"COMPARATIVE EVALUATION OF DEXMEDETOMIDINE AND FENTANYL INFUSION ON HAEMODYNAMIC RESPONSE IN PATIENTS UNDERGOING ELECTIVE SURGERY UNDER GENERAL ANAESTHESIA"

By

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IN

ANAESTHESIOLOGY

Under the Guidance of

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Date : **Dr G N S SRAVANTHI**

Place : Bangalore

ABSTRACT

COMPARATIVE EVALUATION OF DEXMEDETOMIDINE AND FENTANYL INFUSION ON HAEMODYNAMIC RESPONSE IN PATIENTS UNDERGOING ELECTIVE SURGERY UNDER GENERAL ANAESTHESIA

BACKGROUND AND OBJECTIVES:

The procedures like laryngoscopy and intubation evoke stress response in patients undergoing elective surgeries under general anaesthesia. The aim of the study was to compare and evaluate the effect of dexmedetomidine and fentanyl infusion on hemodynamic response during intubation and extubation. The study also evaluates the effect of intraoperative infusion on postoperative analgesia.

MATERIALS AND METHODS:

In this randomised prospective study, 90 patients belonging to American Society of Anaesthesiologists class I/II, Scheduled for surgeries with duration of approx. 90mins were randomly divided into two groups. Group A received IV Dexmedetomidine 1µg/kg as loading dose over 10mns prior to induction followed by infusion at 0.5µg/kg/hr until 10mins prior to extubation.Group B received IV Fentanyl 1µg/kg as loading dose over 10mins prior to induction followed by infusion at 0.5 µg/kg/hr until 10mins prior to extubation. The significance of the difference in quantitative measures was done by using student‘t’ test. ‘Chi’ square test was used to compare the difference in proportion. $P<0.05$ was considered as statistically significant

RESULTS:

With respect to hemodynamic response during intubation and extubation, Group A has shown significantly lower HR, SBP, DBP and MAP in comparison to Group B. Post-operative Visual Analogue Score for first 24hrs was significantly less in Group A compared to Group B.

CONCLUSION:

Dexmedetomidine is better and safe alternative to fentanyl in attenuating hemodynamic response during both intubation and extubation.

KEY WORDS: Dexmedetomidine,Extubation, Fentanyl, General anaesthesia, Hemodynamic response, Intubation, Post-operative pain.

ABBREVATIONS

HR	Heart Rate
Bpm	Beats Per Minute
PR	Pulse Rate
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
NIBP	Non-Invasive Blood Pressure
MAP	Mean Arterial Pressure
ECG	Electrocardiogram
SPO_2	Peripheral capillary oxygen saturation
CVS	Cardiovascular system
PA	Per Abdominal
RS	Respiratory System
CNS	Central Nervous System
VAS	Visual Analogue Scale
Iv	Intravenous
ASA-PS	American Society of Anaesthesiologists – Physical Status
D5W	Dextrose 5% in water
NS	Normal Saline
ICU	Intensive Care Unit
ACTH	Adrenocorticotropin hormone

IL	Interleukin
CBC	Complete Blood Count
HB	Haemoglobin
BT	Bleeding Time
CT	Clotting Time
WBC	White Blood Count
HS	Hora somni- at bedtime
RFT	Renal function tests
i.e.,	That is
µg/mcg	Microgram
Kg	Kilogram
Mm Hg	Millimetre of Mercury
cm	Centimetre
mg	Milligram
ml	Millilitre
mins	Minutes
Secs	Seconds
SD	Standard Deviation
GABA	Gamma Amino Butyric Acid
PACU	Post Anaesthesia Care Unit
FDA	Food and Drug Administration

Tab	Tablet
hr	Hour
$ETCO_2$	Endtidal carbondioxide
No. of	Number of
Approx.	Approximately
Intraop	Intraoperative
Postop	Postoperative
cAMP	Cyclic Adenosinemonophosphate
Sr.Cr	Serum creatinine
RR	Respiratory rate
RBS	Random blood sugar
Na^+	Sodium
K^+	Potassium

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INTRODUCTION

General anaesthesia is the plan of anaesthesia for major head & neck surgeries, neurosurgeries, laparoscopic and dental surgeries. The steps in general anaesthesia include induction, laryngoscopy, intubation and extubation. Laryngoscopy and intubation are associated with sympathetic stimulation and major hemodynamic changes.[1] There was always a need to attenuate the sympathetic response to prevent perioperative stress induced ischemic changes.[2]

Maintenance of anaesthesia is done with inhalational agents. The requirement of volatile anaesthetics depends upon the intraoperative hemodynamic stability.[3] Patients requiring high MAC may take longer time for recovery from anaesthesia and thereby causing delay in extubation.[4] These effects are more pronounced in obese patients. Measures should be taken to minimise the inhalation agent consumption to avoid the untoward effects on the recovery of the patient.

