol right after receiving fentanyl.

After 5 minutes, the mean arterial blood pressures of groups I, II, and III were **99.5, 92.9,** and **97.05** mmHg, respectively; the p value was 0.0008, which is again statistically significant. This indicated that patients who got propofol right after fentanyl had a higher prevalence of hypotension. This outcome was also consistent with a research by Darlong et al. [29] that revealed a higher prevalence of hypotension in patients who took propofol right after fentanyl. These findings corroborated those

of a research by Aken et al.[3] that examined the effects on hemodynamics of the drug inj.fentanyl at three microgram per kilogram iv administered as soon as after injecting inj.propofol and found a drastic reduction on HR ,BP, C.O.

The main explanation for such outcomes can be attributed to the use of propofol soon following fentanyl. For five minutes, compare the mean blood pressure readings of the three groups to determine the prevalence of hypotension.

As there were no unwanted movements, bucking, or vocalisations in our trial, there was no need for extra doses or boluses of propofol. This is in contrast to the work by Darlong et al., in which 20 mg boluses were given to each of the three groups as needed.

SCOPE AND LIMITATIONS

1) Due to logistical limitations, the concentrations of both the drugs in plasma were not determined. The study's conclusions may have been determined and confirmed with the aid of these data.
2) The anaesthesia induction end point was assessed only clinically at loss of verbal contact as per ramsay sedation score alone, and electroencephalography / BIS-based monitors were not used.
3) This study was done only in hemodynamically stable patients, unstable hemodynamic patients were not included for evaluating degree of hazards occurring when these drugs are used especially at different time intervals
4) Fixed fentanyl dosage according to body weight was used, different dosages of fentanyl were not assessed.

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ANNEXURE I

INFORMED CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr. /Mrs. /Miss. _____we are requesting you to enroll you in the study titled **"EFFICACY OF VARYING TIME INTERVALS BETWEEN FENTANYL AND PROPOFOL ADMINISTRATION ON PROPOFOL REQUIREMENT FOR INDUCTON OF ANAESTHESIA – A ONE YEAR RANDOMIZED CONTROL TRIAL"** conducted by REG NO.BA0120006 Post Graduate in M.D. Anaesthesiology under the guidance of Dr. _____., Professor, Department of Anaesthesiology, J.N. Medical College, Belagavi under KAHER, Belagavi.

Respected Sir/Madam, we request you to participate in our study as you are eligible for it. During the study you will be asked some questions regarding your medical history and you are supposed to answer to the best of your knowledge.

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. If you decide to participate you are free to withdraw at any time.

Purpose of the study:

The purpose of research is to examine the efficacy of varying intervals between fentanyl and propofol administration on the dose of propofol required for induction of anaesthesia.

Procedure Involved:

If you agree to enroll in my study, I will ask your present and past medical history and family history. Then you will be clinically examined in detail. Endotracheal intubation will be done by a senior anaesthesiologist and then I will be

comparing the efficacy of varying intervals between fentanyl and propofol administration on the dose of propofol required for induction of anaesthesia in the study.

Voluntary Participation/Withdrawal:

Taking part in the study is voluntary. You may choose not to enrol yourself in this study. Your decision will not change any health care services offered to you or your ward at K.L.E. S Hospital & MRC.

Privacy and Confidentiality:

The only people to know that you are as research subject are you and members of the research team. No 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.

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.

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.

Compensation:

In the event of injury related to the study, treatment will be made available through KLES Hospital and MRC, Belagavi. There is no compensation or payment for such medical treatment by law. If you get injured you may contact REG NO.BA0120006 Lat Department of Anaesthesiology, J.N. Medical College or by Ph. No:_____.

Questions:

In case you have any questions related to the study, in future or in case of study related injury or illness, you can contact REG NO.BA0120006, Department of Anaesthesiology, J.N. Medical College, Belagavi. Phone number: 9845718180 Or Dr. _____., Professor, Dept. Of Anaesthesiology, J.N. Medical College, Belagavi. Ph. No: _____.

If you have any queries about your rights as a study subject, you may call, **DR. HARSHA HEGDE,** Chairperson, JNMC, IEC& Scientist D, ICMR, National Institute of Traditional Medicine, Phone number -9480422500 Belagavi.

