"A RANDOMISED COMPARATIVE STUDY BETWEEN DEXMEDETOMIDINE AND FENTANYL ON ATTENUATING STRESS RESPONSE AND AIRWAY RESPONSE TO TRACHEAL EXTUBATION"

Dissertation submitted to

B.L.D.E.'s (DEEMED TO BE UNIVERSITY),

SHRI B.M.PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE, VIJAYAPUR, KARNATAKA, INDIA

In partial fulfillment of the requirements for the degree of

DOCTOR OF MEDICINE

IN

ANAESTHESIOLOGY

SUBMITTED BY

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POST GRADUATE IN ANAESTHESIOLOGY

Under the guidance of

Dr. D G TALIKOTI **MD**

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2020

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ACKNOWLEDGEMENT

I am extremely indebted to my guide **Dr.D G TALIKOTI, Professor, Department of Anaesthesiology**, Shri. B M Patil Medical College, Vijayapur, for his enlightening guidance and constant encouragement, affectionate attitude, invaluable words of advice and for providing adequate facilities for the completion of this project. I consider myself lucky to be a student of a perfect teacher.

I am extremely thankful to **Dr.VIDYA PATIL, Professor and Head of Department of Anaesthesiology**, Shri.B M Patil Medical College, Vijayapur for her support and encouragement during the study period.

I wish to convey my sincere gratitude to Professors **Dr.Vijaykumar T. K, Dr.Vijay Katti, Dr.Renuka, Dr.Nirmala, Dr.Shivanand L K, Dr.Basavaraj Patil, Dr.Prathiba, Dr.Ramesh, Dr.Santosh K, Dr.Mala, Dr. Anusha and Dr.Santosh A** for their constant supervision and for their scientific, theoretic and practical guidance during the entire course.

I am thankful to **Dr.Shanawaz** for his help in statistical analysis.

I thank senior residents, my colleagues who have helped me through my dissertation work.

I would also like to thank all my seniors and juniors for their co-operation and help during my entire course.

I am deeply indebted to my parents, Chakrapani Tumma, Aruna Tumma, husband Dr.Prashanth S and sister Sannidhi Tumma whose constant encouragement and inspiration led me to successful completion of my dissertation work.

I express my gratitude to Library Staff, Anaesthesia Staff, OT Staff and all Hospital Staff for their co-operation in my study.

I thank the institution , the Director, the Dean and the Medical Superintendent for permitting me to undertake the study.

I owe special debt of gratitude to all my patients, without whose co-operation, this study would be incomplete.

Last but not the least I would like to thank the ALMIGHTY for giving me the opportunity to pursue M.D Anaesthesiology in this prestigious institute.

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LIST OF ABBREVATIONS

ASA	-	American Society of Anaesthesiologists
AEX	-	After extubation
BMI	-	Body Mass Index
CABG	-	Coronary Artery Bypass Graft
DBP	-	Diastolic Blood Pressure
ECG	-	Electrocardiography
Group F	-	Fentanyl Group
Group D	-	Dexmedetomidine group
HR	-	Heart Rate
HTN	-	Hypertension
INJ	-	Injection
IV	-	Intravenous
JBR	-	Just before reversal
Kg	-	Kilogram
LA	-	Local Anaesthetic
MAP	-	Mean Arterial Pressure
Min	-	Minutes
Mg	-	Milligrams
mm of Hg	-	Millimeter of Mercury
NaCl	-	Sodium Chloride
P Value	-	Probability Value
RR	-	Respiratory rate
SBP	-	Systolic Blood Pressure
SPO2	-	Oxygen Saturation
VLPO	-	Ventrolateral Pre optic Nucleus
%	-	Percentage

ABSTRACT

BACKGROUND:

Tracheal extubation and emergence is associated with significant hemodynamic alterations and is poorly tolerated by patients with comorbid conditions. We compared the efficacy of dexmedetomidine and fentanyl in mitigating hemodynamic stress response and assessed extubation quality in study groups.

AIM:

To study the efficacy of dexmedetomidine and fentanyl on the attenuation of hemodynamic responses and airway reflexes during extubation following surgery under general anaesthesia.

OBJECTIVES :

- Hemodynamic changes of dexmedetomidine and fentanyl.
- Adverse effects of dexmedetomidine and fentanyl such as delayed arousal, respiratory depression, bradycardia, hypotension, vomiting.
- Early postoperative complication like laryngospasm.

METHODS:

A Randomised comparative study was conducted in the department of Anesthesia at B.L.D.E. (DEEMED TO BE UNIVERSITY) Shri B. M. Patil Medical College Hospital and Research Centre, Vijayapura.

Ethical Committee permission- Taken

Informed written consent-Taken

Total of 60 patients scheduled for various surgical procedures under general anaesthesia were allotted into two groups.

Group D (Dexmedetomidine)

Intravenous dexmedetomidine 0.4mcg/kg body weight diluted to 20 ml in normal saline is infused over 15 minutes prior to completion of surgery using infusion pump.

Group F (Fentanyl)

Intravenous fentanyl 0.5 mcg/kg body weight diluted to 20 ml in normal saline infused over 15 minutes prior to completion of surgery using infusion pump.

Test used were Chi square test, unpaired t test and Anova test.

Inclusion criteria

- Age 18-60 years of age.
- ASA grade I and II.
- Mallampati grade I and II.
- Patient's giving valid and informed consent.

Exclusion criteria

- Patient's suffering from cardiac and pulmonary disease.
- Patient's with anticipated difficult airway.
- Pathology of oropharyngeal tract.
- Patient's on beta blockers, patients with conduction defects of the heart (heart blocks).
- Pregnant women.
- Morbidly obese (BMI>35kg/m2)
- Patients with anticipated difficult airway.

RESULTS :

Statistically significant lesser increase in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure in the dexmedetomidine group than fentanyl group. Dexmedetomidine group had better extubation quality than the fentanyl group. Bradycardia in two cases observed with dexmedetomidine group than the fentanyl group but none required intervention.

CONCLUSION:

Inj. Dexmedetomidine 0.4mcg/kg body weight in 20 ml normal saline administered 15 minutes before tracheal extubation was better compared to Inj. Fentanyl 0.5 mcg/kg body weight in 20 ml normal saline in attenuating airway and hemodynamic reflexes to a greater extent allowing smooth and easy tracheal extubation , thereby providing comfortable recovery. Hence, dexmedetomidine infusion can be a safer alternative to fentanyl infusion for attenuating stress response.

KEYWORDS:

Dexmedetomidine, Fentanyl, Extubation, Hemodynamic response.

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INTRODUCTION

INTRODUCTION

Tracheal extubation is the discontinuation of an artificial airway when indications for its placement like airway obstruction, protection of airway, suctioning, ventilatory failure and hypoxemia no longer exist. Tracheal extubation is almost always associated with hemodynamic changes due to reflex sympathetic discharge caused by epipharyngeal and laryngo-pharyngeal stimulation. This increase in sympatho–adrenal activity may result in hypertension, tachycardia and arrhythmias[1,2]. This increase in BP and HR are usually transient, variable and unpredictable. It is more hazardous to the patient with HTN, myocardial insufficiency or cerebrovascular diseases[3]. Significant decreases in ejection fractions (from 55%+7% to 45%+7%) after extubation without electrocardiographic signs of myocardial ischemia is demonstrated with coronary artery disease patients[4]. In the clinical practice respiratory complications like coughing, laryngospasm, bronchospasm are three times more common during extubation than during tracheal intubation and induction of anaesthesia (12.6% vs. 4.6%). Coughing cause abrupt increase in intracavitary pressures (intraocular, intrathoracic, intraabdominal, intracranial) which could put patient at high risk[4]. Smooth tracheal extubation requires the absence of straining, movement, coughing, breath holding or laryngospasm[5,6]. Various techinques and anti-hypertensive drugs are available to attenuate airway and circulatory reflexes during extubation but none have been successful[7-10].

Attempts have been made to attenuate the pressor response by the use of drugs such as narcotic analgesics, deep anaesthesia induced by inhalational anaesthetics, local anaesthetics, adrenoceptor blockers and vasodilator drugs[11]. Studies have been

carried out with use of diltiazam[12,13], lignocaine[14], esmolol[15], labetalol[16], and opioids[17] as sole agent or in comparison with each other.

Fentanyl, a synthetic opioid, has been reported to reduce the prevalence of coughing during and after extubation and to suppress the sneezing reflex after abdominal hysterectomy and periocular injections[18]. Fentanyl has also been reported to attenuate the cardiovascular responses to tracheal extubation in elective gynecologic surgery[19].

Dexmedetomidine a highly selective alpha2 adrenoceptor agonist has been studied as single dose at the time of extubation[20,21]. It has a sympatholytic effect through decrease in concentration of norepinephrine[22]. This in turn decreases the blood pressure and heart rate[23,24]. Dexmedetomidine therefore is theoretically appropriate for reducing airway and circulatory reflexes during extubation.

AIMS AND OBJECTIVES OF STUDY OF THE STUDY

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AIM :

To study the efficacy of dexmedetomidine and fentanyl on the attenuation of haemodynamic responses and airway reflexes during extubation following surgery under general anaesthesia with the following objectives.

OBJECTIVES :

PRIMARY OBJECTIVE

To study the effectiveness of dexmedetomidne and fentanyl on attenuating sympathoadrenal response to extubation.

SECONDARY OBJECTIVES

- Haemodynamic changes of dexmedetomidine and fentanyl.
- Adverse effects of dexmedetomidine and fentanyl such as delayed arousal, respiratory depression, bradycardia, hypotension, vomiting.
- Early postoperative complication like laryngospasm.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

- **Nishina.K, Mikawa.K *et al*(1995)**[58] carried out a controlled, randomized, double-blind study to examine the effects of intravenous fentanyl (1 or 2 μg/kg) on hemodynamic changes during tracheal extubation and emergence from anesthesia in 60 ASA physical status I or II patients undergoing elective gynecological surgery. Changes in heart rate (HR) and blood pressure (BP) were measured during and after tracheal extubation. The HR, systolic BP, and diastolic BP increased significantly during tracheal extubation in the control group ($P < 0.05$). Fentanyl 2μg/ kg attenuated the increases in these variables more effectively than fentanyl 1μg/kg. The time interval from the study drug to extubation was similar in each group.
- **Mikawa, Katsuya *et al*(1997)**[59] conducted a study to compare the efficacy of a combination of intravenous verapamil (0.1mg/kg) and intravenous lidocaine (1mg/kg) with that of each drug alone in suppressing the cardiovascular changes during tracheal extubation and emergence from anesthesia, concluded that attenuation of hemodynamic changes was effective with the verapamil-lidocaine combination.
- **Guler G, Akin A *et al* (2005)**[20] studied the ability of single dose of dexmedetomidine to attenuate airway and circulatory reflexes during extubation. The study was conducted in 60 ASA 1-3 patients and divided them into 2 groups. Group D received 0.5μg/kg IV dexmedetomidine over 60 sec and Group P received saline placebo. Authors concluded that single bolus dose of dexmedetomidine before extubation attenuates airway and circulatory reflexes during extubation.
- **Y.Y.S.Lee *et al* (2007)**[60] conducted a double blind randomized control study to explore the sympatholytic property of dexmedetomidine, especially its role in intraocular pressure reduction, hemodynamic stability and attenuation of extubation

response, concluded dexmedetomidine can be used without undue hemodynamic fluctuation and can decrease the excitatory response during extubation. The reduction in intraocular pressure with dexmedetomidine was comparable with placebo.

- **Jain D, khan R *et al* (2008)**[61] conducted a double blind study to see the effect of dexmedetomidine on the stress response to extubation. They concluded that a bolus dose of dexmedetomidine 1μg/kg diluted with 10ml normal saline given in 10min, prior to administration of reversal provided hemodynamic stability associated with extubation.
- **Aksu R, Akin A *et al* (2009)**[62] A double blinded randomized controlled study is done in 40 patients (20 per group) to compare the effects of dexmedetomidine versus fentanyl on airway reflexes and hemodynamic responses to tracheal extubation during rhinoplasty. Five minutes before extubation patients received either dexmedetomidine 0.5μg/kg in 100ml of isotonic saline or fentanyl 1μg/kg in 100ml of isotonic saline IV. They concluded that dexmedetomidine 0.5μg/kg administered before extubation was more effective in attenuating airway reflex response to tracheal extubation and maintaining hemodynamic stability without prolonging recovery compared with fentanyl 1μg/kg in these patients undergoing rhinoplasty.
- **George SE, Singh G *et al* (2013)**[63] conducted a randomized double blind clinical trial to compare the effect of lignocaine installed through the endotracheal tube and intravenous lignocaine on the extubation response in 114 patients undergoing craniotomy with skull pins. patients were divided into three groups and were given 1mg/kg of IV, 2% lignocaine (Group 1) and placebo (Group 2) and 1mg/kg of 2% lignocaine sprayed down the endotracheal tube (Group 3) before skull pin removal. Extubation response, sedation scores were noted. Plasma levels of lignocaine were

measured at extubation and 10min after administration of the study drug. They concluded that intratracheal lignocaine 1mg/kg does not prevent cough at extubation and is not superior to IV route or placebo in attenuating cough or hemodynamic response at extubation when given 20–30 min before extubation.

- **Barkha Bindu *et al* (2013)**[64] done a double blind randomized controlled trial to study the effect of dexmedetomidine on hemodynamic and recovery responses during tracheal extubation. They concluded that intravenous infusion of dexmedetomidine 0.75µg/kg administered 15min before extubation, stabilizes hemodynamics and facilitates smooth extubation.
- **Kothari.D, Tandon N *et al* (2014)**[65] conducted a study to compare the effect of dexmedetomidine versus lignocaine in attenuation of circulatory and airway responses during endotracheal extubation in craniotomies for intracerebral space occupying lesions and concluded that single dose of dexmedetomidine (0.5µg/kg) given 5 min before extubation produced significant attenuation of circulatory and airway responses produced during extubation as compared to lignocaine (1.5mg/kg).
- **Sharma VB, Prabhakar H *et al* (2014)**[66] conducted randomised, double blind, placebo-controlled study to compare the effects of dexmedetomidine and lignocaine on the attenuation of airway and pressor responses during tracheal extubation. The attenuation of pressor response is comparable between dexmedetomidine 0.5µg/kg and lignocaine 1.5mg/kg. However, airway response was better controlled with use of dexmedetomidine allowing a smooth tracheal extubation, thereby providing a comfortable recovery and early neurological examination.
- **Gosai ND, Jansari AH *et al* (2015)**[67] conducted a study to compare the effect of dexmedetomidine and lignocaine on hemodynamic responses and recovery following

tracheal extubation in patients undergoing intracranial surgery concluded that single bolus dose of IV dexmedetomidine 0.5µg/kg given before tracheal extubation effectively attenuates hemodynamic response to extubation as compared to 1.5mg/kg lignocaine.

- **Moustafa AM, Atalla H *et al* (2015)**[68] A comparative study was done with dexmedetomidine (0.25µg/kg), lignocaine (1.0mg/kg) and their combination in attenuation of cardiovascular and catecholamine response to tracheal extubation and anesthesia emergence in hypertensive patients. They concluded that dexmedetomidine, lignocaine alone or their combination failed to suppress the catecholamine responses to tracheal extubation and emergence from anesthesia. But the dexmedetomidine–lignocaine combination was superior to each drug alone in attenuating the cardiovascular changes in hypertensive patients.
- **Shrirang Rao, Somasekharam P *et al* (2015)**[69] conducted a study to now the effect of bolus dose of dexmedetomidine (0.5µg/kg) on the hemodynamic and airway reflexes during extubation. The authors concluded that single dose of dexmedetomidine 0.5µg/kg given over 10 minutes before extubation attenuates the hemodynamic and airway reflexes during emergence from anaesthesia without causing undue sedation, but may prolong time to extubation and eye opening.
- **P.Rani, V.R.Hemanth kumar *et al* (2016)**[71] compared the effects of fentanyl 1 µg/kg and dexmedetomidine 0.75 µg/kg in attenuating airway and circulatory reflexes during emergence and extubation of the endotracheal tube. Hemodynamic parameters and patient response for laryngoscopy and oral suctioning and during extubation were graded. The authors concluded that extubation quality was found to be superior in dexmedetomidine group with patients arousable and tolerating suctioning and

extubation. Whereas in fentanyl group, patients were awake during extubation and had tachycardia after extubation.