One of the factors contributing for intraoperative hemodynamic instability include inadequate analgesia. Poor control of intraoperative pain may cause hypertension leading to increased bleeding at the surgical site.[5] Analgesia should be taken care of to provide bloodless field for the surgeon.

Extubation also is associated with stress response.[6] Violent extubation may lead to development of pulmonary edema or bleeding from the pack sites especially in case of ENT surgeries.[7] Abrupt increase in blood pressure during extubation may lead to post-operative haematoma in neurosurgery cases.[8] Measures to be followed which lead to smooth extubation.

Post-operative analgesia is also of utmost concern for anaesthesiologist especially in first 24hours.Inappropriate pain management may lead to immobility, deep vein thrombosis, poor rehabilitation and progression to chronic pain.[9]

To combat the above-mentioned problems, several drugs have been used like beta blockers, calcium channel blockers, combined alpha and beta blockers, vasodilators, lignocaine, alpha-2 agonists like clonidine and dexmedetomidine and high doses of opiods.[10] The present study is being conducted to evaluate the efficacy of intraoperative dexmedetomidine and fentanyl infusion on hemodynamic changes during intubation, extubation and postoperative analgesia.

Dexmedetomidine is a highly selective α_2 agonist. It maintains hemodynamic stability through its central sympatholytic action.[11] It provides analgesia without causing respiratory depression. Dexmedetomidine has been extensively used as an adjuvant to general anaesthesia owing to its anaesthetic sparing and sedative properties.[12] However, hypotension and bradycardia remain to be the major side effects associated with it. The aim of this study is to evaluate its efficacy in reducing stress response during intubation and extubation.

Fentanyl is synthetic potent μ receptor agonist.[13] It controls both heart rate and blood pressure responses during intubation and extubation.[14] It requires shorter time to reach its peak analgesic effect. The main side effects include respiratory depression and truncal rigidity.

Present study compares the efficacy of both fentanyl and dexmedetomidine infusion on attenuating the pressor response during intubation and extubation.

AIMS &OBJECTIVES

OBJECTIVES

This prospective randomized controlled study was undertaken from January 2019-June 2020 with the following objectives:

Primary Objective:

- To compare and evaluate dexmedetomidine and fentanyl on hemodynamic response like Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP) in patients during intubation and extubation.

Secondary Objective:

- To assess the inhalational agent requirement throughout the procedure
- To assess the pain in the recovery period by Visual Analogue scale (VAS)

PHARMACOLOGY

PHARMACOLOGY OF DEXMEDETOMIDINE

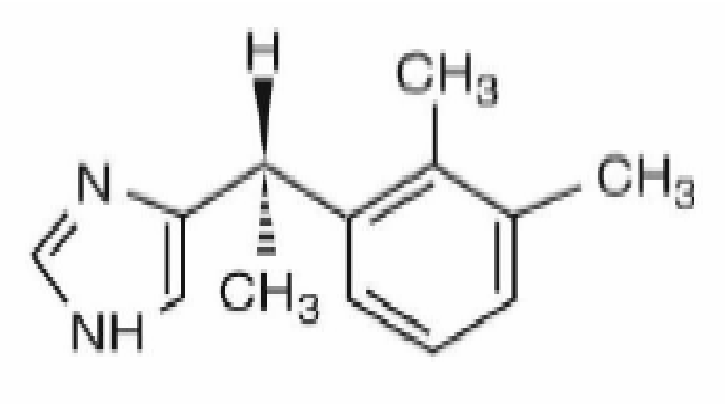

FIGURE NO 1: CHEMICAL STRUCTURE OF DEXMEDETOMIDINE

Medetomidine (4-[1-(2,3-dimethylphenyl) ethyl]-1H-imidazole) is a newly developed sedative/analgesic compound that has potent and selective activity at α_2 – adrenoreceptors.[11]

Dexmedetomidine, an imidazole compound, is the dextro isomer (s-enantiomer) of medetomidine. Its empirical formula and molecular weight are $C_{13}H_{16}N_2HCL$ and 236.7 Da.

Dexmedetomidine has a relatively high ratio of α_2/α_1-activity (1620:1 as compared with 220:1 for clonidine) and, therefore, is considered a full agonist of the α_2 - receptor. This may result in more potent effects of sedation without unwanted cardiovascular effects from α_1 receptor activation.[15]

In 1999, FDA gave approval for dexmedetomidine to be used as short-term sedative analgesic in ICU for sedation and analgesia.[16]