INFORMED CONSENT FOR PARTICIPATION IN RESEARCH TRIAL

"EFFICACY OF VARYING TIME INTERVALS BETWEEN FENTANYL AND PROPOFOL ADMINISTRATION ON PROPOFOL REQUIREMENT FOR INDUCTON OF ANAESTHESIA – A ONE YEAR RANDOMIZED CONTROL TRIAL"

Mr./Ms./Mrs. _____ voluntarily agree for the participation of as a subject of study. By signing this consent form, I am not giving up any of my legal rights; I may withdraw from the study anytime. I am signing the consent form after having read or been read for me in vernacular language, including the risks and the benefits and having all my questions answered.

Subject Name: _____

Signature or the Left Thumb Print of Subject/Guardian: _____

Date:

Witness Name:_____ Signature: _____

Investigators Name:_____ Signature: _____

Date :

Place :_____.

ANNEXURE II

PROFORMA

"EFFICACY OF VARYING TIME INTERVALS BETWEEN FENTANYL AND PROPOFOL ADMINISTRATION ON PROPOFOL REQUIREMENT FOR INDUCTON OF ANAESTHESIA – A ONE YEAR RANDOMIZED CONTROL TRIAL"

GROUP ALLOTED :

Name	:	Age	:
Gender	:	Weight	:
Height	:	Date of Examination	:
Address	:	Occupation	:

Pre anaesthetic evaluation

Past History

•HTN ☐ DM ☐ IHD ☐ Arrhythmia ☐ Valvular heart diseases

•H/o previous surgery/(s) where airway difficulty was encountered. Yes ☐ No ☐

General physical examination

Weight (Kg):		Temperature (^{0}F)	:	Pallor	:
Cyanosis	:	Pedal oedema	:	Clubbing	:
PR	:	BP	:	RR	:

Systemic examination:

RS	:	CNS	:
CVS	:	GIT	:

Preoperative physical status ☐ ☐ ☐ ☐ ☐

ASA Grade I II III IV V

METHODOLOGY:

Methodology:

- After obtaining approval from institutional ethics committee, written informed consent will be obtained during pre-anaesthetic check-up.
- All patients will be pre medicated as per institutional protocol the night before surgery except sedatives
- An 18 gauge intravenous access and routine monitoring (ECG, SpO_2, NIBP) will be established prior to general anaesthesia.
- Preoxygenation for 3minutes will be done.
- Intravenous fentanyl 2 mcg/kg will be administered.
- **Group 1** patients will be given propofol immediately after fentanyl injection,
- Patients in **Group 2** will receive propofol 3minutes after fentanyl injection, and
- Those in **Group 3** will be given propofol 5minutes after the fentanyl injection.
- Propofol will be injected through infusion pump at a rate of 1 ml/3 s while communicating verbally with the patient.
- Completion of anaesthesia will be considered using Ramsay Sedation Scale score of 6

Ramsay sedation scale

Score Response

1 Anxious or restless or both

2 Cooperative, orientated and tranquil

3 Responding to commands

4 Brisk response to stimulus

5 Sluggish response to stimulus

6 No response to stimulus

Data shall be collected as per following tables

Total propofol dose (mg)	
Propofol dose for induction (mg/kg)	
Movement(%)	
Vocalization (%)	
Bucking (%)	
Additional propofol requirement (%)	

SpO_2	
Heart rate	
Systolic blood pressure	
Diastolic blood pressure	
Mean arterial pressure	

- The dose of propofol required for induction will be noted. After confirmation of mask ventilation,
- Succinylcholine 1mg/kg will be administered to facilitate tracheal intubation.
- Hemodynamic responses like blood pressure, pulse rate, heart rate, respiratory rate will be monitored and recorded throughout the procedure.
- At the end of the surgery, patients will be reversed with Inj. Glycopyrrolate 0.01 mg/kg and Inj. Neostigmine 0.05 mg/kg after thorough oral suctioning and extubated.