PHYSIOLOGY OF HEMODYNAMIC RESPONSE

PHYSIOLOGY OF HEMODYNAMIC RESPONSE

Autonomic nervous system does the biological house keeping of the internal environment of the body. Sympathico-adrenal system regulates the body response to combat any stress. The neurotransmitters of the sympathico-adrenal system are noradrenaline and adrenaline[27,28]. Normal basal secretion by adrenal medulla of adrenaline is 0.2µg/kg/minute and that of noradrenaline is 0.05µg/kg/minute which are adequate to maintain the body physiology. In situations of stress the sympathoadrenal system is stimulated by hypothalamus resulting in an increase in the catecholamine secretion. This reaction is closely correlated with endocrine system in combating stress[27,28,29].

The sympathetic system in response to stress acts to increase heart rate, blood pressure, cardiac output, dilates bronchial tree and shunts blood away from skin and viscera to muscles[27,28,29].

A powerful noxious stimulus like laryngoscopy and tracheal intubation and extubation induces hypothalamic activity and results in an increased outflow in the sympathetic tracts. Consequently norepinephrine is released by post ganglionic sympathetic fibers and increased secretion from adrenal medulla[27,28,29].

Attempts have been made to assess sympathetic activity directly by measurement of plasma catecholamine concentrations with the use of radio enzymatic assays and high pressure liquid chromatography by various workers[27,28,29].

It was concluded by the study of changes of plasma catecholamine concentration during laryngoscopy and endotracheal intubation by Russell WJ and Mortis RG that a positive correlation existed between arterial pressure and plasma noradrenaline concentration[25]. The magnitude of increase in blood pressure paralleled the increase in plasma noradrenaline concentration. Plasma adrenaline did not change

significantly.

This was further confirmed by Derbyshire and Smith who showed that the plasma noradrenaline concentration increased by 34% in samples obtained from central venous line and by 74% in samples obtained from radial artery[26]. This can be explained by uptake of noradrenaline in lungs.

The adrenergic response was maximum by one minute and had diminished by five minutes. This hemodynamic response due to activation of sympathico-adrenal system increases heart rate, blood pressure and these serve as indirect indices to measure the response. Thus heart rate and blood pressure have been used as indirect indices to measure levels of sympathetic activity clinically.

In addition to activation of the autonomic nervous system, endotracheal extubation also stimulates central nervous system activity as evidenced by increase in electroencephalographic activity and basal metabolic rate.

In patients with compromised intracranial compliance, the increase in cerebral blood flow may result in elevated intracranial pressure which in turn may result in herniation of brain contents and severe neurologic compromise.

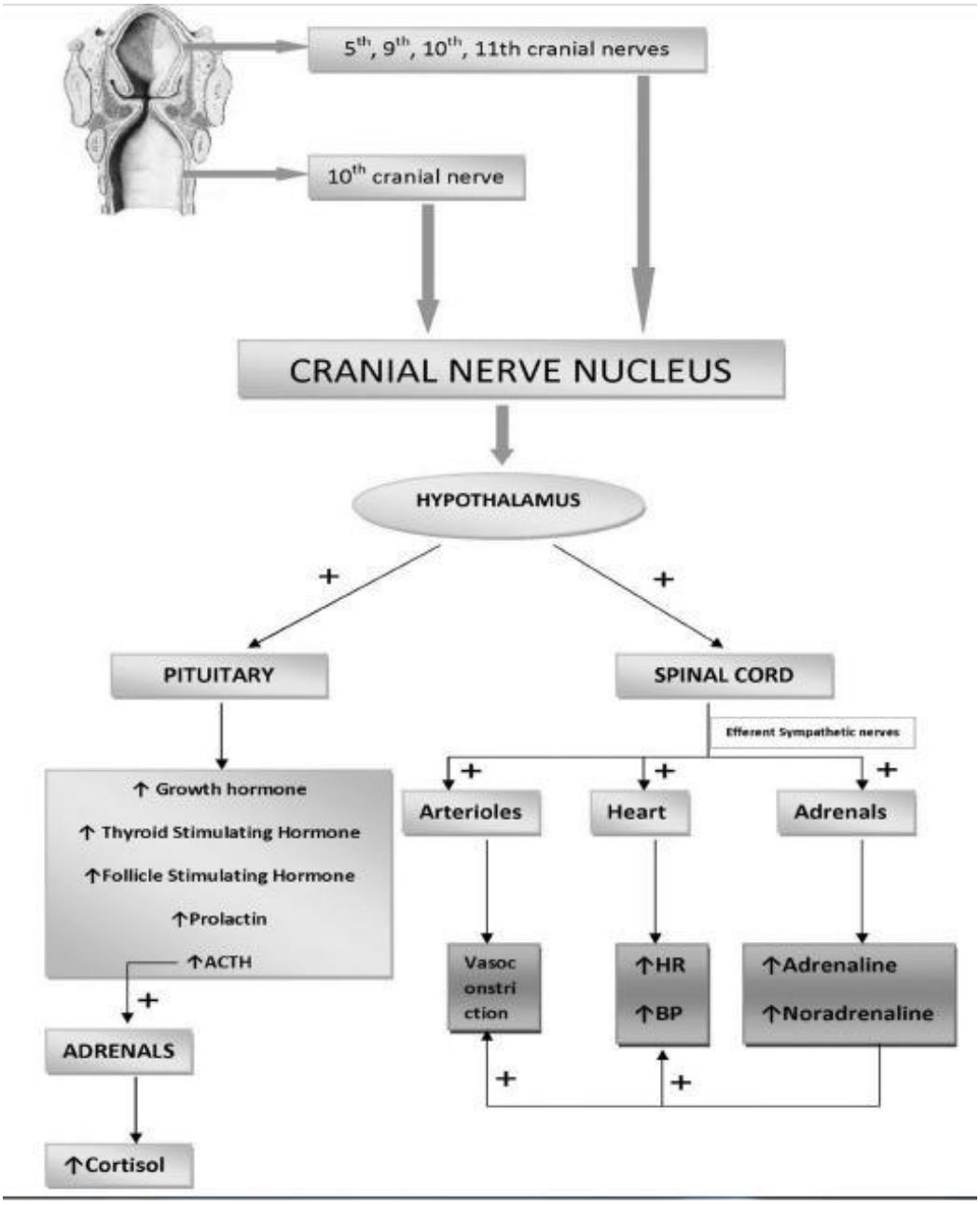


Figure 1 : Pressor Response Pathway

PHYSIOLOGY OF ADRENOCEPTORS

PHYSIOLOGY OF ADRENOCEPTORS

α-2 receptors are found in many sites throughout the body. They are found in peripheral and central nervous system, and in effector organs such as liver, kidney, pancreas, eye, vascular smooth muscles and platelets. Physiologic responses mediated by α-2 adrenoceptors vary with location and can account for the diversity of their effects[27,28,29].

The classification of α-2 receptors based on anatomical location is complicated since these receptors are found in presynaptic, postsynaptic and extrasynaptic locations. They have been divided into three subtypes ; each type is responsible uniquely for some actions of α-2 receptors[33,34]. The subtype A, the predominant subtype in CNS, is responsible for the sedative, analgesic and sympatholytic effect; the subtype B, found mainly in the peripheral vasculature, is responsible for the short term hypertensive response and the subtype C, found in CNS is responsible for anxiolytic effect[27,28].

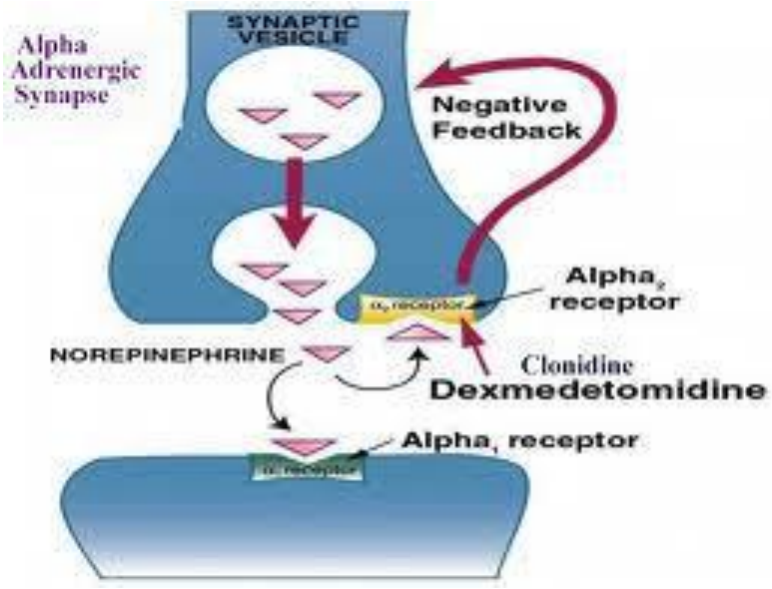


Figure 2 : Physiology of α-2 adrenoceptors

The α-2 adrenergic receptor mediates its effect by activating guanine-nucleotide regulatory protein (G proteins). Activated G proteins modulate cellular activity by signaling a second messenger system, which when activated leads to inhibition of adenylate cyclase which in turn, results in decreased formation of 3,5-cyclic adenosine monophosphate (c-AMP). This will lead to hyperpolarization of the excitable cell membranes and provides effective means of suppressing neuronal firing. Stimulation of α-2 receptor also suppresses calcium entry into the nerve terminal, which may be responsible for its inhibitory effect on secretion of neurotransmitters[27,28,29].

PHARMACOLOGY OF FENTANYL

PHARMACOLOGY OF FENTANYL

Fentanyl is a phenylpiperidine-derivative[27] synthetic opioid agonist that is structurally related to meperidine. As an analgesic, fentanyl is 75 to 125 times more potent than morphine[29].

It was first synthesized by Janssen Pharmaceutical in 1960[29].

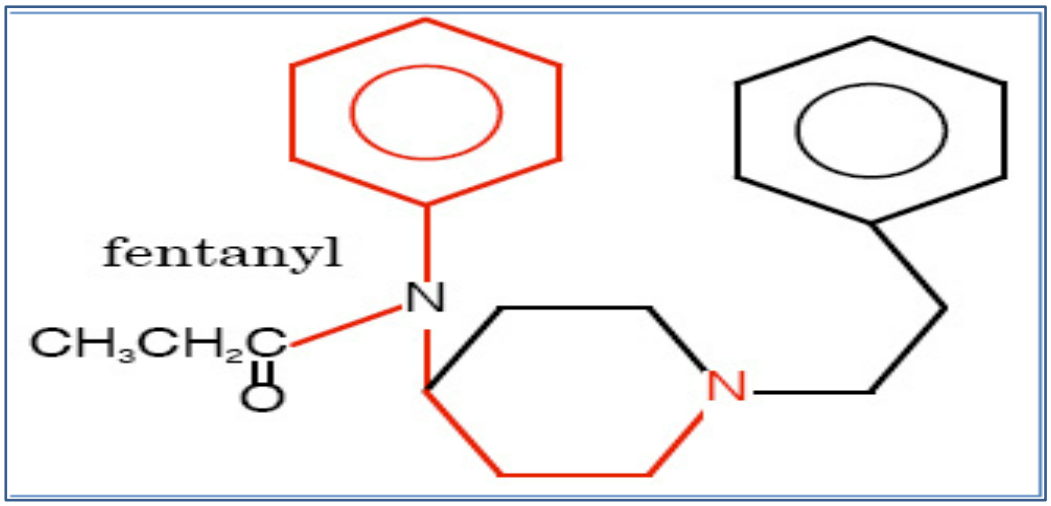


Figure 3: Structure of Fentanyl

Mechanism of action :

Fentanyl is a potent opioid analgesic, which is administered by the intravenous or intramuscular routes of injection. Activation of μ-opioid receptor will inhibit Adenylate cyclase, promote K+ efflux and an overall reduction in Ca++ influx which will result in hyperpolarisation of the cell and hence a reduction in cell signalling and pain transmission.

Fentanyl has a propensity to cause dose-dependent analgesia, ventilatory depression via the medullary respiratory center, sedation and at high doses, unconsciousness[29]. During open heart surgery and certain more complicated procedures, the stress response to surgery would be detrimental to the well being of the patient. Dosages of 20-50 mcg/kg of Fentanyl have been shown to attenuate the

stress response. The main objective of this technique is to produce "stress free" anaesthesia.

Tidal volume will increase but minute volume will decrease as rate decreases. Fentanyl is hemodynamically stable and is an ideal opioid for patients with cardiac morbidities. It will also produce pinpoint pupillary response called miosis through the action on the edinger-westphal nucleus. Less emetic activity and minimal histamine release (upto 50 mcg/kg).

Fentanyl is lipophilic and readily binds to plasma proteins. Fentanyl will cross the blood-brain barrier and placenta due to its lipophilicity. There is also inherent risk for truncal rigidity (mahogany chest) at higher doses[27].

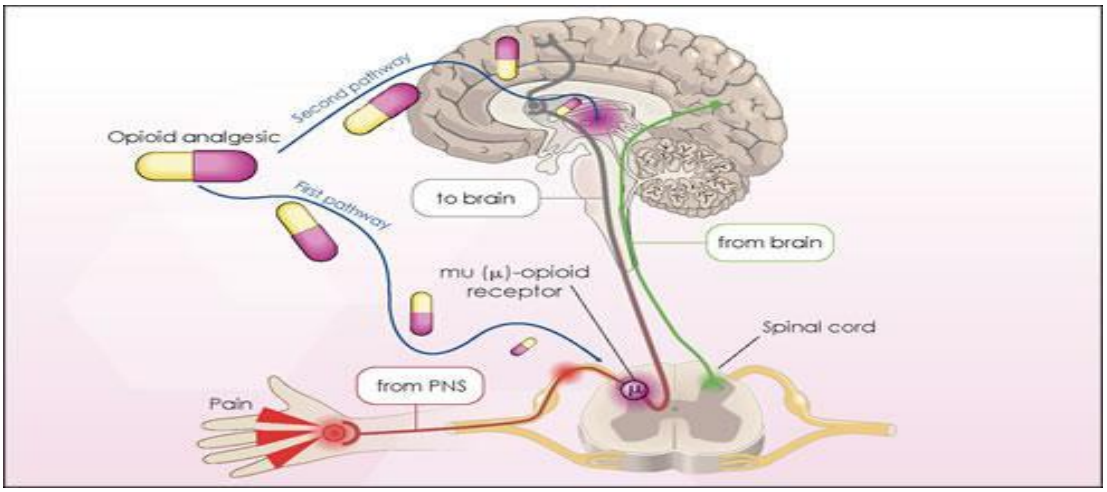


Figure 4 : Mechanism of action of Fentanyl

The combination of adenylate cyclase inhibition, blockade of voltage-gated calcium channels and activation of potassium channels, leading to hyperpolarisation of the cell, there by causing reduction of cell signaling and pain transmission.

Pharmacokinetics of Fentanyl:

The greater potency and more rapid onset of action reflect the greater lipid solubility of fentanyl, which facilitates its passage across the blood-brain barrier. Consequently, plasma concentrations of fentanyl correlate well with CSF concentrations[29]. The lungs also serves as large inactive storage site, with an estimated 75% of the initial fentanyl dose undergoing first-pass pulmonary uptake. This nonrespiratory function of the lungs play an important role in determining the pharmacokinetic profile of fentanyl[29].

a) 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 in humans. It is excreted by the kidneys and can be detected in the urine for 72 hours after single IV dose of fentanyl. Less than 10% of fentanyl is excreted unchanged in the urine[29].

b) Elimination Half-time:

The elimination half-time of fentanyl is 3-6 hours. Despite the clinical impression that fentanyl has short duration of action, its elimination half-time is longer than that for morphine. This longer elimination half-time reflects a larger volume of distribution of fentanyl because clearance of both opioids is similar.