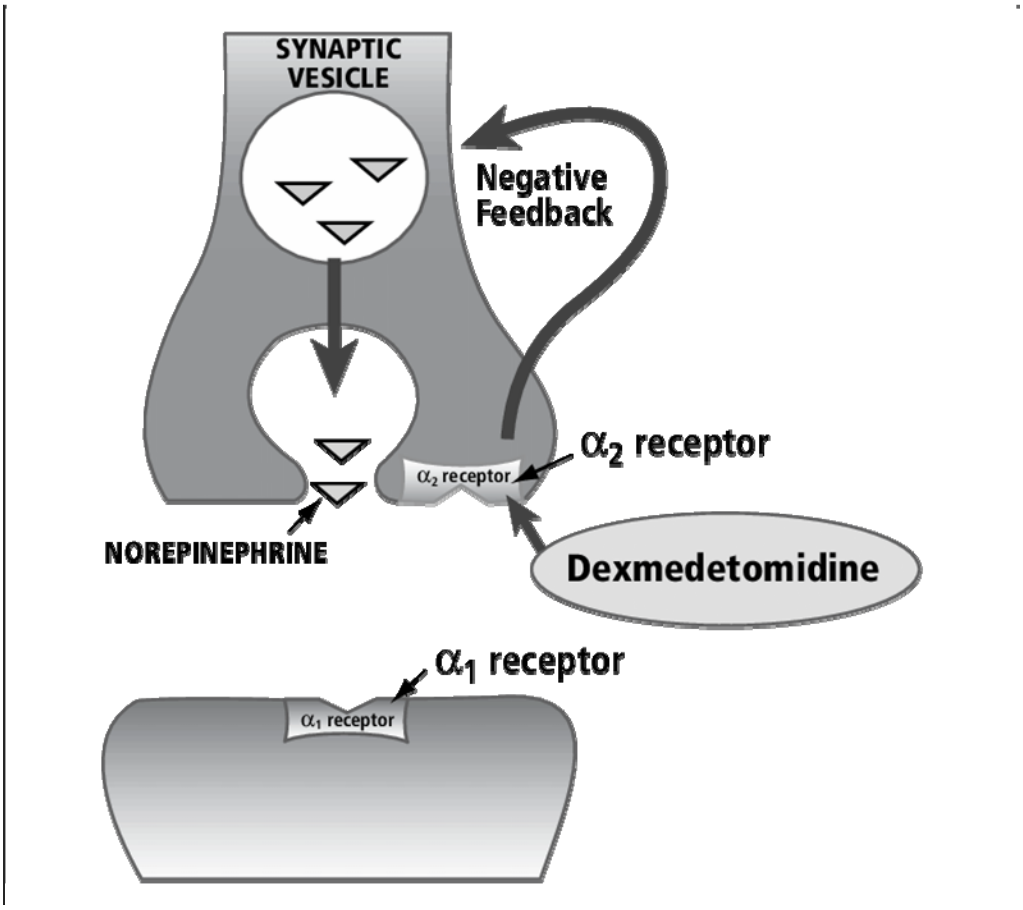

FIGURE NO 2: MECHANISM OF ACTION

Adrenergic receptors were originally differentiated into α and β receptors.Presynaptic α2 receptors may be of the greatest clinical import because they regulate the release of norepinephrine and adenosine triphosphate through a negative feedback mechanism. Presynaptic activation of the α2 adrenoceptor inhibits the release of norepinephrine, terminating the propagation of pain signals. Postsynaptic activation of α2 adrenoceptors in the central nervous system (CNS) inhibits sympathetic activity and thus can decrease blood pressure and heart rate. Combined, these effects can produce analgesia, sedation, and anxiolysis.[9]