ANNEXURE III

S.No.	Age	Sex	Weight	Height	ASA	Total Propofol Dose	Propofol dose for induction	Movement(%)	Vocalization(%)	Bucking(%)	Additional propofol requirement(%)	Heart Rate	Systolic blood pressure		Diastolic blood pressure	Mean arterial pressure	Spo2
1	60	M	70	170	2	100	1-2mg/kg	0	0	0	0	90	138		92	107	100
2	60	F	60	160	1	100	1-2mg/kg	0	0	0	0	86	132		84	100	100
3	21	F	52	150	1	100	1-2mg/kg	0	0	0	0	88	118		78	91	100
4	46	M	66	166	1	100	1-2mg/kg	0	0	0	0	88	126		84	98	100
5	23	M	90	172	1	100	1-2mg/kg	0	0	0	0	96	126		90	102	100
6	44	F	55	160	1	100	1-2mg/kg	0	0	0	0	96	140		90	106	100
7	59	M	70	176	1	100	1-2mg/kg	0	0	0	0	86	132		84	100	100
8	29	M	75	168	1	100	1-2mg/kg	0	0	0	0	88	132		88	102	100
9	60	F	60	162	2	100	1-2mg/kg	0	0	0	0	96	166		98	120	100
10	59	M	66	170	1	100	1-2mg/kg	0	0	0	0	86	132		86	102	100
11	21	M	66	170	1	100	1-2mg/kg	0	0	0	0	86	130		90	103	100
12	53	M	80	170	1	100	1-2mg/kg	0	0	0	0	88	138		82	100	100
13	35	F	62	164	1	100	1-2mg/kg	0	0	0	0	92	126		86	99	100
14	18	M	66	172	1	100	1-2mg/kg	0	0	0	0	82	122		74	90	100
15	45	F	63	160	1	100	1-2mg/kg	0	0	0	0	90	130		80	96	100
16	60	F	60	150	2	100	1-2mg/kg	0	0	0	0	88	130		90	103	100
17	60	M	85	170	1	100	1-2mg/kg	0	0	0	0	90	135		88	99	100
18	37	M	80	170	1	100	1-2mg/kg	0	0	0	0	68	122		84	94	100
19	42	F	66	152	1	100	1-2mg/kg	0	0	0	0	84	128		84	98	100
20	20	F	56	150	1	100	1-2mg/kg	0	0	0	0	79	126		88	97	100
21	27	M	65	176	1	100	1-2mg/kg	0	0	0	0	82	126		84	94	100
22	43	M	70	178	1	100	1-2mg/kg	0	0	0	0	88	130		90	103	100
23	54	F	80	160	2	100	1-2mg/kg	0	0	0	0	82	134		78	97	100
24	21	F	40	156	1	80	1-2mg/kg	0	0	0	0	92	126		86	99	100
25	52	M	70	172	1	100	1-2mg/kg	0	0	0	0	86	136		94	108	100
26	23	F	50	150	1	100	1-2mg/kg	0	0	0	0	90	126		88	97	100
27	31	F	60	150	1	100	1-2mg/kg	0	0	0	0	78	126		94	104	100
28	40	F	66	160	1	100	1-2mg/kg	0	0	0	0	86	130		80	96	100
29	33	F	55	150	2	100	1-2mg/kg	0	0	0	0	88	122		76	91	100
30	36	M	63	168	1	100	1-2mg/kg	0	0	0	0	68	116		76	88	100
31	53	F	66	150	1	100	1-2mg/kg	0	0	0	0	76	136		82	100	100
32	50	M	50	160	1	100	1-2mg/kg	0	0	0	0	92	128		88	101	100
33	57	F	66	160	1	100	1-2mg/kg	0	0	0	0	100	138		90	106	100
34	58	M	62	166	2	100	1-2mg/kg	0	0	0	0	90	122		84	92	100