The larger volume of distribution of fentanyl is due to its greater lipid solubility and thus more rapid passage into tissues[29]. After an IV bolus, fentanyl distributes rapidly from the plasma to highly vascular structures (brain, lungs, heart). More than 80% of the injected dose leaves the plasma in less than 5 minutes. 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[29].

c) Context-Sensitive Half-Time:

The context sensitive half-time of fentanyl is about 260 min. This reflects saturation of inactive tissues sites with fentanyl during prolonged infusions and return of the opioid from peripheral compartments to the plasma. This tissue reservoir of fentanyl replaces fentanyl eliminated by hepatic metabolism so as to slow the rate of decrease in the plasma concentration of fentanyl when the infusion is discontinued[29].

d) Cardiopulmonary Bypass:

All opioids show a decrease in plasma concentration with initiation of cardiopulmonary bypass. The degree of this decrease is greater with fentanyl because a significant proportion of the drug adheres to the surface of the cardiopulmonary bypass circuit. Elimination of fentanyl is shown to be prolonged by cardiopulmonary bypass[29].

Clinical uses of Fentanyl :

Fentanyl is administered clinically in a wide range of doses.

1. Low doses of fentanyl, 1-2 mcg/kg IV, are injected to provide analgesia.
2. Fentanyl 2-20 mcg/kg IV, may be given as an adjuvant to inhaled anaesthetics in an attempt to blunt circulatory responses to direct laryngoscopy for intubation of trachea or sudden changes in the level of surgical stimulation.[28]
3. Administration of fentanyl, 1.5 or 3 mcg/kg IV, five minutes before induction of anaesthesia decreases the subsequent doses of isoflurane or desflurane with 60% nitrous oxide needed to block the sympathetic nervous system response to surgical stimulation.

4. Large doses of fentanyl, 50-150 mcg/kg IV, have been used alone to produce surgical anaesthesia.
5. Intrathecal fentanyl can produce rapid, profound analgesia for early labor with minimal side effects.
6. Fentanyl may be administered as transmucosal preparation designed to deliver 5-20 mcg/kg of fentanyl. The goal is to decrease the preoperative anxiety and facilitate the induction of anaesthesia, especially in children.
7. Transdermal fentanyl preparations delivering 75 to 100 mcg/hour can be used to provide adequate analgesia for chronic pain[27,29].

Advantages of using Fentanyl as sole anaesthetic are

- lack of direct myocardial depressant effects
- absence of histamine release
- suppression of stress responses to surgery[29].

Disadvantages of using Fentanyl as sole anaesthetic are

- Failure to prevent sympathetic nervous system responses to painful surgical stimulus at any dose.
- Unpredictable amnestic effects potentially leading to recall.
- Postoperative depression of ventilation[29].

Side effects of Fentanyl:

Persistent or recurrent depression of ventilation due to fentanyl is a potential postoperative problem. Secondary peaks in the plasma concentrations of fentanyl have been attributed to sequestration of fentanyl in acidic gastric fluid. Sequestered fentanyl could be absorbed from the more alkaline small intestine back into circulation to increase the plasma concentration of opioid and cause depression of ventilation to recur[29].

a. Cardiovascular effects:

Fentanyl, even in large doses (50 mcg/kg IV) does not evoke the release of histamine. As a result, dilatation of venous capacitance vessels leading to hypotension is unlikely. Carotid sinus baroreceptor reflex control of heart rate is markedly depressed by fentanyl (10 mcg/kg) when given to neonates[29].

Therefore changes in the systemic blood pressure occur during fentanyl anaesthesia have to be carefully considered because cardiac output is rate-dependent in neonates. Bradycardia is more prominent with fentanyl and may lead to occasional decrease in blood pressure and cardiac output[29].

b. Seizure Activity:

Seizure activity has been described to follow rapid IV administration of fentanyl[28]. In the absence of EEG evidence of seizure activity, it is difficult to distinguish opioid induced skeletal muscle rigidity from seizure activity[29].

c. Intracranial pressure:

Administration of fentanyl to head injury patients has been associated with modest increase in ICP, despite maintenance of an unchanged Paco2[28]. These increase in ICP is typically accompanied by decrease in mean arterial pressure and cerebral perfusion pressure[29].

Drug Interactions of Fentanyl:

Analgesic concentrations of fentanyl greatly potentiate the effects of midazolam and decrease the dose requirements of propofol. The opioid-benzodiazepine combination displays marked synergism with respect to hypnosis and depression of ventilation[29]. Preinduction administration of fentanyl IV may be associated with cough reflex.

PHARMACOLOGY OF DEXMEDETOMIDINE

PHARMACOLOGY OF DEXMEDETOMIDINE

History: Dexmedetomidine was first synthesised in late 1980, co inventor Dr.Maze. Dexmedetomidine hydrochloride, an imidazole compound is the pharmacologically active s-enantiomer of medetomidine, a veterinary anaesthetic agent. It is described chemically as (+)-4-(s)[2,3–(dimethylphenyl) ethyl]-11 H-imidazole monohyrochloride. Its empirical formula is C13H16N2HCl and its molecular weight is 236.7.[30,31]

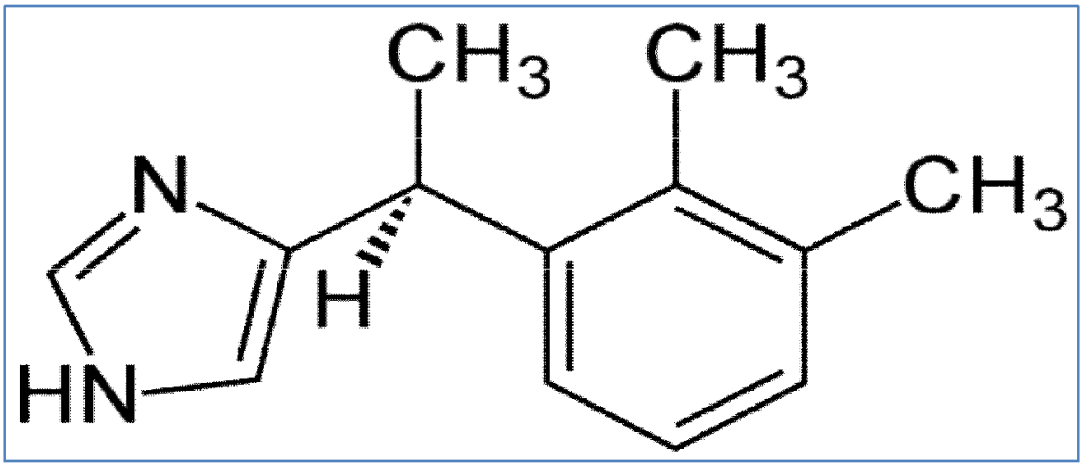


Figure 5 : Chemical structure of Dexmedetomidine

PHYSIOCHEMICAL PROPERTIES

A white or almost white powder that is freely soluble in water with Pka of 7.1. Partition coefficient in octanol : water at pH 7.4 is 2.89.

Preservative free Dexmedetomidine is available in 2ml ampoule as Dexmedetomidine hydrochloride for intravenous use. It can also be used for intrathecal and epidural anaesthesia.

MECHANISM OF ACTION OF DEXMEDETOMIDINE

Dexmedetomidine is the dextro enantiomer of medetomidine, the methylated derivative of etomidine, its specificity for the alpha2receptor is 8 times that of clonidine, with an alpha2 : alpha1 binding affinity ratio of 1620:1 and its effects are dose dependently reversed by administration of a selective alpha2 antagonist such as atipamezole.[32] Specific alpha2 receptor subtypes mediate the varied pharmacodynamic effects of dexmedetomidine. Agonism at alpha2Areceptor appears to promote sedation, hypnosis, analgesia, sympatholysis, neuroprotection and inhibition of insulin secretion.[33] Agonism at the alpha2B receptor suppresses shivering centrally, promotes analgesia at spinal cord sites and induces vasoconstriction in peripheral arteries. The alpha2C receptors are associated with modulation of cognition, sensory processing, mood and stimulant-induced locomotor activity and regulation of epinephrine outflow from the adrenal medulla. Inhibition of nor epinephrine release appears to be equally affected by all three alpha2 receptor subtypes.[34]

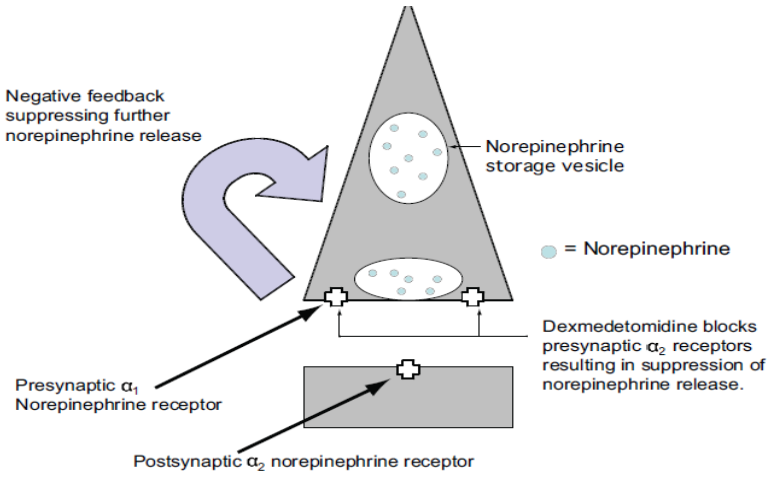


Figure 6 : Action at presynaptic α-2 adrenoceptors. Negative feedback loop modulating norepinephrine release

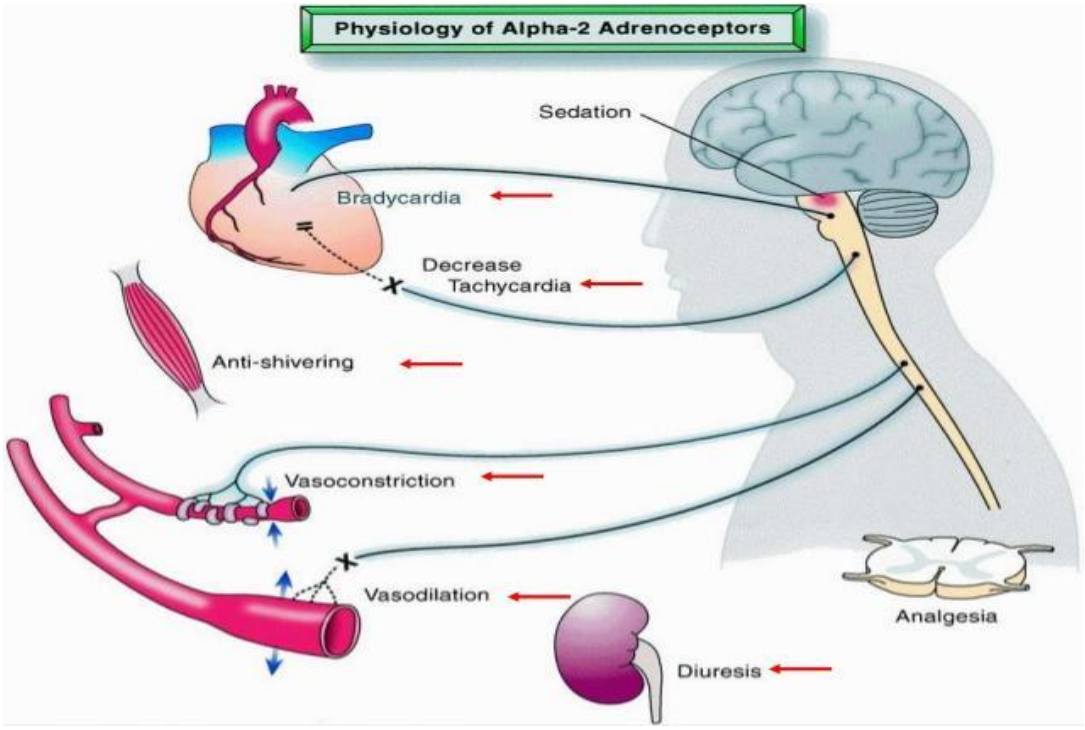


Figure 7 : Responses mediated by Alpha2 adrenergic receptors

The mechanism of action of dexmedetomidine is unique and differs from currently used sedative drugs. Alpha2 adrenoceptors are found in CNS in highest densities in the locus coeruleus, the predominant noradrenergic nuclei of the brainstem and an important modulator of vigilance. Presynaptic activation of alpha2A adrenoceptor in the locus coeruleus inhibits the release of nor-epinephrine and results in the sedative and hypnotic effects.[35] In addition, the locus coeruleus is the site of origin for the descending medullospinal nor adrenergic pathway, known to be an important modulator of nociceptive neurotransmission. Stimulation of alpha2 adrenoceptors in this area terminates the propagation of pain signals leading to analgesia. Postsynaptic activation of alpha2 receptors in the CNS results in decrease in sympathetic activity leading to hypotension and bradycardia.

At the spinal cord, stimulation of alpha2 receptors at the substantia gelatinosa

of the dorsal horn leads to inhibition of the firing of nociceptive neurons and inhibition of release of substance P. Also the alpha2 adrenoceptors located at the nerve endings have a possible role in the analgesic mechanism by preventing norepinephrine release. The spinal mechanism is the principal mechanism for the analgesic action of dexmedetomidine even though there is a clear evidence for both supraspinal and peripheral sites of action.[36]

Peripheral action: Alpha2 receptors are located on blood vessels where they mediate vasoconstriction and on sympathetic terminals, where they inhibit norepinephrine release. The responses of activation of alpha2 receptors in other areas include contraction of vascular and other smooth muscles, decreased salivation and decreased bowel motility in the gastrointestinal tract, inhibition of renin release, increased glomerular filtration and increased secretion of sodium and water in the kidney, decreased release of insulin from the pancreas, decreased intraocular pressure, decreased platelet aggregation and decreased shivering threshold by 2˚C.[36]

Pharmacodynamics of Dexmedetomidine

Dexmedetomidine is considered as the full agonist at alpha2 receptors compared to clonidine which is considered as a partial agonist at alpha2 adrenoceptors. The selectivity of dexmedetomidine to alpha2 receptors compared to alpha1 receptors is 1620:1, whereas with clonidine it is 200:1. The selectivity is dose dependent, at low to medium doses and on slow infusion, high levels of alpha2 selectivity is observed, while high doses or rapid infusions of low doses are associated with both alpha1 and alpha2 activities.

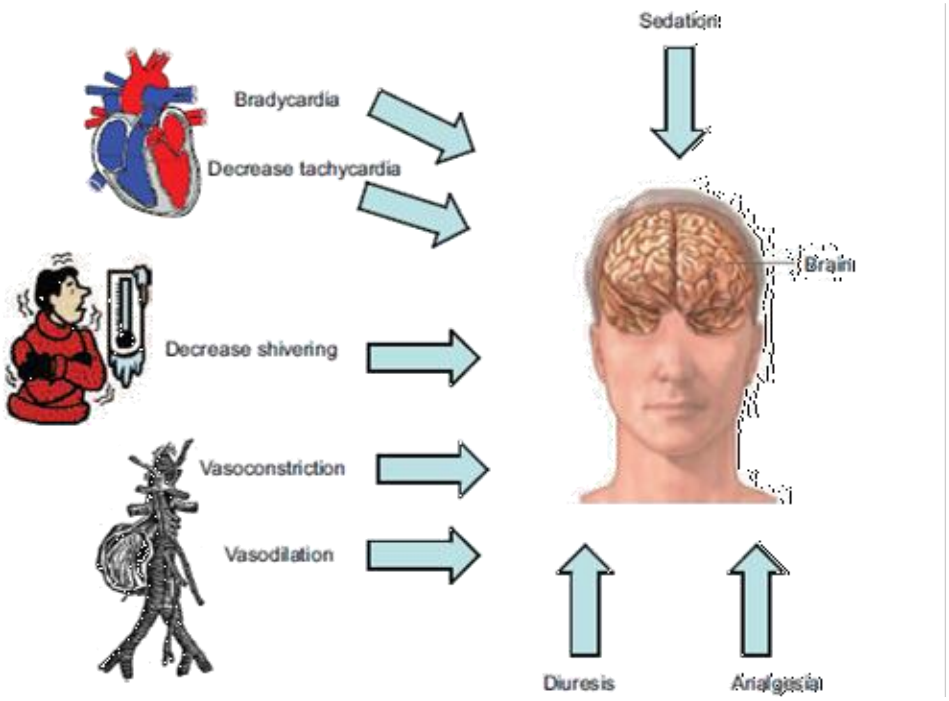


Figure 8 : Multiple sites of action of Dexmedetomidine

Central nervous system

Sedation, anxiolysis, hypnosis and amnesia[36]. Dexmedetomidine provides dose dependent increase in anxiolysis and sedation. However, the quality of sedation appears to be unique in comparison with gammaaminobutyric acid (GABAergic) agents such as midazolam or propofol. Arousability is maintained at deep levels of sedation, with good correlation between the level of sedation and the bispectral EEG (BIS). Once aroused subjects performed well on tests of vigilance, such as the critical flicker-fusion frequency. Dexmedetomidine induced sedation qualitatively resembles normal sleep. Dexmedetomidine induces sleep by activating endogenous non-rapid eye movement pathways. Stimulation of alpha2A receptors in the nucleus coeruleus inhibits noradrenergic neurons and disinhibits GABAergic neurons in the ventrolateral preoptic nucleus (VLPO). Incontrast, GABAergic agents such as propofol or benzodiazepines, directly enhance the inhibitory effects of the

GABAergic system at the VLPO. As such norepinephrine release remains unaffected, thus leading to less restful sleep.