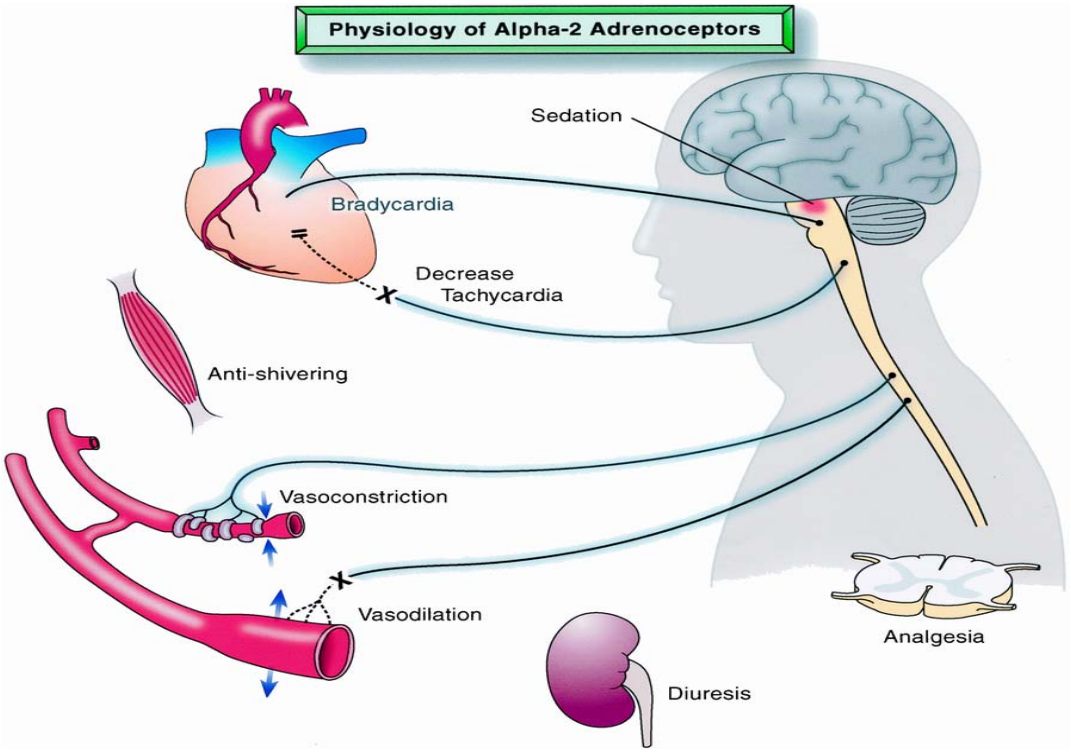

FIGURE NO 3: SITE OF ACTION

The hypnotic and sedative effect of these agents is thought to occur through supraspinal pathways, involving the locus ceruleans (LC). While the antinociceptive response to alpha (2) agonists, given intrathecally, is mediated predominantly in the spinal cord.[17]

Cardiac effect is a decrease in heart rate through vagomimetic action and also through cardio accelerator nerve block. Peripheral vascular effects are vasoconstriction via smooth muscle receptors and vasodilation via sympatholysis. Due to the decrease in the release ofvasopressin and rennin and increase in the release of atrial natriuretic factor there may be diueresis.[18]

The mechanism of the analgesic effects of alpha 2 receptor agonists is modulated by transmission of nociceptive signals including both spinal and

supraspinal sites. It stimulates both presynaptic and post synaptic alpha 2 receptors causing inhibition of firing of nociceptive neurons.[19] The action on

G1-protein-gated potassium channels causes hyperpolarisation of membranes. This mechanism is said to be significant for a receptor inhibitory activity.[20]

An additional important physiologic action attributed to alpha2adrenoreceptor is the decrease in conductance of calcium into cells causing inhibition of secretion of neurotransmitter. This is directly regulated by entry of calcium via the voltage- gated N- type calcium channels and it does not depend on cyclicAMP and protein phosphorylation. This is facilitated by Gproteins. Dexmedetomidine acts on α_2 receptors causing calcium entry inhibition into the cells thereby inhibiting the neurotransmitter release.

The above two mechanisms illustrate two different means of effective pain relief. In the first mechanism, hyperpolarization of membranes prevents stimulation of nerve fibres. Whereas in the second mechanism there is inhibition of neurotransmitter release. A numerous site like supraspinal and spinal sites modulate the transmission of pain signals in the CNS.[18]

The activity of the noradrenergic neurons is decreased by agonists acting at a2-adrenergic receptors on the locus coeruleus cell bodies. Therefore, inhibition of the locus coeruleus results in disinhibition of the noradrenergic nuclei and exerts descending inhibitory action on nociception in the spinal cord.[12]

PHARMACOKINETICS OF DEXMEDETOMIDINE

Dexmedetomidine is administered by oral, intramuscular and transdermal routes.Itfollows zero order kinetics and not first order kinetics. Following IV administration, dexmedetomidine shows the following pharmacokinetic characteristics - a rapid distribution phase with distribution half -life of about 6 mins; context sensitive half time ranges from 4 mins following 10min infusion to 250 min following 8 hr infusion; a terminal elimination half -life of about 2 hr s; and steady-state volume of distribution of about 118 litres. Clearance is found to be about 39L/ hr. The mean body weight related to the estimated clearance was 72kg.[21]

Dexmedetomidine shows linear pharmacokinetics in dose ranging from 0. 2-0. 7mcg/ kg/hour while given by i.v infusion up to 24hrs.[21]

Distribution:

94% of the drug is approximately bound to serum proteins like α1 glycoprotein and albumin. In patients with deranged liver function tests, dose should be reduced as free fraction of drug is elevated due to decreased serum proteins.[22]

The drug dosage also depends upon the age of the patient. In elderly patients, the side effects of dexmedetomidine are more pronounced like hypotension and bradycardia, so we tend to give small doses. In children as the volume of distribution is more, we tend to give more dosage.

Metabolism:

Dexmedetomidine is metabolised by cytochrome p450 enzyme in liver. It also undergoes glucuronide conjugation. 94% of the metabolites are excreted in urine and 4% by feces.[23]

PHARMACODYNAMICS OF DEXMEDETOMIDINE

Central Nervous System

Sedation

The sedative action of dexmedetomidine varies from those produced by other drugs causing sedation. The other drugs act t through the GABA (Gamma Amino Butyric Acid) systems while dexmedetomidine acts by promoting the endogenous sleep pathways. Patients will be in a state from where they can be easily wake up and they follow commands. This property is used during awake fibreoptic intubation.