S.No.	Name	Age	Sex	Weight	Height	ASA	Total Propofol Dose	Propofol dose for induction	Movement(%)	Vocalization(%)	Bucking(%)	Additional propofol requirement(%)	Heart Rate	Systolic blood pressure	Diastolic blood pressure	Mean arterial pressure	Spo2
1	vinayak	22	male	55	162	1	60	0.8-1.2mg/kg	0	0	0	0	84	112	70	80	100
2	deepika	34	female	60	160	1	50	0.8-1.2mg/kg	0	0	0	0	72	122	82	95	100
3	kamlavathi	36	female	60	160	1	50	0.8-1.2mg/kg	0	0	0	0	76	130	86	100	100
4	kamaxi	47	female	75	154	2	60	0.8-1.2mg/kg	0	0	0	0	66	128	95	102	100
5	sachin	36	male	70	172	2	70	0.8-1.2mg/kg	0	0	0	0	60	108	62	78	100
6	sayeda	37	female	50	155	2	50	0.8-1.2mg/kg	0	0	0	0	76	126	86	99	100
7	rajeshwari	38	female	60	160	1	50	0.8-1.2mg/kg	0	0	0	0	88	122	76	91	100
8	jagadeesh	30	male	60	166	1	60	0.8-1.2mg/kg	0	0	0	0	88	130	86	100	100
9	shrikant	58	male	70	170	2	70	0.8-1.2mg/kg	0	0	0	0	70	130	82	98	100
10	vishnu	58	male	50	160	1	50	0.8-1.2mg/kg	0	0	0	0	72	140	90	102	100
11	vidya	29	female	52	158	1	40	0.8-1.2mg/kg	0	0	0	0	88	126	82	96	100
12	divya	25	female	80	166	1	70	0.8-1.2mg/kg	0	0	0	0	84	122	70	87	100
13	indira	48	female	80	170	1	70	0.8-1.2mg/kg	0	0	0	0	72	120	80	93	100
14	vimal	50	female	56	158	1	60	0.8-1.2mg/kg	0	0	0	0	92	118	82	94	100
15	mahadevi	49	female	70	170	1	70	0.8-1.2mg/kg	0	0	0	0	82	136	88	104	100
16	yallappa	54	male	80	170	2	80	0.8-1.2mg/kg	0	0	0	0	88	122	80	94	100
17	bharati	33	female	72	166	1	75	0.8-1.2mg/kg	0	0	0	0	90	140	90	106	100
18	meenakshi	60	female	60	156	2	60	0.8-1.2mg/kg	0	0	0	0	92	118	82	94	100
19	najeer	49	male	60	160	2	80	0.8-1.2mg/kg	0	0	0	0	92	134	88	103	100
20	aayushi	25	female	56	162	1	60	0.8-1.2mg/kg	0	0	0	0	76	112	72	85	100
21	vilas	43	male	59	169	2	50	0.8-1.2mg/kg	0	0	0	0	80	132	84	100	100
22	gurudas	56	male	70	168	2	70	0.8-1.2mg/kg	0	0	0	0	88	136	86	102	100
23	kanchana	19	female	66	170	1	60	0.8-1.2mg/kg	0	0	0	0	82	124	82	97	100
24	md shafi	45	male	66	170	1	60	0.8-1.2mg/kg	0	0	0	0	90	130	80	96	100
25	bhagawan	34	male	60	170	1	60	0.8-1.2mg/kg	0	0	0	0	80	122	80	94	100
26	pragathi	38	female	50	155	1	50	0.8-1.2mg/kg	0	0	0	0	80	114	70	84	100
27	narayan	46	male	75	170	1	70	0.8-1.2mg/kg	0	0	0	0	82	120	80	93	100
28	ravindra	41	male	60	160	2	55	0.8-1.2mg/kg	0	0	0	0	70	110	70	83	100
29	prasanth	33	male	75	170	1	75	0.8-1.2mg/kg	0	0	0	0	76	110	76	87	100
30	ningappa	36	male	70	170	1	70	0.8-1.2mg/kg	0	0	0	0	80	130	76	94	100
31	sanjothi	43	female	67	163	1	60	0.8-1.2mg/kg	0	0	0	0	70	118	78	91	100
32	tirakappa	30	male	70	166	1	60	0.8-1.2mg/kg	0	0	0	0	70	112	68	82	100
33	goudappa	42	male	80	176	2	75	0.8-1.2mg/kg	0	0	0	0	88	130	84	99	100
34	manjula	40	female	61	157	1	50	0.8-1.2mg/kg	0	0	0	0	76	102	68	79	100