The participation of non-rapid eye movement sleep pathways seems to explain why patients who appear to be deeply asleep from dexmedetomidine are relatively easily aroused in much the same way as occurs with natural sleep. This type of sedation is "cooperative or arousable", to distinguish it from sedation induced by drugs acting on the GABA system, such as midazolam or propofol which produce a clouding of consciousness.[37] Even low doses of dexmedetomidine might be sufficient to produce sedation.[38] Dexmedetomidine may lack amnestic properties but amnesia is achieved with dexmedetomidine only at high plasma levels (>1.9 ng/ml) without retrograde amnesia.[39]

Analgesia

Dexmedetomidine appears to exert analgesic effects at the spinal cord level and at supraspinal sites. However there has been a considerable debate as to whether its analgesic effects are primary or simply opioid sparing. In comparison with hypnotic agents such as propofol or postoperative opioids used alone, dexmedetomidine significantly decreases opioid requirement.[40]

Dexmedetomidine may also provide antinociception through nonspinal mechanisms. Intra-articular administration during knee surgery improves postoperative analgesia, with less sedation than IV route.[41] Suggested mechanisms are activation of alpha2A receptors, inhibition of the conduction of nerve signals through C and Aδ fibres and the local release of encephalin.[42]

Respiratory effects

Dexmedetomidine is able to achieve its sedative, hypnotic and analgesic effects without causing any clinically relevant respiratory depression unlike opioids. The changes in ventilation[43] appeared similar to those observed during natural sleep. Dexmedetomidine do not cause any changes in arterial oxygenation, pH and respiratory rate.[44] It also exhibited a hypercarbic arousal phenomenon, which has been described during normal sleep and is a safety feature. The obstructive respiratory pattern and irregular breathing seen with high doses of 1-2μg/kg given over 2 minutes and are probably related more to deep sedation and anatomical features of the patient and this could be easily overcome by insertion of an oral airway. Co-administration of dexmedetomidine with anaesthetic agents, sedatives, hypnotics or opioids is likely to cause additive effects.[45]

Intravenous or inhaled dexmedetomidine has been implicated in blocking histamine induced bronchoconstriction in dogs.[46]

Dexmedetomidine is effective in achieving excellent sedation without respiratory depression during fibreoptic intubation or other difficult airway procedures. Intubating conditions are further enhanced because dexmedetomidine decreases saliva production and airway secretions.

Cardiovascular effects

Dexmedetomidine does not appear to have any direct effects on the heart. A biphasic cardiovascular response has been described after the application of dexmedetomidine.[47] The administration of a bolus of 1 μg/kg body weight, initially results in a transient increase of the blood pressure and a reflex decrease in heart rate, especially in young healthy patients. The initial reaction can be explained by the

peripheral alpha2B adrenoceptors stimulation of vascular smooth muscles and can be attenuated by a slow infusion over 10 or more minutes. Even at slower infusion rates however the increase in mean arterial pressure over the first 10 minutes was shown to be in the range of 7% with a decrease in heart rate between 16% and 18%. The initial response lasts for 5-10 minutes and is followed by a decrease in blood pressure of approximately 10%-20% below baseline values, both these effects are caused by the inhibition of the central sympathetic outflow over riding the direct stimulant effects. Another possible explanation for the subsequent heart rate decrease is the stimulation of presynaptic alpha2 adrenoceptors, leading to a decrease in norepinephrine release. The application of a single high dose of dexmedetomidine reduced norepinephrine release by as much as 92% in young healthy volunteers.

The release of epinephrine is also reduced by the same amount. The baroreceptor reflex is well preserved in patients who received dexmedetomidine and the reflex heart rate response to a pressor stimulus is augmented.These results illustrate that cardiovascular response is evoked mainly by decrease in central sympathetic outflow.[47] Dexmedetomidine could result in cardiovascular depression like bradycardia and hypotension. The incidence of postoperative bradycardia has been reported as high as 40% in healthy surgical patients who received dexmedetomidine, especially high doses. Usually these temporary effects were successfully treated with atropine or ephedrine and volume infusions.

Effect on adrenocorticotrophic hormone (ACTH) secretion

Although dexmedetomidine has no significant effect on ACTH secretion at therapeutic doses, cortisol's response to ACTH may be reduced after prolonged use or high doses. The ratio of levels of inhibition caused by etomidate and

dexmedetomidine was shown to be in the order of 100:1, suggesting that the biologic effects of the inhibitory activities of dexmedetomidine are not clinically important.[48]

Effect on renin release

Renin release is stimulated by β-adrenoceptor mechanisms, whereas alpha2 adrenoceptor agonists directly inhibit renin release.

Effect on insulin release

Stimulation of alpha2 adrenoceptors on islet cells directly inhibits the release of insulin, this effect has unproven clinical importance, because hyperglycemia has never been reported to be significant in patients receiving clonidine.

Effect on thermoregulation

Like clonidine, dexmedetomidine is associated with lower rates of shivering. Intravenous infusion of dexmedetomidine reduced the vasoconstriction and shivering threshold but do not change the sweating threshold.[49] Therefore with dexmedetomidine, thermoregulatory response were inhibited within a wider range of temperature. Dexmedetomidine and other alpha2 agonists suppress shivering, possibly by their activity at alpha2B receptors in the hypothalamic thermoregulatory centre of the brain. Low dose dexmedetomidine has an additive effect with meperidine on lowering the shivering threshold and dexmedetomidine may be beneficial in decreasing patient discomfort from post anaesthetic shivering.

Effects on renal function

Alpha2 agonists exert a diuretic effect by inhibiting the antidiuretic action of arginine vasopressin at the collecting duct, resulting in decreased expression of

aquaporin-2 receptors and decreased salt and water absorption.

Organ protective effects

The ability of alpha2 agonists to decrease tachycardia and hypertension suggests that they may play a role in cardioprotection by enhancing myocardial oxygen balance. There is considerably more experimental evidence that dexmedetomidine has neuroprotective effects by several mechanisms. These include sympatholysis, preconditioning and attenuation of ischemic reperfusion injury.[50] There is also evidence that dexmedetomidine decreases cerebral blood flow. But its ratio with cerebral metabolic rate i.e, flow metabolism coupling appears to be preserved.[51]

PHARMACOKINETICS :

After intravenous injection, dexmedetomidine has an onset of action after approximately 15 minutes. Peak concentrations are usually achieved within 1 hour after continuous infusion. It has a rapid distribution half life (t1/2α) of 6 minutes and a terminal elimination half life (t1/2β) of between 2 and 2.5 hrs. The drug is highly protein bound (94%) with a 6% free fraction. It has a steady state volume of distribution (Vd, 1.33 l/kg). Dexmedetomidine is rapidly distributed and extensively metabolized in the liver. It undergoes conjugation (41%), n-methylation (21%) or hydroxylation followed by conjugation. Dexmedetomidine is 94% protein bound and its concentration ratio between blood and plasma is 0.66. The elimination half life is 2 to 3 hours with a context sensitive half time ranging from 4 minutes after a 10 minute infusion to 250 minutes after an 8 hour infusion.[52] Total plasma clearance is age

independent, thus similar rates of infusion can be used in children and adults to effect a steady state plasma concentration. Plasma protein binding is similar to adults.[53]

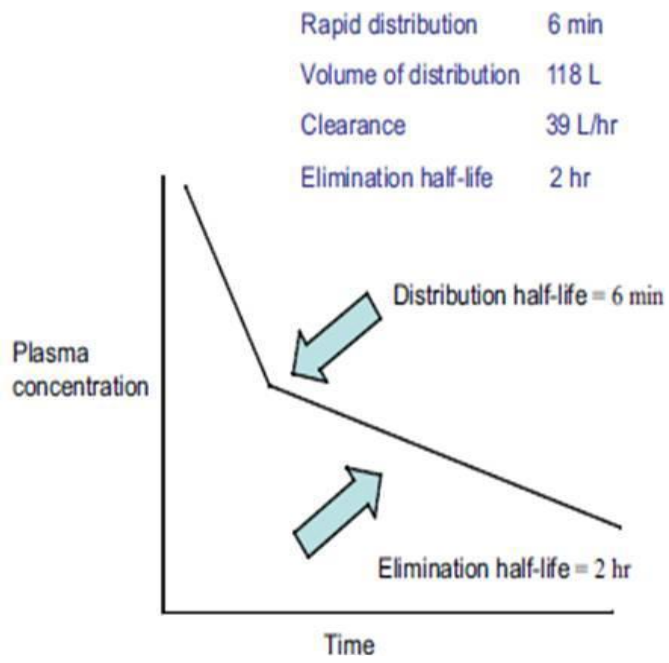


Figure 9: Pharmacokinetics of Dexmedetomidine

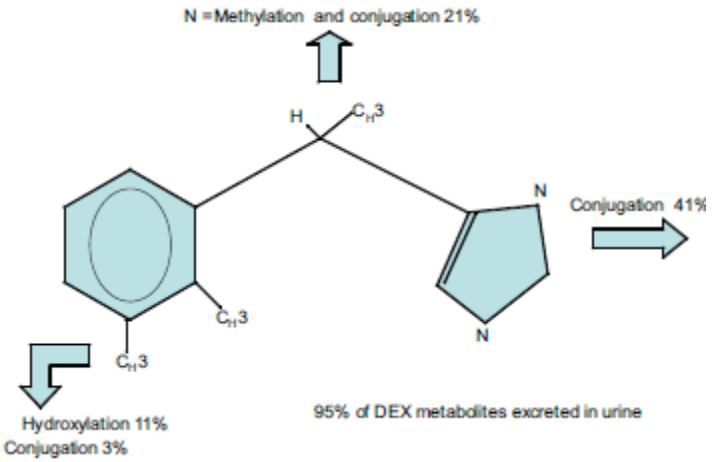


Figure 10 : Pathways of metabolism of Dexmedetomidine

Dexmedetomidine is also absorbed systematically through transdermal, buccal or intramuscular routes, with a mean bioavailability from the latter 2 routes of 82% and104% respectively. After intramuscular administration, the time to maximum

concentration (Tmax) in the blood is 1.6 to 1.7 hrs, with an absolute bioavailability of 73%. After transdermal administration, the Tmax is six hours with an absolute bioavailability of 88%.[54]

PERIOPERATIVE USES OF DEXMEDETOMIDINE

1. Premedication

Dexmedetomidine has anxiolytic, sedative, analgesic, antisialogogue and sympatholytic properties which render it suitable as a premedication agent.

As a premedicant, dexmedetomidine, at IV doses 0.33 to 0.67μg/kg given 15 minutes before surgery, seems efficacious, while minimizing the cardiovascular side effects of hypotension and bradycardia.

a) It reduces thiopentone sodium requirements.
b) Reduces the requirements of volatile anaesthetics.[55]
c) More effectively attenuates the haemodynamic responses to endotracheal intubation.
d) Decreases plasma catecholamine concentrations.
e) Improves perioperative haemodynamic and sympathoadrenal stability.

2. Use of dexmedetomidine for regional anaesthesia

a) Epidural dexmedetomidine at a dose of 100μg decreased the incidence of postoperative shivering[56].
b) Intrathecal dexmedetomidine at a dose of 3μg causes significant prolongation of sensory and motor blockade[57].
c) Addition of 0.5μg/kg body weight of dexmedetomidine to lidocaine for intravenous regional anaesthesia improves the quality of anaesthesia and

perioperative analgesia.

3. Use in monitored anaesthesia care (MAC) : Dexmedetomidine confers arousable sedation with ease of orientation, anxiolysis, mild analgesia without respiratory depression.
4. Dexmedetomidine has also been used as sole anaesthetic agent upto doses of 10μg/kg/hr.
5. Use of dexmedetomidine in postoperative period: infusion can be continued in extubated and spontaneously breathing patients. The ongoing sedation and sympatholytic effects is beneficial in reducing postoperative myocardial ischemic events in high risk patients undergoing non-cardiac surgery.
6. Use of dexmedetomidine in paediatric age group - addition of dexmedetomidine 2μg/kg body weight to bupivacaine for caudal analgesia promotes analgesia after anaesthetic recovery without increasing the incidence of side effects.
7. Use of dexmedetomidine in intensive care unit (ICU): it provides adequate sedation with minimal respiratory depression and can be used for weaning patients from ventilator.

Adverse effects

Other side effects of dexmedetomidine other than hypotension and bradycardia are hypertension after loading dose, dystonic movements, atelectasis, nausea and vomiting, dry mouth, tachycardia, atrial fibrillation, haemorrhage, acidosis, confusion, agitation and rigors which are rare.

Withdrawal phenomenon is reported after abrupt discontinuation with

prolonged administration of dexmedetomidine, leading to development of hypertension, tachycardia, emesis, agitation, dilated pupils, diarrhoea, increased muscle tone and tonic clonic seizures.

Dosage and administration

The recommended dexmedetomidine dose is an IV infusion bolus of 1 μg/kg body weight over a 10 minute period, followed by a continuous IV infusion of 0.2 - 0.7 μg/kg/hr. The maintenance dose is titrated until the sedation goal is reached.

Dose up to 2.5μg/kg/hr for up to seven days, with no rebound effect on withdrawal and no compromise in hemodynamic stability have been used in clinical trials.

Drug interactions

Dexmedetomidine has shown to inhibit CYP2 D6 in vitro, but the clinical significance of this inhibition is not well established. Dexmedetomidine appears to have little potential for interactions with drugs metabolized by the cytochrome p450 system. Co-administration of dexmedetomidine with sevoflurane, isoflurane, propofol, alfentanil and midazolam may result in enhancement of sedative, hypnotic or anaesthetic effects.

METHODOLOGY

MATERIALS AND METHODS

A prospective randomized clinical study was conducted in the Department of Anaesthesiology at the Shri B. M. Patil Medical College, Hospital and Research Centre, Vijayapur after approval by the Medical Ethical Committee of BLDE (Deemed to be University) Vijayapur, The study was carried out on 60 patients belonging to American Society of Anaesthesiology (ASA) classification for physical status I and II of either sex in the age range of 18 to 60 years undergoing surgery under general anaesthesia. They were randomized into two groups of 30 each.

Group D - Dexmedetomidine Group

Group F - Fentanyl Group

Inclusion criteria

1. Patients of age between 18 - 60 years
2. ASA Grade I & II patients
3. Mallampati grade I and II
4. Patients giving valid and informed consent

Exclusion criteria

1. Patients suffering from cardiac and pulmonary disease
2. Patients with anticipated difficult airway
3. Pathology of oropharyngeal tract.
4. Patients on beta blockers, patients with conduction defects of the heart (heart blocks)
5. Pregnant women.
6. Morbidly obese (body mass index > 35 kg/m^2)

PROCEDURE :

The ethical clearance for the study was obtained from the Medical Ethical Committee, **Shri B. M. Patil Medical College Hospital and Research Centre, Vijayapur**. Patients posted for elective surgery under general anaesthesia were screened for the eligibility. Patients fulfilling selection criteria were selected for the study and briefed about the nature of study and explained about anesthetic procedure in their vernacular language. A written informed consent was obtained from the patient.

A preanesthetic evaluation with detailed medical history and systemic examination was done and relevant investigations were advised and reviewed on the previous day and on the day of surgery. Patients were randomized into two groups:

Group D (Dexmedetomidine) :

Intravenous dexmedetomidine 0.4 mcg/kg body weight diluted to 20 ml in normal saline was infused over 15 minutes prior to completion of surgery using infusion pump.