It is said to have wide safety margin as it provides good sedation with minimal effect on respiration.[24]

Analgesia

The primary site of action for analgesia is Spinal cord. It provides analgesia when it is injected via epidural or intrathecal route. The mechanism of action is by inhibiting the release of substance P from the dorsal horn of the spinal cord and thereby exerting its primary analgesic effects.[25]

Cardiovascular System

Dexmedetomidine does not affect heart directly. It is said to have biphasic cardiovascular response.[27]

In younger patients when dexmedetomidine is given at a rate of 1mcg/kg, there will be transient increase in blood pressure with reflex decrease in heart rate.[28] This is propagated to be due to direct stimulation of vascular smooth muscle receptors. This can be managed by giving the drug slowly over 10min.Even then,

there was 7% increase in the mean arterial pressure and 16-18% reflex decrease in the heart rate.[15]

The initial transient response is followed by decrease in both blood pressure and heart rate below the baseline. These effects resulted due to the inhibition of central sympathetic outflow that overcomes the direct stimulating effect.[29] The drop in HR and BP is thought to be due to presynaptic a2-adrenoceptor stimulation which leads to decrease in norepinephrine release.[30]

Even though baroreceptor reflex is well preserved in patients receiving dexmedetomidine, episodes of bradycardia and hypotension may be seen, and these can be treated with atropine or ephedrine.[31]

Respiratory System

Oxygenation and compliance are improved with dexmedetomidine. It also reduces the dead space ventilation.[32] When administered intravenously, dexmedetomidine causes bronchodilation.[33] Though it is seen to reduce the pulmonary blood pressure in patients with pulmonary vasoconstriction, there are no studies done on it extensively.[34]

Endocrine System

Serum cortical and ACTH levels are not altered in patients on dexmedetomidine infusion.[24] Dexmedetomidine does not inhibit cytochrome P450 enzyme, including those taking part in steroidogenesis.[35] Dexmedetomidine acts on α_2 receptors in pancreas and decreases insulin production thereby causing hyperglycemia.[36] It also stimulates growth hormone and decreases inflammatory response and the levels of IL-6.[37]

Renal System

The norepinephrine release is decreased because of its α_2B receptor action on locus coeruleus. This leads to vasodilatation and increase in renal blood flow.[38]

INDICATIONS OF DEXMEDETOMIDINE

Dexmedetomidine is available in 0.5, 1 and 2ml ampoules. 1ml contains 100mcg of dexmedetomidine. It can be mixed safely with D5W, NS, Mannitol20%.

Premedication[39] – because of its anxiolytic, sedative, analgesic, anti-sialagogue and sympatholytic properties. It is given at the dose of 1mcg/kg over 10minutes.

ICU sedation[39] - loading dose is given at 1mcg/kg iv over 10 minutes, followed by maintenance dose of 0.2-1.4 mcg/kg/hr iv.

For attenuation of intubation response[39] - loading dose of 0.25-1mcg/kg iv over 10 minutes.

For maintenance of anaesthesia[39] - maintenance dose of 0.2-0.7 mcg/kg/hr iv [titrated according to hemodynamics].

For attenuation of extubation response[39] - loading dose of 0.5-1.0mcg/kg iv over 10 minutes.

For subarachnoid block[39] - 3-5 mcg is added to local anaesthetic.

For epidural anesthesia[39] - 1-2 mcg/kg is added to local anaesthetic.

For caudal anesthesia[39] - 1-2 mcg/kg is added to local anaesthetic.

IVRA[39] - 0.5 mcg/kg is added to local anaesthetic solution.

Fibre-optic intubation[40] - loading dose of 1mcg/kg iv over 10 minutes, followed by maintenance dose of 0.7mcg/kg/hr iv.

Procedural sedation[40] - loading dose of 1mcg/kg iv over 10 minutes, followed by maintenance dose of 0.6mcg/kg/hr iv.

CONTRAINDICATIONS OF DEXMEDETOMIDINE

1. Infusion over 24 hours.
2. In obstetrics, as the safety has not been studied.
3. In patients with pre-existent bradycardia, heart blocks and related bradyarrhythmia.
4. In hypovolemic or hypotensive patients.
5. Allergy or known hypersensitivity to dexmedetomidine

SIDE EFFECTS OF DEXMEDETOMIDINE

The adverse effects of dexmedetomidine include bradycardia, hypotension, nausea, atrial fibrillation and hypoxia, first degree or second-degree heart block. Many of the adverse events associated with dexmedetomidine use occur during or briefly after loading dose of the drug. By reducing the loading dose or omitting it altogether, adverse effects can be reduced.[9]