S.No.	Name	Age	Sex	Weight	Height	ASA	Total Propofol Dose	Propofol dose for induction	Movement(%)	Vocalization(%)	Bucking(%)	Additional propofol requirement(%)	Heart Rate	Systolic blood pressure	Diastolic blood pressure	Mean arterial pressure	Spo2
1	shankarappa	55	male	60	158	1	55	1-1.2mg/kg	0	0	0	0	82	116	70	85	100
2	lata desai	56	female	60	152	1	80	1-1.2mg/kg	0	0	0	0	83	113	86	96	100
3	suneetha	40	female	50	150	1	40	1-1.2mg/kg	0	0	0	0	72	100	70	79	100
4	basavaraj	26	male	68	170	1	85	1-1.2mg/kg	0	0	0	0	82	122	84	96	100
5	ashwini	25	female	66	160	2	80	1-1.2mg/kg	0	0	0	0	86	132	76	94	100
6	shrishail	22	male	70	180	1	90	1-1.2mg/kg	0	0	0	0	86	124	84	97	100
7	neelavva	48	female	60	160	2	75	1-1.2mg/kg	0	0	0	0	86	128	82	97	100
8	neelavva.p	46	female	60	156	1	60	1-1.2mg/kg	0	0	0	0	86	128	84	98	100
9	parappa	59	male	70	166	2	85	1-1.2mg/kg	0	0	0	0	96	136	90	105	100
10	siddappa	34	male	70	170	1	90	1-1.2mg/kg	0	0	0	0	86	122	84	96	100
11	maloji	47	male	69	170	2	85	1-1.2mg/kg	0	0	0	0	90	136	88	104	100
12	sanjeev	49	male	70	170	2	80	1-1.2mg/kg	0	0	0	0	88	138	90	106	100
13	kavita	54	female	60	160	2	80	1-1.2mg/kg	0	0	0	0	88	138	88	105	100
14	jayawant	42	male	80	176	2	100	1-1.2mg/kg	0	0	0	0	88	136	88	104	100
15	siddagouda	46	male	80	170	1	95	1-1.2mg/kg	0	0	0	0	80	120	80	93	100
16	rajesab	54	male	65	160	2	68	1-1.2mg/kg	0	0	0	0	78	138	86	104	100
17	shobha.p	41	female	68	160	1	70	1-1.2mg/kg	0	0	0	0	92	118	82	92	100
18	shankarappa	60	male	60	166	2	60	1-1.2mg/kg	0	0	0	0	86	140	88	105	100
19	sumitra	60	female	59	159	2	60	1-1.2mg/kg	0	0	0	0	78	130	86	100	100
20	shainaj	40	female	70	166	1	65	1-1.2mg/kg	0	0	0	0	80	130	80	96	100
21	halappa	47	male	70	167	1	70	1-1.2mg/kg	0	0	0	0	98	132	90	104	100
22	sarita	34	female	55	160	2	60	1-1.2mg/kg	0	0	0	0	80	120	82	95	100
23	pundalik	60	male	65	168	2	80	1-1.2mg/kg	0	0	0	0	88	128	90	102	100
24	gayatri	26	female	57	156	1	60	1-1.2mg/kg	0	0	0	0	76	108	72	84	100
25	dinesh	23	male	60	170	2	80	1-1.2mg/kg	0	0	0	0	90	152	90	110	100
26	amaresh	28	male	60	176	1	70	1-1.2mg/kg	0	0	0	0	80	122	80	94	100
27	savitri	48	female	68	160	2	80	1-1.2mg/kg	0	0	0	0	90	110	70	83	100
28	malakondaiah	55	male	70	160	2	90	1-1.2mg/kg	0	0	0	0	86	136	90	105	100
29	savita	36	female	50	156	1	80	1-1.2mg/kg	0	0	0	0	86	122	80	95	100
30	parashuram	40	male	85	176	1	90	1-1.2mg/kg	0	0	0	0	96	140	90	106	100
31	sevanta	39	female	60	158	2	80	1-1.2mg/kg	0	0	0	0	88	122	88	99	100
32	vrishab	19	male	70	170	1	85	1-1.2mg/kg	0	0	0	0	86	96	70	78	100
33	shrimant	60	male	72	168	2	70	1-1.2mg/kg	0	0	0	0	88	140	86	104	100
34	mallikarjun	40	male	62	163	2	65	1-1.2mg/kg	0	0	0	0	82	130	82	98	100
35	bharamanna	40	male	64	169	2	75	1-1.2mg/kg	0	0	0	0	74	128	88	101	100
36	eranna	52	male	63	167	2	70	1-1.2mg/kg	0	0	0	0	92	116	82	93	100