Group F (Fentanyl) :

Intravenous fentanyl 0.5 mcg/kg body weight diluted to 20 ml in normal saline infused over 15 minutes prior to completion of surgery using infusion pump

INVESTIGATIONS :

- Hb%, TC, DC, and ESR,
- Random blood sugar levels,
- Blood urea and serum creatinine,
- Electrocardiogram,
- Chest X-ray,

- Bleeding time,
- Clotting time,
- Liver function tests
- HIV and HBsAg tests.

Standard monitoring with electrocardiography (ECG), pulseoximetry (SpO_2), $ETCO_2$ and noninvasive blood pressure was done in the operation theatre. Intravenous line was established using 18 guage intravenous cannula. In order to attain double blinding, the person who was not involved in recording, prepared fentanyl 0.5µg/kg diluted to 20ml in normal saline and dexmedetomidine 0.4 µg/kg diluted to 20ml in normal saline. Patients were randomly allocated to two equal groups of 30 each by means of a computer generated table of random number to receive either fentanyl 0.5µg/kg (Group F) or dexmedetomidine 0.4 µg/kg (Group D) over a period of 15 minutes,15 min prior to extubation.

After preoxygenation, patients are preinduced with injection. midazolam 0.025mg/kg and fentanyl 1-2 mcg/kg. They are induced with injection. propofol 2 mg/kg and intubation facilitated with injection atracurium 0.8mg/kg intravenously.

Patients were maintained on 60% nitrous oxide in oxygen and isoflurane percentage is adjusted to maintain hemodynamics within the normal range. Atracurium initial bolus and intermittent thereafter is used for maintainence of muscle paralysis.

Intraoperatively patients were ventilated to maintain partial pressure of ET CO_2 between 30-35 mmHg. About 15 minutes prior to extubation, inhalational agent was stopped and the infusion was started over a period of 15 minutes by the anaesthesia resident (who was unaware of the contents of the infusion).

After onset of spontaneous breathing, intravenous neostigmine 0.05mg/kg and

glycopyrrolate 0.01mg/kg is administered to antagonize the effect of muscle relaxants. Patients were extubated when the extubation criteria were fulfilled.

Heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were recorded just before reversal, during extubation, 1min of tracheal extubation and thereafter 5 min, 10 min and 15 minutes of tracheal extubation.

THE FOLLOWING PARAMETERS WERE OBSERVED:

1. Heart rate (HR) in beats per minute.
2. Systolic blood pressure (SBP) in mmHg.
3. Diastolic blood pressure (DBP) in mmHg.
4. Mean arterial pressure (MAP) in mmHg.

THE ABOVE PARAMETERS WERE OBSERVED AT FOLLOWING TIME INTERVALS:

1. Before reversal.
2. At the time of extubation.
3. 1min after extubation.
4. 5min after extubation.
5. 10min after extubation.
6. 15min after extubation.

SIDE EFFECTS :

Hypotension was defined as a decrease in systolic blood pressure >20% from baseline or a mean arterial pressure of <60 mmHg and was corrected with intravenous fluids and if required, with small dose of mephenteramine 3 mg IV. Bradycardia was defined as a heart rate of <50 beats/min and was corrected, if associated with hemodynamic instability, with atropine 0.6 mg IV.

EXTUBATION QUALITY SCORE :

Quality of extubation was evaluated based on cough immediately after extubation using extubation quality score[62] .

1= No coughing

2= Smooth extubation, minimal coughing (1 or 2 times)

3= Moderate coughing(3-4 times)

4= Severe coughing and straining(5-10 times)

5= Poor extubation, very uncomfortable (laryngospasm and cough 10 times).

RAMSAY SEDATION SCORING :

Post-operative sedation was evaluated on a Ramsay sedation scale (6 point scale)[70] at extubation and thereafter at every 15 minutes for 1 hour.

1. anxious and agitated, restless
2. co-operative, oriented, tranquil
3. responsive to verbal commands, drowsy
4. asleep, responsive to light stimulation(loud noise, tapping)
5. asleep, slow response to stimulation
6. no response to stimulation

Adverse events like bradycardia, hypotension, vomiting, laryngospasm, respiratory depression, delayed arousal were noted and treated accordingly.

STATISTICAL ANALYSIS

METHOD OF STATISTICAL ANALYSIS

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean± standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square (χ^2) test was used for association between two categorical variables.

The formula for the chi-square statistic used in the chi square test is:

$$\chi_c^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

The subscript "c" are the degrees of freedom. "O" is observed value and E is expected value. C= (number of rows-1)* (number of columns-1)

The difference of the means of analysis variables between two independent groups was tested by unpaired t test.

The t statistic to test whether the means are different can be calculated as follows:

$$t = \frac{(\overline{x_1} - \overline{x_2}) - (\mu_1 - \mu_2)}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$

where $\bar{x}_1$ = mean of sample 1

$\bar{x}_2$ = mean of sample 2

n_1 = number of subjects in sample 1

n_2 = number of subjects in sample 2

s_1^2 = variance of sample 1 = $\frac{\Sigma(x_1 - \bar{x}_1)^2}{n_1}$

s_2^2 = variance of sample 2 = $\frac{\Sigma(x_2 - \bar{x}_2)^2}{n_2}$

If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analyzed using SPSS software v.23 (IBM Statistics, Chicago, USA) and Microsoft office 2007.

OBSERVATION AND RESULTS

OBSERVATIONS AND RESULTS

This randomised comparative study was designed to study the effect of dexmedetomidine and fentanyl on attenuating stress response and airway response to tracheal extubation.

For the purpose of the study 60 patients of ASA I and II aged 18-60 yrs and of either sex were randomly divided into two groups of 30 each.

1. Group F (n=30), the study group received infusion of fentanyl 0.5µg/kg in 20 ml normal saline over 15 minutes, 15 minutes prior to extubation.
2. Group D (n=30), the study group received infusion of dexmedetomidine 0.4µg/Kg diluted in 20 ml normal saline over 15 minutes, 15 minutes prior to extubation.

The following data was collected and analysed statistically.

1. Age, gender.
2. Hemodynamic parameters including heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure were recorded as follows:

- Just before reversal.
- During extubation.
- 1 minute, 5 minutes, 10 minutes and at 15 minutes after tracheal extubation.

3. Quality of extubation was evaluated by means of extubation quality score using five point extubation quality scale.
4. Post operative sedation was evaluated using Ramsay sedation scale.

TABLE 1 : AGE DISTRIBUTION BETWEEN STUDY GROUPS.

Parameters	Group D		Group F		Mean Difference	p value
	Mean	SD	Mean	SD		
AGE(yrs)	42.6	10.4	39.6	7.1	2.9	0.207

Table I shows distribution of patients age between both groups. The minimum age in Group D and Group F were 18 and 20yrs respectively. The maximum age in both groups was 55yrs. The mean age in Group D and F were 42.6 and 39.6 respectively. There was no significant difference in the age of patients between the Group D and Group F [p=0.207]

FIGURE 11: DISTRIBUTION OF AGE BETWEEN STUDY GROUPS

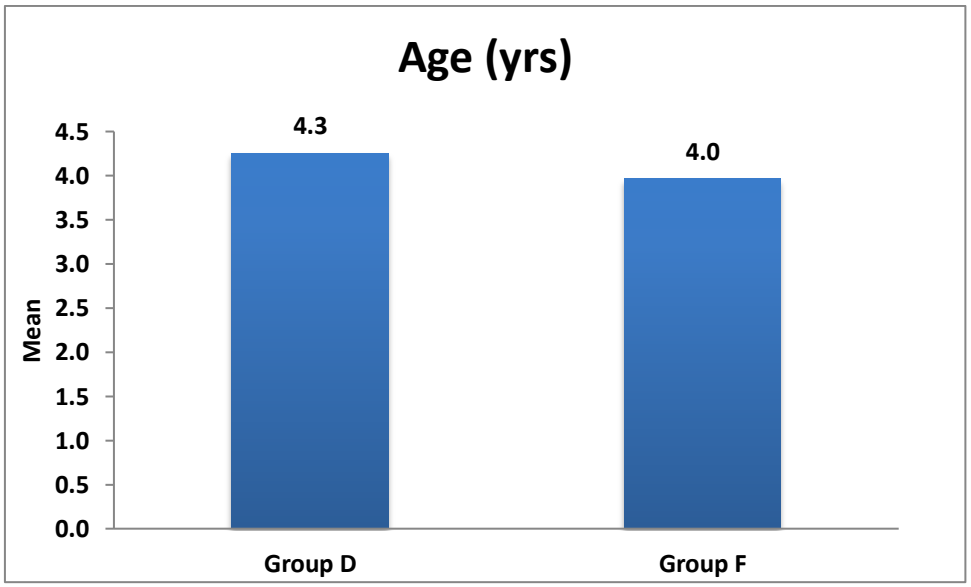


TABLE 2: DISTRIBUTION OF SEX BETWEEN STUDY GROUPS

Sex	Group D		Group F		p value
	N	%	N	%	
Male	14	46.7%	15	50.0%	0.796
Female	16	53.3%	15	50.0%	
Total	30	100.0%	30	100.0%	

Table 2 shows 46.7% of Group D and 50% of Group F were males. Females are 53.3% in Group D and 50% in Group F. The sex distribution did not have any statistically significant difference [p=0.796]

FIGURE 12: DISTRIBUTION OF SEX BETWEEN STUDY GROUPS

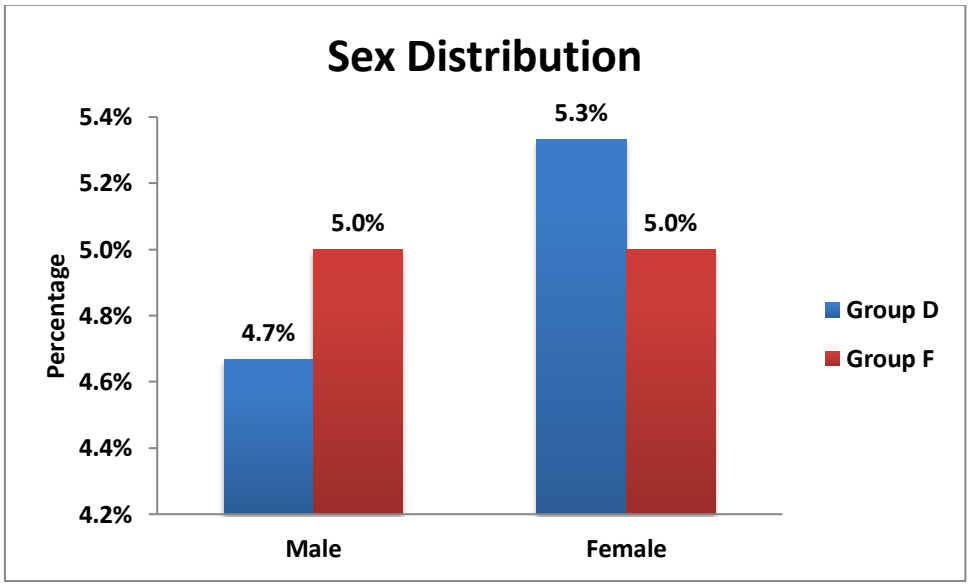


TABLE 3 : DISTRIBUTION OF HR BETWEEN STUDY GROUPS

HR	Group D		Group F		Mean Difference	p value
	Mean	SD	Mean	SD		
JBR	75.2	10.8	92.5	7.2	-17.4	<0.001*
AEX	83.7	12.2	113.2	7.7	-29.5	<0.001*
1min	86.7	11.8	117.5	8.0	-30.8	<0.001*
5min	82.0	10.3	103.9	7.3	-21.8	<0.001*
10min	78.8	9.0	94.6	6.4	-15.8	<0.001*
15min	79.3	8.4	88.9	5.9	-9.5	<0.001*

Table 3 shows comparison of mean HR between Group D and Group F. The basal HR were comparable in both groups and the difference was not statistically significant. The mean HR was compared at different time intervals and it was observed that, after administration of drug in Group D, the mean HR at 1min and 5min were 86.7 and 82 respectively showing continuous raise of HR before extubation. While in Group F mean HR at 1min and 5min was 117.5 and 103.9 respectively showing continuous fall in HR. The difference in the HR is statistically significant (P=0.001). The mean HR at extubation in Group F was 113.2 is significantly more than mean HR in Group D, 83.7 (P=0.001).The peak raise in mean HR was at 1min after extubation in both Group D and Group F, 86.7 and 117.5 respectively and the difference is statistically significant. At 5,10,15 min after drug administration the HR in Group F remained significantly high compared to Group D.

FIGURE 13 : DISTRIBUTION OF HR BETWEEN STUDY GROUPS

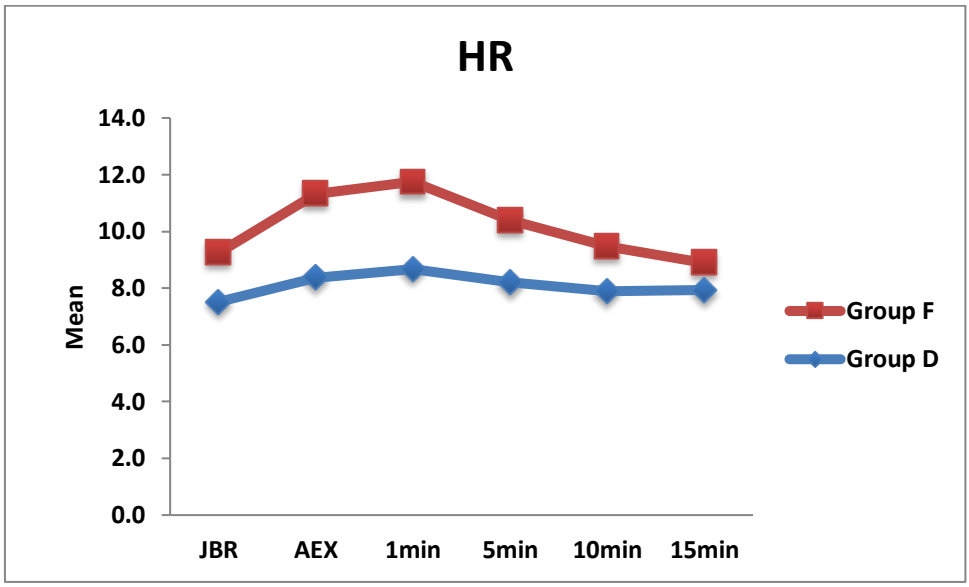


TABLE 4: DISTRIBUTION OF SBP BETWEEN STUDY GROUPS

SBP	Group D		Group F		Mean Difference	p value
	Mean	SD	Mean	SD		
JBR	108.8	10.8	127.5	7.1	-18.6	<0.001*
AEX	101.7	12.2	148.0	7.8	-46.3	<0.001*
1min	109.8	10.9	150.3	7.8	-40.5	<0.001*
5min	103.4	11.8	125.6	4.0	-22.2	<0.001*
10min	101.9	11.8	118.5	5.2	-16.6	<0.001*
15min	104.2	9.6	116.0	4.8	-11.8	<0.001*

Table 4 shows comparison of SBP between Group D and Group F. After extubation mean SBP in Group F was148 which was significantly more than mean SBP 101.7 in Group D. Peak raise in SBP occurred at 1min after extubation in both Group D and Group F are 150.3 and 109.8 respectively, but the peak raise was more in Group F compared to Group D and the difference is statistically significant (p= 0.001). Mean SBP at 1,5,10,15 min after extubation in Group F was comparatively more than Group D and it is statistically significant (p=0.001).