PHARMACOLOGY OF FENTANYL

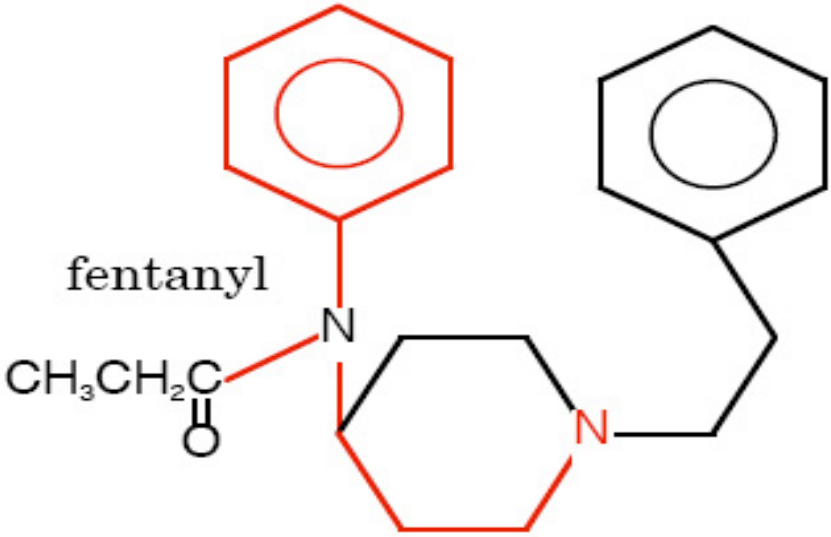

FIGURE 4: CHEMICAL STRUCTURE OF FENTANYL

Paul Janssen has synthesized fentanyl in 1960. It is a synthetic, lipophilic phenylpiperidine opioid agonist N-(1-(2-phenethyl)-4-piperidinyl-N-phenyl-propanamide

Molecular formula: $C_{22}H_{28}N_2O$; Molecular weight: 336.471 g/mol

MECHANISM OF ACTION

Opioid receptors are present in both CNS and PNS. They are normally stimulated by endogenous peptides which are released in response to noxious stimuli. These receptors can be broadly classified into mu, kappa and delta receptors. Fentanyl exerts its pharmacological actions by acting on mu opioid receptor with less affinity towards delta and kappa receptors. Mu receptor can be again divided into mu1 and mu2 receptors. Mu1 receptor is responsible for analgesia. Bradycardia, respiratory depression and physical dependence are mediated by mu2 receptors.

Opioids action is mediated through G protein coupled receptors. Once this receptor is activated by opioid agonists, voltage-dependent calcium channels are inhibited thereby decreasing cAMP levels. This blocks the release of neurotransmitters like glutamate, substance P from the nociceptive fibres leading to analgesia.[13]

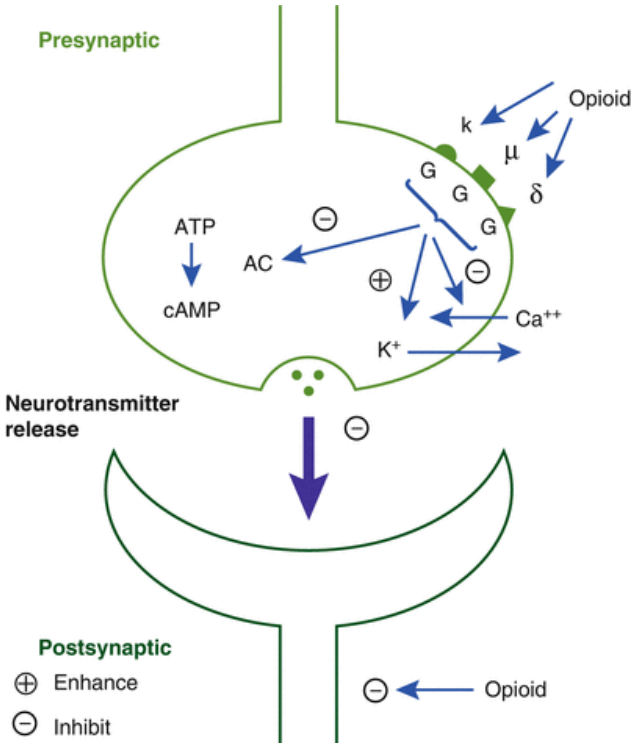

FIGURE 5: MECHANISM OF ACTION OF OPIOD AGONISTS[13]