FIGURE 14: DISTRIBUTION OF SBP BETWEEN STUDY GROUPS

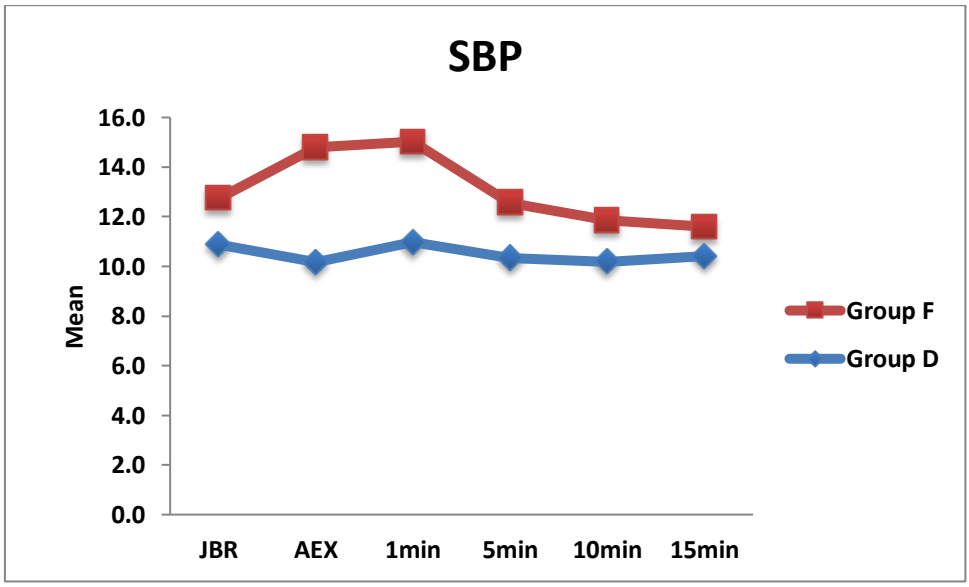


TABLE 5: DISTRIBUTION OF DBP BETWEEN STUDY GROUPS

DBP	Group D		Group F		Mean Difference	p value
	Mean	SD	Mean	SD		
JBR	71.7	10.6	82.8	7.0	-11.1	<0.001*
AEX	70.0	11.9	98.3	7.0	-28.3	<0.001*
1min	78.2	8.7	98.9	5.2	-20.7	<0.001*
5min	70.3	9.0	81.5	4.7	-11.2	<0.001*
10min	70.6	8.1	77.6	4.9	-7.1	<0.001*
15min	71.6	7.7	78.6	5.4	-7.0	<0.001*

Table 5 shows the comparison of DBP between both Group F and Group D. The mean DBP at extubation in Group F were significantly high compared to mean DBP in Group D (P=0.001). Peak raise in DBP occurred at 1min after extubation in both Group F (98.9) and Group D (78.2) but the raise was more in Group F compared to Group D and the difference was statistically significant. The mean DBP at 5,10,15 min in Group F were significantly more compared to mean DBP in Group D and the difference was statistically significant (p=0.001).

FIGURE 15 : DISTRIBUTION OF DBP BETWEEN STUDY GROUPS

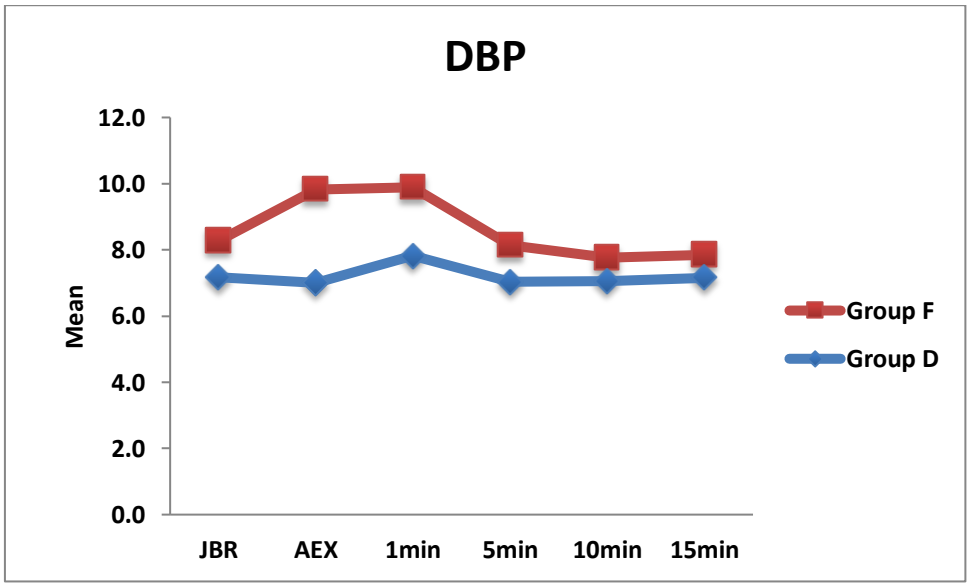


TABLE 6: DISTRIBUTION OF MAP BETWEEN STUDY GROUPS

MAP	Group D		Group F		Mean Diffrence	p value
	Mean	SD	Mean	SD		
JBR	82.3	8.0	97.4	5.2	-15.1	<0.001*
AEX	80.1	8.7	114.5	5.4	-34.4	<0.001*
1min	88.2	7.9	115.7	5.1	-27.5	<0.001*
5min	80.4	7.6	96.5	3.9	-16.1	<0.001*
10min	80.8	8.4	91.0	3.9	-10.3	<0.001*
15min	81.7	6.7	87.5	4.2	-5.9	<0.001*

Table 6 shows comparison of MAP between Group F and Group D. After extubation the MAP continued to increase in Group F, while there was a decrease in MAP in Group D and the difference was statistically significant (p=0.001). The peak raise in mean MAP occurred at 1min after extubation in both Group F (115.7) and Group D (88.2) and the difference was statistically significant. The peak raise in MAP was more in Group F compared to Group D. The mean MAP at 5,10,15 min in Group F was significantly more compared to Group D.

FIGURE 16 : DISTRIBUTION OF MAP BETWEEN STUDY GROUPS

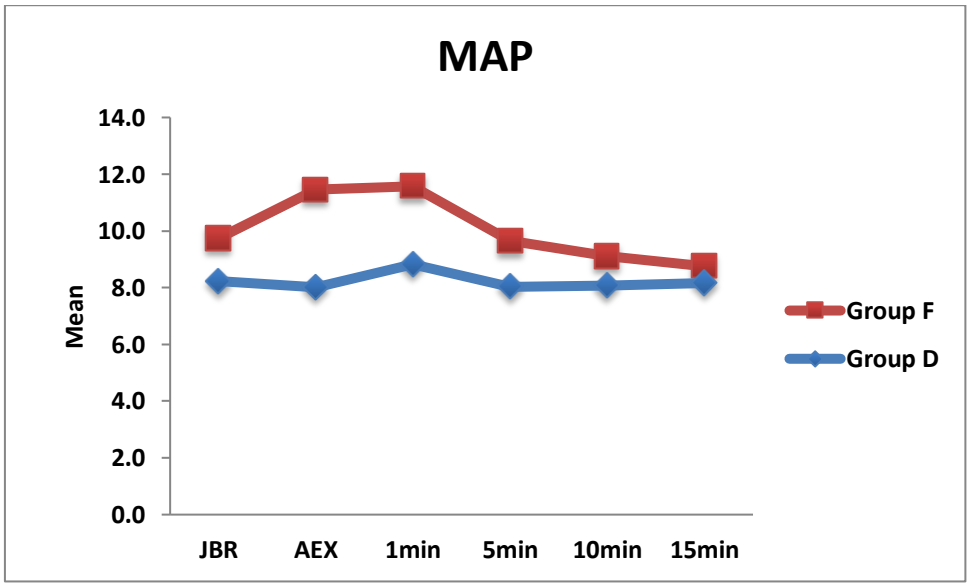


TABLE 7: SIDE EFFECTS BETWEEN STUDY GROUPS

Side Effects	Group D		Group F		p value
	N	%	N	%	
Brady	2	6.7%	0	0.0%	0.026*
Hypo	3	10.0%	0	0.0%	
Shivering	0	0.0%	2	6.7%	
Vomiting	0	0.0%	4	13.3%	
Total	30	100.0%	30	100.0%	

Table 7 shows the distribution of side effects among the two groups. In Group F, four patients had vomiting and two had shivering. In Group D, two patients developed bradycardia and three patients developed hypotension. None had shivering or hypotension.

FIGURE 17: SIDE EFFECTS BETWEEN STUDY GROUPS

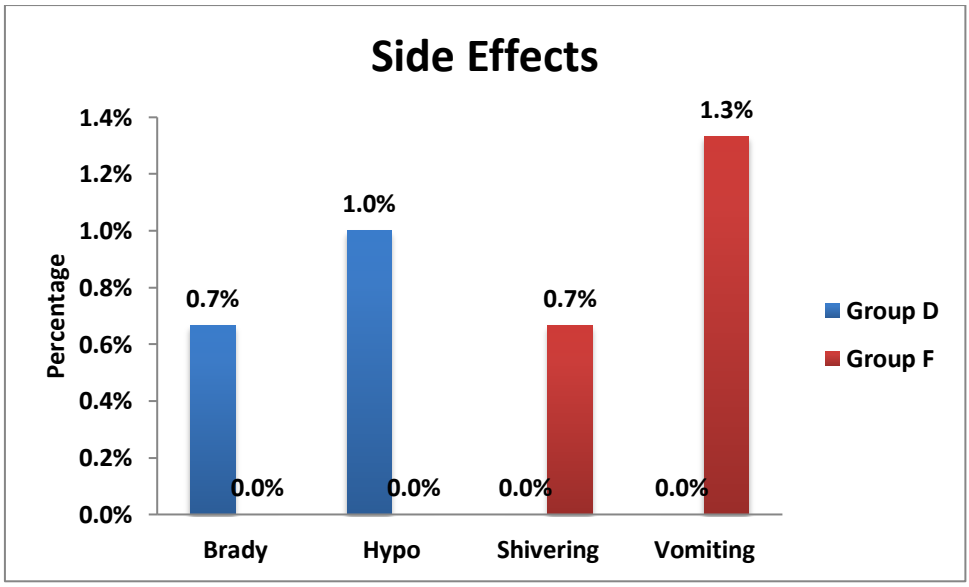


TABLE 8: DISTRIBUTION OF RAMSAY SEDATION SCORE BETWEEN STUDY GROUPS

RSS	Group D		Group F		p value
	N	%	N	%	
1	0	0.0%	25	83.3%	<0.001*
2	20	66.7%	5	16.7%	
3	10	33.3%	0	0.0%	
Total	30	100.0%	30	100.0%	

Table 8 Shows distribution of ramsay sedation score among two groups. There was a significant difference in the sedation score between the two groups (p=0.001). In Group F, twenty five patients that is 83.3% have a score of 1. Five patients that is 20% have a score of 2. In Group D, twenty patients that is 66.7% have a score of 2 and ten patients that is 33.3% have score of 3.

FIGURE 18: DISTRIBUTION OF RAMSAY SEDATION SCORE BETWEEN STUDY GROUPS

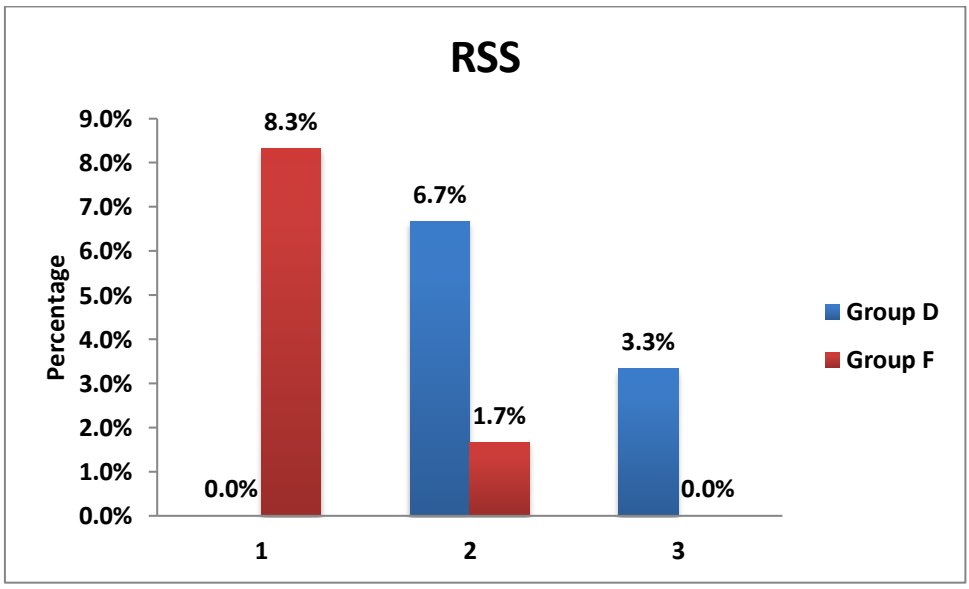
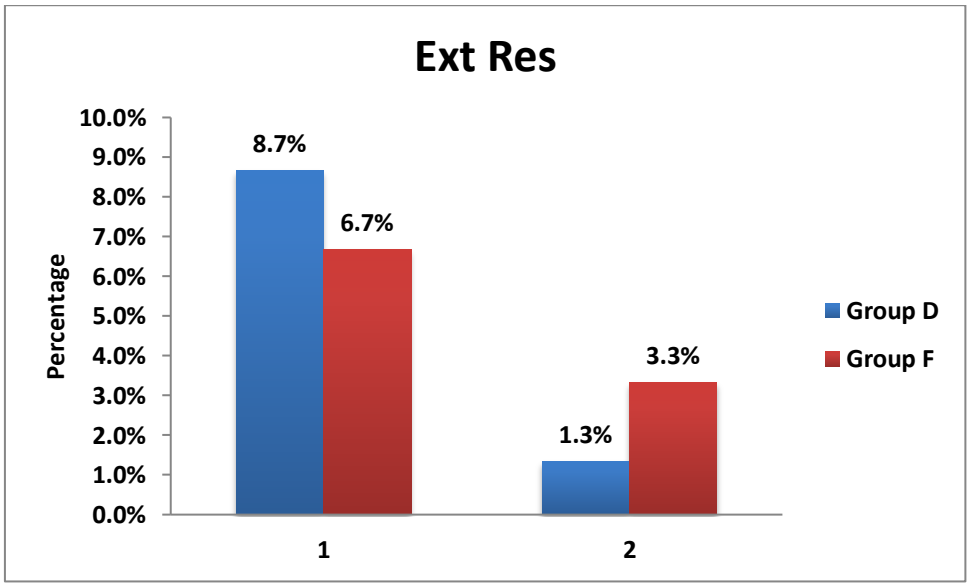


TABLE 9: DISTRIBUTION OF EXTUBATION RESPONSE BETWEEN STUDY GROUPS

Ext Res	Group D		Group F		p value
	N	%	N	%	
1	26	86.7%	20	66.7%	0.067
2	4	13.3%	10	33.3%	
Total	30	100.0%	30	100.0%	

Table 9 Shows extubation quality in both the groups. There was a significant difference in the quality of extubation between the two groups(p=0.067). 86.7% of the patients in Group D could be extubated smoothly whereas 13.3% patients showed minimal coughing at the time of extubation. 66.7% of patients in Group F could be extubated smoothly where as 33.3% patients showed minimal coughing.

FIGURE 19: DISTRIBUTION OF EXT RES BETWEEN STUDY GROUPS



DISCUSSION

DISCUSSION

Most of the general anaesthetic procedures in the modern anaesthetic practice are carried out with endotracheal intubation. Laryngoscopy, tracheal intubation and extubation are considered as the most critical events during administration of general anaesthesia as they provoke transient but marked sympatho-adrenal response manifesting as hypertension and tachycardia.[1,2] The increase in the pulse rate and blood pressure are usually transient, variable and unpredictable. Transient hypertension and tachycardia are probably of no consequence in healthy individuals but either or both may be hazardous to those with hypertension, myocardial insufficiency or cerebrovascular diseases.[3] Pressor response is exaggerated in hypertensive patients even though rendered normotensive preoperatively by antihypertensive medication. Pressor response may result in post-operative myocardial infarction, acute left ventricular failure, intracranial bleed and dysrrythmias in individuals with end organ decompensation. Many methods like use of inhalational anaesthetic agents, lidocaine,[14] opioids,[17]direct acting vasodilators,[11] calcium channel blockers[12,13] and β-blockers[15] have been tried by various authors for blunting haemodynamic responses to extubation. But all such maneuvers had their own limitations. For example, use of halothane was associated with dysrrythmias, calcium channel blockers produced reflex tachycardia, direct acting vasodilators needed invasive hemodynamic monitoring and lidocaine did not give consistent results in blunting the hemodynamic responses to extubation.

Fentanyl, a synthetic opioid, has been reported to reduce the prevalence of coughing during and after extubation and to suppress the sneezing reflex after abdominal hysterectomy and periocular injections.[17] Fentanyl has also been reported to attenuate the cardiovascular responses to tracheal extubation in elective

gynecologic surgery.[18]

Alpha2- agonists like dexmedetomidine[19,20] decrease the sympathetic outflow and noradrenergic activity, thereby counteracting hemodynamic fluctuations occurring at the time of extubation due to increased sympathetic stimulation..

This study was undertaken to compare the effect of intravenous fentanyl 0.5 μg/kg with dexmedetomidine 0.4 μg/kg on attenuation of hemodynamic responses and airway reflexes during extubation.

The present study was done in 60 patients, planned for various elective surgical procedures under general anaesthesia. Patients were selected after thorough preoperative evaluation. Patients with cardiac, pulmonary disease, first, second and third degree heart block, anticipated difficult airway, pathology of oropharyngeal tract, pregnant women and obese patients (BMI > 35kg/m^2) are excluded from the study. Patients were divided into two groups, Group D and Group F, 30 in each group. In both the groups there was no statistical difference with respect to their age, sex, ASA grading, preoperative heart rate and blood pressure.

The premedication, induction agent, muscle relaxant and maintenance agent were standardized for both groups. About 15 minutes prior to extubation, inhalational agent was stopped and Group D patients received 0.4 μg/kg body weight dexmedetomidine diluted to 20ml in normal saline infused intravenously over 15 minutes using infusion pump while Group F patients received 0.5μg/kg body weight fentanyl diluted to 20ml in normal saline infused intravenously over 15 minutes using infusion pump. After onset of spontaneous breathing, intravenous neostigmine 0.05mg/kg and glycopyrrolate 0.01mg/kg was administered to antagonize the effect of residual muscle relaxants. Patients were extubated when extubation criteria were fulfilled. HR, SBP, DBP, MAP were recorded just before reversal, during extubation,

1min, 5min, 10min and 15min of tracheal extubation. The HR in Group D did not show a significant raise at extubation compared to 1min of drug administration, and any time in post extubation period. Though there was a raise in HR at extubation and 1min after extubation, the raise in HR was significantly below the baseline HR. This observation was in concurrence with the study done by Rani P *et al*[71], where the HR in the dexmedetomidine group remained below the baseline value at all the time intervals following extubation. The raise in the HR that occurred during extubation and 1min after extubation in Group D was less compared to the raise in HR in Group F. In Group F there was a significant raise in HR compared to baseline value. The raise HR in Group F was more persistent than the Group D. This is in accordance with the study done by Rani P *et al*[71].

Bradycardia was observed in two patients at 1min and 2min after giving IV dexmedetomidine in Group D, but none of the patients required treatment. No patients in Group F developed bradycardia. These results correlate with the study done by Bindu *et al*[64]. The study done by Aksu R *et al*[62] also found that the incidence of bradycardia was higher in Group D compared to Group F which correlates with this study. In this study the SBP increased in the first 1min after the dexmedetomidine was given and returned to normal after 2min. This is because the effect of α-2 agonists on the hemodynamics is biphasic, an immediate increase in systemic arterial pressure which is mediated by stimulation of peripheral α-2B receptor followed by a longer lasting reduction in pressure caused by stimulation of α-2 adrenoceptor in central nervous system. SBP decreased minimally after 1min in fentanyl group.

Aksu R *et al*[62] and Rani p *et al*[71] observed similar increase in SBP after the initial administration of dexmedetomidine. We observed that at extubation SBP was significantly low in Group D and was 24mmHg less than SBP measured just before

reversal. While in Group F, SBP at extubation was significantly high and was 25mmHg greater than the SBP measured just before reversal. Maximum increase in SBP occurred at 1min after extubation in both the groups. In Group D though there was an increase in SBP at 1min after extubation it was 14mmHg less than just before reversal value. In Group F the increase in SBP was 29 mmHg greater than the just before reversal value. Dexmedetomidine attenuated the increase in SBP to greater degree than fentanyl.

In Group D, DBP at extubation was significantly low and is 9 mmHg less than just before reversal value. In Group F at extubation the DBP was significantly high compared to Group D.

Maximum increase in DBP occurred at 1 min after extubation in both groups but it was significantly high in Group F compared to Group D. These observations correlates with the observations made by Nishina K *et al*[19].

In our study the MAP increased in the first 1 min after the dexmedetomidine was given and returned to normal after 2 min. This is because the effect of α-2 agonists on the hemodynamics is biphasic. MAP also increased after 1min in fentanyl group but the difference is statistically not significant.

Similar observation was made by Rani P *et al*[71] wherein they found initial transient raise in MAP in 20% of cases after IV dexmedetomidine. In another study Aksu R *et al*[62] also observed similar increase in MAP after the initial administration dexmedetomidine.

We observed that at extubation MAP was significantly low (80.1) in Group D and is 14mmHg less than the baseline MAP. While in Group F, MAP at extubation was significantly high (114.5) and is 23 mmHg greater than MAP measured just before reversal. Maximum increase in MAP occurred at 1 min after extubation in both

the groups. In Group D compared to the MAP measured just before reversal, the increase in MAP was 6 mmHg and in Group F, it was 25 mmHg. Dexmedetomidine attenuated the increase in MAP to greater degree than fentanyl. MAP remained below the just before reversal value till 15 min after extubation in Group D, while in Group F it reached just before reversal value 10 min after extubation. These results correlate with the studies conducted by Tao J *et al*[18] they found that dexmedetomidine 0.5µg/kg administered 5 min before the end of surgery stabilized hemodynamics. Jain D *et al*[61] carried out a study on the effect of dexmedetomidine on the stress response to extubation and inferred that bolus of drug administered before reversal provided hemodynamic stability that may prove beneficial for cardiac patients.

In this study Hypotension was seen in three patients in dexmedetomidine group.

Hypotension was managed with IV fluids. None of the patients required vasopressors for the correction of hypotension. In Fentanyl group no patients had hypotension. These results correlate with Guler G *et al*[20] study. They suggested that single dose of dexmedetomidine 0.5µg/kg given IV over 60 sec before tracheal extubation attenuated airway-circulatory reflexes during extubation . In the same study one patient had bradycardia and three had hypotension.

Sedation in this study was assessed using Ramsay sedation scale[71]. Following extubation significant number (66.7 %) of patients in Group D were co-operative , oriented and tranquil (score of 2), 33.3 % patients were drowsy but responding to oral commands (score of 3) as against 83.3 % of patients in Group F were anxious or restless or both (score of 1). This observation was in agreement with the comparative study done between dexmedetomidine and lignocaine by Rani P *et al*[71].

Quality of extubation was evaluated based on cough immediately after extubation, using five point extubation quality scale. Dexmedetomidine by virtue of its analgesic and sedative properties is known to blunt airway reflexes. In our study 86.7% of patients in the Group D had smooth extubation (score 1) as against to only 66.7% patients in Group F. Incidence of coughing was significantly higher in Group F than Group D (33.3 % VS 13.3 %). This observation was concurrence with the study done by Aksu R *et al*[62] where most Patients in dexmedetomidine group could be extubated smoothly with less coughing compared to fentanyl group. The results of Shrirang *et al*[69] study also correlates with this study. Guler G *et al*[20] noted the effect of dexmedetomidine in children undergoing adeno-tonsillectomy where in dexmedetomidine group had significantly decreased incidence and severity of agitation and smooth extubation without any increase in incidence of side effects.

In this study, insignificant number of patients in Group F had vomiting and shivering with none in Group D. The absence of shivering among Group D patients may be due to dexmedetomidine suppressing shivering, possibly by its activity at alpha2B receptors in the hypothalamic thermoregulatory center of the brain. None of the patients in either groups developed undue sedation and respiratory depression. Similar findings were observed by Bindu *et al*[64], Guler G *et al*[20] and Gosai ND *et al*[67] studies also correlate with these findings.

SUMMARY AND CONCLUSION

SUMMARY AND CONCLUSION

This study was carried out at Shri. B.M Patil medical college hospital and research center, vijayapur, Karnataka, in 60 patients who were undergoing various surgical procedures under general anaesthesia. They were divided into two groups of 30 each, Group D and Group F. There was no statistically significant differences in both the groups respect to age, sex and ASA physical status.

Group D (Dexmedetomidine)

Intravenous dexmedetomidine 0.4 μg/kg body weight diluted to 20 ml in normal saline was infused over 15 minutes prior to completion of surgery using infusion pump.

Group F (Fentanyl)

Intravenous fentanyl 0.5 μg/kg body weight diluted to 20 ml in normal saline, infused over 15 minutes prior to completion of surgery using infusion pump.

This study showed that:

1. The heart rate increased in both the groups during extubation but the increase was more in Group F patients.
2. Group D attenuated the increase in blood pressure to a greater degree than Group F.
3. The airway response (coughing) was better attenuated in Group D than Group F.
4. The patients in Group D were drowsy but responding to verbal commands when compared to Group F.
5. The incidence of bradycardia and hypotension though minimal is present in Group D, which was easily managed.

CONCLUSION

From the data and statistical analysis we conclude that, compared to fentanyl 0.5 μg/kg, dexmedetomidine 0.4μg/kg administered intravenously before extubation attenuates hemodynamic stress response and airway reflexes to a greater extent allowing smooth and easy tracheal extubation , thereby providing comfortable recovery.

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ANNEXURES

ANNEXURE - I

ETHICAL CLEARANCE CERTIFICATE

B.L.D.E (Deemed to be University)
SHRI.B.M.PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE
VIJAYAPUR – 586103

IEC/NO: 286/2018
17-11-2018

INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 13-11-2018 at 03-15 PM scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.

Title : A randomized comparative study between dexmedetomidine and fentanyl on attenuating stress response and airway response to tracheal extubation.

Name of P.G. Student : Dr Nikhila Tumma.
Department of General Anaesthesiology

Name of Guide/Co-investigator: Dr. D.G.Talikoti, Professor & HOD Department of Anaesthesiology.

DR RAGHAVENDRA KULKARNI
CHAIRMAN
Institutional Ethical Committee
BLDEU's Shri B.M. Patil
Medical College,BIJAPUR-586103.

Following documents were placed before E.C. for Scrutinization:

1) Copy of Synopsis/Research Project
2) Copy of informed consent form.
3) Any other relevant documents.

B.L.D.E.Us, SHRI.B.M.PATIL MEDICAL COLLEGE, VIJAYAPUR – 586103

INSTITUTIONAL ETHICAL COMMITTEE, Date : 13-11-18

1. Name of UG/PG Student/Researcher : Dr Nikkila Tumma
2. Department : Anaesthesiology
3. Title : A Randomised - - - - - - - - - extubation
4. Guide/Co-Guide/Principal Researcher : Dr D.G. Jalikatti
5. Date of Admission (PG Only) : May 2018

Observation:

OK

I.E.C. Remarks: Ethical clearance accorded/be chairman after corrected revised version is submitted by stipulated time.

1. Any alternation in Synopsis protocol should be intimated to E.C. in writing for review and approval.
2. Any adverse effects to subject of the study should be intimated in writing to E.C.
3. If study is stopped or an included patient is out of study inform E.C. the same with reason.

Signature of the Committee Members:

1. DR RAGHAVENDRA KULKARNI
2. DR TEJASWINI VALLABHA
3. DR.B.R.YELIKAR
4. DR P.B.JAJU
5. DR CHANDRASHEKHAR BHUYYAR
6. DR PRANESH JAHAGIRDAR
7. SHRI.SURESH HAKKI
8. DR G V KUKARNI
9. DR.MOHD SHANNAWAZ
10. DR RAGHAVENDRA RAO

ANNEXURE – II

SAMPLE INFORMED CONSENT FORM

B.L.D.E.'S (DEEMED TO BE UNIVERSITY)

SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPURA– 586103, KARNATAKA

TITLE OF THE PROJECT: "A RANDOMISED COMPARATIVE STUDY BETWEEN DEXMEDETOMIDINE AND FENTANYL ON ATTENUATING STRESS RESPONSE AND AIRWAY RESPONSE TO TRACHEAL EXTUBATION"

PRINCIPAL INVESTIGATOR : **Dr. NIKHILA TUMMA**
Department of Anaesthesiology
BLDE'S (Deemed To Be University)
Shri. B.M Patil Medical College Hospital & Research Centre, Sholapur Road,
Vijayapura.
Email id : nikhila1048@gmail.com

PG GUIDE : **Dr.D G TALIKOTI**
Professor,
Department of Anaesthesiology.
BLDE'S (Deemed To Be University)
Shri B.M Patil Medical College Hospital & Research Centre, Sholapur Road,
Vijayapura.
Email id : dtalikoti@yahoo.co.in

PURPOSE OF RESEARCH

I have been informed that this study is **"A RANDOMISED COMPARATIVE STUDY BETWEEN DEXMEDETOMIDINE AND FENTANYL ON ATTENUATING STRESS RESPONSE AND AIRWAY RESPONSE TO TRACHEAL EXTUBATION"**

I have been explained about the reason for doing this study and selecting me/my ward as a subject for this study. I have also been given free choice for either being included or not in the study.

PROCEDURE:

I understand that I will be participating in the study **"A RANDOMISED COMPARATIVE STUDY BETWEEN DEXMEDETOMIDINE AND FENTANYL ON ATTENUATING STRESS RESPONSE AND AIRWAY RESPONSE TO TRACHEAL EXTUBATION"**

BENEFITS:

I understand that my wards participation in this study will help in finding out: **"A RANDOMISED COMPARATIVE STUDY BETWEEN DEXMEDETOMIDINE AND FENTANYL ON ATTENUATING STRESS RESPONSE AND AIRWAY RESPONSE TO TRACHEAL EXTUBATION"**

CONFIDENTIALITY:

I understand that medical information produced by this study will become a part of this Hospital records and will be subjected to the confidentiality and privacy regulation of this hospital.

If the data are used for publication in the medical literature or for teaching purpose, no names will be used and other identifiers such as photographs and audio or video tapes will be used only with my special written permission. I understand that I may see the photograph and videotapes and hear audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. **Dr. NIKHILA TUMMA** is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

If during this study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me. And that a copy of this consent form will be given to me for keep for careful reading.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital.

I also understand that **Dr.NIKHILA TUMMA** will terminate my participation in this study at any time after he has explained the reasons for doing so

and has helped arrange for my continued care by my own physician or therapist, if this is appropriate.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me/my ward, resulting directly due to my participation in this study, such injury will be reported promptly, then medical treatment would be available to me, but no further compensation will be provided.

I understand that by my agreement to participate in this study, I am not waiving any of my legal rights.

I have explained to _____ the purpose of this research, the procedures required and the possible risks and benefits, to the best of my ability in patient's own language.

Date: **DR.NIKHILA TUMMA**

(Investigator)

Patient's signature Witness to above signature

STUDY SUBJECT CONSENT STATEMENT:

I confirm that **Dr. NIKHILA TUMMA** has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own language.

I have been explained all the above in detail in my own language and I understand the same. Therefore I agree to give my consent to participate as a subject in this research project.