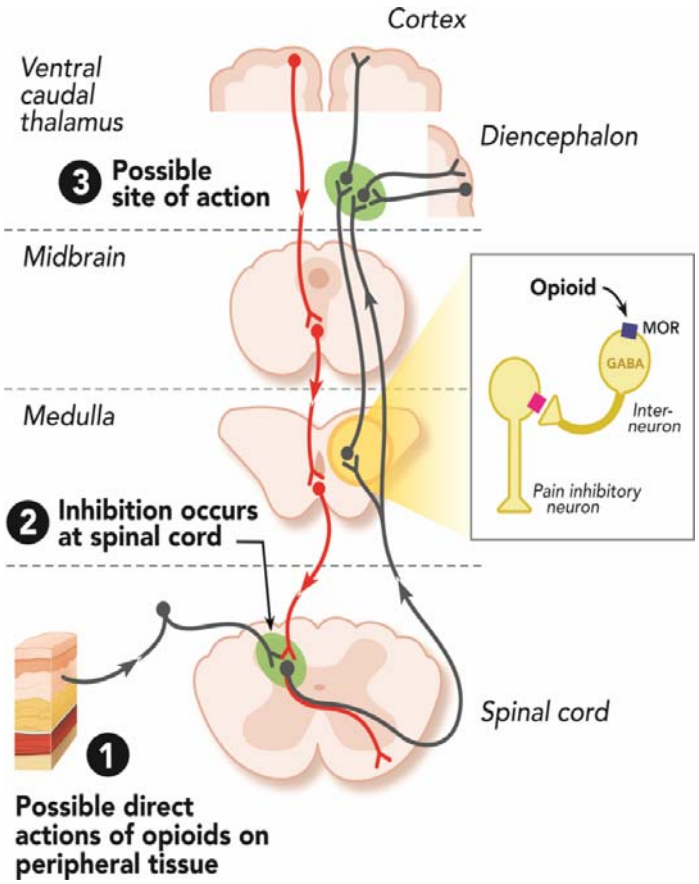

FIGURE 6: GREY PATHWAY SHOWS PAIN CONDUCTANCE FROM PERIPHERY TO CNS. THE RED PATHWAY SHOWS PAIN MODULATING ZONES IN MIDBRAIN AND MEDULLA[41].

PHARMACOKINETICS OF FENTANYL

On intravenous bolus, fentanyl is distributed rapidly from plasma into highly vascularised compartments. From the systemic circulation, it gets redistributed into muscle and fat tissues. Elimination half- life varies from 219mins-853mins. Its volume of distribution is 3.5-8l/kg. Its clearance is relatively high (30-72L/hr).[42]

DISTRIBUTION

Fentanyl is highly lipophilic and binds to plasma proteins. Patients with serum albumin less than 3.5g/dl had significantly reduced dose adjusted serum fentanyl concentrations. [42] The unionized fraction of the drug is 8.5% at the pH of 7.4

METABOLISM

Fentanyl is metabolized in the liver by CYP3A4 mediated dealkylation to form inactive metabolites like norfentanyl. Severe liver failure led to seven times lower clearance of fentanyl compared to mild liver failure.[42] 10% of the metabolites are excreted unchanged in urine and 9% of the metabolites are found in feces[14]

PHARMACODYNAMICS OF FENTANYL

ANALGESIA

Compared to morphine, it is 75-100 times more potent. Fentanyl mainly exerts its effects on mu1 receptors which are primarily responsible for analgesia. Reduction in pain by 50% is seen with plasma fentanyl concentration of 1.3 ng/ml.[43]

CARDIOVASCULAR SYSTEM

Myocardial oxygen demand will be reduced due to peripheral vasodilatation and thereby causing a drop in preload and afterload. Cardiac output mean arterial pressure and heart rate are also decreased slightly. Change in hemodynamics is minimal[44].

RESPIRATORY SYSTEM

Upper airway reflexes are abolished in a dose dependent manner. Only with subsequent doses laryngospasm and apnoea occurs.[45]

Fentanyl give rise to respiratory depression. It is shown by elevated $ETCO_2$ levels, dose response curve for carbon dioxide will be declined. Once the end tidal carbon dioxide reaches 50 mmHg, then minute ventilation will be increased.[27] When fentanyl is accompanied with other sedatives like midazolam, respiratory depression will be more enhanced. Therefore, such patients are monitored and also supplemented with oxygen.[46]

ENDOCRINE SYSTEM

When fentanyl is administered at dose of 10mcg/kg, there will be fall in plasma levels of epinephrine, growth hormone, cortisol, glucose and free fatty acids. On contrary, when it was given in a dose less than 5 mcg/kg, there is no effect on hormones.[47]

FENTANYL INDUCED COUGH (FIC)

The incidence of fentanyl induced cough ranges from 18-65%[48.] FIC is backed up by various theories. Some of such theories include the stimulation of vagal C-fibers in the airway, derangement of irritant receptors presents in the tracheobronchial tree, release of histamine from mast cells in the lung, sudden adduction of vocal cords and release of neuropeptides from prejunctional μ opioid receptors.[49]

INDICATIONS FOR FENTANYL

1. Analgesic: dose- 1-2 mcg/kg IV.
2. Adjuvant to GA: dose-2-10 mcg/kg [It blunts hemodynamic responses.]
3. Individual anaesthetic agent: at 50-150 mcg/kg.
4. As an adjuvant in spinal anaesthesia. A dose of 25 mcg of fentanyl is added to bupivacaine.
5. As a adjuvant in labour analgesia in epidural anaesthesia in a dose of 2 mcg/ml.[5]