_____ _____

(Participant) Date

_____ _____

(Witness to above signature) Date

ANNEXURE – III

SCHEME OF CASE TAKING

PROFORMA

STUDY: "A RANDOMISED COMPARATIVE STUDY BETWEEN DEXMEDETOMIDINE AND FENTANYL ON ATTENUATING STRESS RESPONSE AND AIRWAY RESPONSE TO TRACHEAL EXTUBATION "

PATIENT DETAILS:

DATE:

I. Name: Age/ Sex: I.PNo:

Ward:

Group allotted by randomization: Group D / Group F

II. 1. Type of the surgery:

Duration of surgery:_____ (min)

2. Indication:

III. Significant History:

IV. General Physical Examination:

Pallor: Icterus: Cyanosis: Clubbing: Koilonychia:

Lymphadenopathy: Oedema: Teeth: Dentures:

V. Vital Parameters

Pulse: Blood Pressure: Respiratory Rate: Temperature:

VI. Systemic Examination

1. CVS: 2.RS: 3. CNS:

4.Per Abdomen:

VII. Airway Assessment:

Mallampati Grade: Cervical Spine:

Mouth opening: Neck Movement:

VIII. ASA Grade:

IX. Investigation :

Hemoglobin: CBC: Blood Urea: ECG:

S.Creatinine: Urine Routine: Chest Xray:

Hemodynamic Parameters of Dexmedetomidine (Group D) and Fentanyl (Group F) :

	HR	SBP	DBP	MAP
Just before Reversal				
During Extubation				
1 min of Tracheal extubation				
5 min of tracheal extubation				
10 min of tracheal extubation				
15 min of tracheal extubation				

Five point extubation quality scale :

Score	**1**	**2**	**3**	**4**	**5**
Dexmedetomidine (Group D)					
Fentanyl (Group F)					

Ramsay sedation scale at the end of 10 minutes of tracheal extubation:

Sedation score	**1**	**2**	**3**	**4**	**5**	**6**
Dexmedetomidine (Group D)						
Fentanyl (Group F)						

Incidence of complication in two groups:

	Dexmedetomidine (Group D)	Fentanyl (Group F)
Bradycardia (< 60bpm)		
Hypotension (MAP<60mmHg)		
Vomiting		
Laryngospasm		
Respiratory Depression		
Delayed arousal		

BIO-DATA OF THE GUIDE

GUIDE NAME	:	DR. D G TALIKOTI
DATE OF BIRTH	:	14.07.1955
EDUCATION	:	M.B.B.S – 1979 M.R.M.C GULBARGA KARNATAKA UNIVERSITY,DHARWAD M.D. ANAESTHESIOLOGY – 1990 V.M.M.C SHOLAPUR. SHIVAJI UNIVERSITY, KHOLAPUR.
DESIGNATION	:	PROFESSOR, DEPARTMENT OF ANAESTHESIOLOGY.
TEACHING	:	UG TEACHER – 33 YEARS. PG TEACHER – 25 YEARS.
ADDRESS	:	PROFESSOR, DEPARTMENT OF ANAESTHESIOLOGY, B.L.D.E.'S(DEEMED TO BE UNIVERSITY) SHRI BM PATIL MEDICAL COLLEGE & RESEARCH CENTRE, VIJAYAPURA, KARNATAKA.
PHONE	:	(08352)262770 EXT 2052.
MOBILE NUMBER	:	9844260391.

INVESTIGATOR

NAME	:	DR. NIKHILA TUMMA
QUALIFICATION	:	M.B.B.S (March 2015) B.L.D.E.'S (DEEMED TO BE UNIVERSITY), SHRI BM PATIL MEDICAL COLLEGE , HOSPITAL & RESEARCH CENTRE , VIJAYAPURA, KARNATAKA.
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KEY TO MASTER CHART

AEX	:	At Extubation
ACDF	:	Anterior cervical discectomy and fusion
EXP	:	Exploratory
EDH	:	Extradural hemorrhage
EXT.RES	:	Extubation response
F	:	Female
IP. No:	:	Inpatient Number
M	:	Male
LAVH	:	Laproscopic Assisted Vaginal Hysterectomy
Lt	:	Left
Lap	:	Laparoscopic
ORIF	:	Open reduction and internal fixation.
PCNL	:	Percutaneous nephrolithotomy.
Rt	:	Right
Sr.No:	:	Serial number.
TAH	:	Total Abdominal Hysterectomy
JBR	:	Just before reversal.

MASTER CHART

GROUP D (DEXMEDITOMIDINE)

S.NO:	NAME	AGE	SEX	IP.NO:	TYPE OF SURGERY	HEART RATE						SYSTOLIC BLOOD PRESSURE						DIASTOLIC BLOOD PRESSURE						MEAN ARTERIAL BLOOD PRESSURE						RSS	SE	Ext resp
						JBR	AEX	1min	5min	10min	15min	JBR	AEX	1min	5min	10min	15min	JBR	AEX	1min	5min	10min	15min	JBR	AEX	1min	5min	10min	15min			
1	RAJAKUMARI	38	F	14979	MASTOIDECTOMY	79	78	88	86	82	80	102	104	119	109	108	110	64	50	79	58	76	78	76	68	92	75	86	88	2	Hypo	2
2	SUBHAS	59	M	14111	TONSILLECTOMY	102	108	106	106	104	101	125	88	119	116	117	119	78	78	87	80	80	81	93	80	97	88	92	93	2		1
3	ZASIM	39	F	8043	L3-L4 LAMINECTOMY	70	84	92	78	72	70	119	120	114	103	103	108	70	77	88	72	68	70	87	92	96	82	79	82	3		1
4	SHRISHAIL	23	M	7659	C5-C6 ACDF	80	83	88	84	83	83	120	130	128	107	93	103	88	99	90	75	70	71	80	90	102	80	77	81	2	Hypo	1
5	SOMAWWA	40	F	9243	LEFT PCNL	71	86	91	93	97	95	113	105	105	82	78	86	86	80	86	55	56	60	88	80	92	64	63	68	2		1
6	AKASH	26	M	9030	CRANIOPLASTY	79	84	90	83	79	77	114	107	114	118	110	111	83	82	86	78	80	78	84	90	95	90	90	89	3		1
7	ASHOK	25	M	12643	ORIF WITH PLATING	67	78	79	72	68	69	120	125	129	101	98	99	58	74	60	65	68	68	78	91	83	77	78	78	3		1
8	BABU	48	M	9337	EXP LAPAROTOMY	62	77	80	78	76	76	110	112	115	93	92	95	75	80	83	65	66	65	86	90	93	74	74	75	3	Brady	1
9	KASHIMBI	45	F	16738	LAP.CHOLECYSTECTOMY	60	90	95	86	69	71	103	102	103	105	88	95	66	65	64	77	57	60	79	77	77	86	65	71	2		2
10	SIDALINGAPPA	52	M	7910	MASTOIDECTOMY	80	88	74	80	76	80	99	84	100	100	102	105	73	67	80	75	78	75	81	78	94	83	86	85	2		1
11	ASHOK	57	M	13809	LAP.APPENDICECTOMY	90	101	90	92	90	90	113	98	102	102	99	101	82	78	78	73	72	71	90	84	86	78	81	81	3		1
12	MAHADEVI	50	F	2541	LAP.CHOLECYSTECTOMY	68	90	92	100	80	82	92	92	98	97	106	104	52	69	76	60	78	73	66	78	83	72	87	83	3		1
13	RAHUL	48	M	6257	LAP.APPENDICECTOMY	75	86	90	84	77	77	102	92	101	97	106	103	82	65	73	71	76	72	88	74	82	79	86	82	2		1
14	SALIMABEGUM	42	F	2050	LAP.CHOLECYSTECTOMY	88	90	78	89	92	93	120	91	94	77	104	100	72	64	64	50	66	64	89	73	74	59	78	76	2		1
15	NAGAPPA	45	M	1585	LAP.APPENDICECTOMY	99	109	113	82	76	78	129	99	105	117	89	93	86	65	83	83	61	65	90	76	90	90	70	74	2		1
16	SUNANDA	56	F	9301	LAP.CYSTECTOMY	72	80	92	74	73	74	112	111	118	97	93	98	78	75	82	70	66	70	90	87	94	79	75	79	2	Hypo	1
17	SUDHABHAI	58	F	13321	HEMI- THYROIDECTOMY	82	90	95	89	80	80	112	100	106	108	109	110	68	82	88	70	72	70	82	88	94	82	84	83	2		1
18	BASAMMA	35	F	8188	HEMI- THYROIDECTOMY	75	71	85	70	69	71	113	85	120	90	88	92	80	69	90	64	62	64	90	74	100	78	70	73	2		1
19	BASAVARAJ	38	M	8713	EXP LAPAROTOMY	60	67	72	71	77	76	100	111	102	109	115	113	66	72	76	78	77	78	78	85	84	88	89	89	2		1
20	YALLAWWA	30	F	8098	LAP.CHOLECYSTECTOMY	87	92	90	70	77	79	109	100	110	112	98	102	76	70	76	66	60	63	80	80	87	80	72	76	2		2
21	SANDEEP	46	M	20827	LEFT SEPTOPLASTY	73	70	72	70	68	69	111	100	104	97	95	100	65	71	65	60	62	60	81	80	78	72	73	73	2		1
22	GURUSIDAPPA	28	M	17585	LAP. APPENDICECTOMY	77	82	88	81	77	76	102	96	122	101	101	103	74	60	91	77	76	75	87	72	90	85	84	84	2		1
23	SANAMMA	42	F	41067	L4S1 PEDICLE FIXATION	57	63	70	79	70	71	109	104	111	117	116	110	74	72	78	91	91	86	85	82	89	89	99	94	3		1
24	MAHESHWARI	37	F	42611	LAP.CHOLECYSTECTOMY	70	88	90	78	78	79	117	90	108	101	97	100	84	73	74	67	70	72	90	78	85	78	79	81	3		1
25	SUKAMMA	35	F	47430	LAP.APPENDICECTOMY	62	65	70	66	67	67	97	108	109	93	94	99	65	82	84	69	70	71	75	90	92	77	78	80	2	Brady	1
26	HANAMAWWA	55	F	12120	LAVH	79	78	82	90	86	88	102	104	108	119	124	120	64	40	76	79	60	64	76	61	88	90	81	82	3		1
27	IRANNA	34	M	42213	CRANIOPLASTY	78	77	82	75	73	74	81	77	85	108	106	108	47	47	62	70	79	81	60	57	69	82	88	90	2		1
28	MEENAKSHI	57	F	7611	C5-C6 ACDF	76	110	117	105	92	93	122	117	134	135	135	135	68	68	80	71	72	73	87	84	98	92	93	93	3		1
29	VITTAL	47	M	40327	RIGHT EDH EVALUATION	69	70	68	70	76	79	105	107	112	95	95	98	75	75	72	80	70	91	86	89	80	85	79	80	2		2
30	VAISHALI	42	F	43083	LAP.CHOLECYSTECTOMY	68	77	82	80	80	82	92	92	98	97	97	106	52	52	76	60	78	79	66	76	83	77	87	87	2		1

GROUP F (FENTANYL)

S.NO:	NAME	AGE	SEX	IP NO:	TYPE OF SURGERY	HEART RATE						SYSTOLIC BLOOD PRESSURE						DIASTOLIC BLOOD PRESSURE						MEAN ARTERIAL PRESSURE						RSS	SE	Ext resp
						JBR	AEX	1min	5min	10min	15min	JBR	AEX	1min	5min	10min	15min	JBR	AEX	1min	5min	10min	15min	JBR	AEX	1min	5min	10min	15min			
1	SHIVAPPA	45	M	14669	ORIF WITH PLATING	96	116	118	104	92	90	121	136	140	124	126	118	75	91	95	75	77	73	90	106	110	91	93	88	1		1
2	PARVEEN	45	M	7223	D3 - D5 FIXATION	84	98	102	96	90	84	127	141	149	132	128	119	81	104	101	87	79	73	96	116	117	102	95	88	1		1
3	JYOTHI	44	F	29652	HEMITHYROIDECTOMY	103	112	119	111	104	96	136	150	152	126	121	118	75	90	97	81	79	70	95	110	115	96	93	86	1		1
4	NIMBHAL	25	F	7459	EXP. LAPAROTOMY	105	113	117	110	101	94	125	149	153	125	123	121	81	92	96	83	78	73	95	111	115	97	93	89	1	Vomiting	2
5	SHANTAMMA	40	F	7263	THECOPERITONEALSHUNT	84	98	101	96	87	81	128	152	156	127	120	120	79	96	99	79	75	68	95	114	118	95	90	85	2		1
6	KESHAV	31	M	27161	ACDF	97	105	110	103	94	92	134	150	144	126	123	121	77	93	98	85	78	74	96	112	113	98	93	88	1		1
7	MAHADEVI	35	F	30863	HERNIA MESH REPAIR	84	96	99	93	84	79	118	142	139	116	114	116	76	84	90	84	77	70	90	103	106	94	89	85	1		1
8	MITHUN	49	M	30587	ORIF WITH PLATE FIXING	83	120	123	114	98	90	125	147	144	121	118	119	85	90	94	87	84	79	98	109	110	98	95	92	1	Vomiting	1
9	VITTAL	46	M	31697	SUBTOTALTHYROIDECTOMY	99	121	126	108	91	86	130	151	149	118	115	120	82	104	100	80	81	77	98	119	116	92	92	91	1		2
10	DEEPA	35	F	7772	LAP. CHOLECYSTECTOMY	83	109	114	104	86	79	136	160	158	132	125	123	93	115	110	82	79	78	107	130	126	98	94	93	2		1
11	SWARNA	37	F	42410	DIAGNOSTIC LAP	96	106	110	104	98	95	140	158	158	126	121	118	73	95	96	75	69	67	95	116	117	98	86	84	1		2
12	DEVAPPA	32	M	18846	LAP. FUNDOPLICATION	93	119	125	107	96	92	111	135	140	1233	116	114	80	99	101	90	82	77	90	111	114	101	93	89	1	Shivering	2
13	BHASKAR	42	M	41430	LAP. CHOLECYSTECTOMY	91	122	127	103	93	89	128	152	154	128	120	116	85	100	94	79	70	71	99	117	114	95	87	86	1		1
14	SIDRAM	47	M	30994	MESH HERNIOPLASTY	95	117	119	115	107	96	120	153	155	125	115	113	97	110	108	90	88	85	104	123	124	101	97	94	1		1
15	PREMA	45	F	19470	TRANSPEDICULAR FIXATION	86	108	111	95	90	86	121	132	135	122	112	109	71	100	88	70	66	60	87	110	103	87	81	76	1		2
16	YALLAWWA	35	F	15130	L4-L5 FIXATION	90	109	113	91	88	83	120	140	144	126	117	118	85	98	92	81	79	70	96	112	109	96	91	86	1		1
17	DONDABAI	42	F	16855	LAP.FUNDOPLICATION	99	115	117	98	95	90	131	144	146	127	112	111	73	96	99	79	77	68	92	112	114	105	88	82	2		1
18	LALITHABAI	45	F	17972	LAP CHOLYCYSTECTOMY	90	107	111	97	92	88	137	152	154	127	114	106	77	91	95	81	76	70	97	111	114	97	89	82	1	Vomiting	2
19	SRIDHAR	28	M	20690	LAP.APPENDICECTOMY	105	116	120	113	104	100	117	130	133	119	110	108	86	110	104	80	78	72	96	116	113	93	88	84	1		1
20	YALLAPPA	42	M	42019	CRANIOTOMY	87	105	112	100	91	87	127	150	155	128	119	117	81	101	106	79	70	69	96	117	122	95	86	85	1		1
21	LAXMIBAI	35	F	29657	FIBROADENOMA EXCISION	107	123	127	114	106	99	121	146	147	125	114	109	85	90	98	73	71	67	97	108	114	90	85	81	1		1
22	MAHANTESH	48	M	28770	JEJUNOSTOMY	96	118	123	109	94	90	129	144	146	129	121	115	79	100	99	80	75	77	95	114	115	96	90	89	2	Vomiting	1
23	SIDAPPA	25	M	29331	C2-C6 LAMINECTOMY	95	118	124	102	94	91	127	154	157	121	108	107	90	105	99	83	80	79	102	120	118	97	89	88	1		2
24	SUBHADRA	38	F	29236	MESH HERNIPLASTY	94	119	122	98	91	88	140	152	155	126	119	118	93	104	101	84	79	77	108	121	117	98	92	90	1		1
25	GANISHYA	35	F	15176	CRANIOPLASTY	87	114	120	108	96	87	133	153	158	127	115	111	81	98	104	81	80	75	98	116	122	96	91	87	12		2
26	JAKAWWA	45	F	13394	TOTAL THYROIDECTOMY	91	115	118	100	98	93	132	162	163	131	116	115	84	96	98	84	79	80	100	118	119	99	91	91	1	Shivering	2
27	KUPENDRA	47	M	13816	CRANIOTOMY	95	122	128	109	92	86	127	150	154	129	120	117	93	106	108	82	79	81	104	120	123	97	92	93	1		1
28	CHANDRAPPA	32	M	13547	C5-C6 ACDF	81	116	121	104	89	78	132	152	158	132	128	122	96	102	103	90	87	82	108	118	121	104	100	95	1		1
29	KASTURIBAI	45	F	48215	D10 LAMINECTOMY	94	126	131	117	108	96	130	156	161	128	125	123	83	92	94	79	75	70	98	113	116	95	91	87	2		2
30	JUBRAYIL	49	M	4162	LAP.APPENDICECTOMY	86	114	117	93	89	81	121	146	151	122	120	118	89	97	100	81	82	75	99	113	117	94	97	92	1		1