SIDE EFFECTS

1. Respiratory depression
2. Apnoea
3. Myoclonic movements
4. Muscle rigidity
5. Nausea and vomiting
6. Bradycardia

CONTRAINDICATIONS FOR FENTANYL

1. Allergic to opioids
2. Patient with history of bronchial asthma and COPD
3. Patients with head injury and increased intracranial pressure
4. Patients on MAO inhibitors.[50]

REVIEW OF LITERATURE

Kautto UM in 1982, studied the effect of fentanyl on heart rate, arterial pressure and rate-pressure product after laryngoscopy and intubation, in 45 patients scheduled for elective orthopaedic surgeries. Study concluded that low doses of fentanyl 2µg/kg is sufficient to attenuate the heart rate and pressure response.[51]

B.C.Campbell, R.K.Parikh, A.Naismith, D.Sewnauth , J.L.Reid in 1984, conducted study in 20 subjects undergoing upper abdominal surgery to compare the effect of fentanyl and halothane on the stress response during surgery. They have concluded that low dose fentanyl blocks the sympathetic response to surgery without causing respiratory depression as shown by low plasma noradrenaline concentrations.[52]

Ghignone M, Quintin L, Duke PC, Kehler CH, Cavillo O in 1986, studied 24 patients undergoing aortocoronary bypass surgery and concluded that α_2 – adrenoreceptor agonist can effectively decrease anaesthetic narcotic requirements and stable hemodynamic conditions during induction and intubation.[53]

Aho M, Lehtinen AM, Erkola O, Kallio A, Korttila K in 1991, conducted study in 96 subjects undergoing abdominal hysterectomy to assess the effect of iv dexmedetomidine on perioperative hemodynamics and isoflurane requirements. They found that 0.3mcg/kg/hr dose was ineffective in attenuating Heart Rate and Systolic Blood Pressure as compared with 0.6mcg/kg/hr. Reported that there was remarkable

reduction of isoflurane requirement and thus proved the synergism between dexmedetomidine and isoflurane.[4]

Scheinin B, Lindgren L, Randell T, et al in 1992 studied the efficacy of dexmedetomidine as the preanaesthetic agent, its effect on sympathetic response and opioid requirements during surgery in 24 patients posted for elective surgery.
Infusion decreased the dose of thiopentone for induction, attenuated the pressor response during intubation and the perioperative fentanyl requirement.[2]

JaakolaML, Ali -Melkki la T, Kanto J, et al conducted a study in 30 patients undergoing cataract surgery and found that dexmedetomidine reduced IOP, attenuated sympathoadrenal response and requirements of thiopentone for induction, opioid and inhalational agents during surgery were reduced.[54]

Aantaa R, Jaakola ML, Kallio A, Kanto J in 1997, did a study to define the interaction between intravenous dexmedetomidine and isoflurane. The study was conducted on 49 women posted for abdominal hysterectomy. Minimum alveolar concentration of isoflurane is used as the measure of anaesthetic potency. The study concluded that the MAC of isoflurane is much lower in dexmedetomidine group.[3]

Lawrence CJ, De Lange S in 1997 conducted a study in 50 patients posted for minor orthopaedic surgeries to evaluate the effects of dexmedetomidine on isoflurane requirements and perioperative hemodynamic stability. They concluded that a single dose of 2μg/kg attenuates pressor response and also decreases postoperative analgesic and anti emetic requirements.[55]

Ko HS, Kim DC, Han YH in 1998, conducted study in 170 patients to examine the optimal time of injection of small dose of fentanyl during induction to attenuate the pressor response for laryngoscopy and intubation. The study concluded that the effective time to administer fentanyl to decrease the laryngoscopic response is 5min before tracheal intubation.[56]

Hall JE, Uhrich TD, Braney JA, Arian SR, Ebert TJ in 2000 studied the safety and efficacy of two low dose dexmedetomidine infusions i.e.; 0.2 and 0.6 µg/kg/hr in 7 healthy volunteers. The study showed that dexmedetomidine infusion at such low doses resulted in reversible sedation , analgesia and memory impairment without causing cardio respiratory depression.[15]

PekkaTalke, Richard Chen, Brian Thomas, Anil Agarwal , Alexandra Gottlieb, Per Thorberg, Stephen Heard, Albert Cheung, Stan Lee Son in 2000 have tested the hemodynamic and adrenergic effects of dexmedetomidine infusion in patients undergoing vascular surgery. They have concluded that dexmedetomidine attenuated increase in heart rate and norepinephrine concentrations during emergence from anaesthesia.[57]

Hofer RE, Sprung MG, Wedel DJ in 2005 conducted a study using dexmedetomidine infusion intraop at 0.7µg/kg/hr in an extremely obese patient posted for bariatric surgery. The study showed that dexmedetomidine infusion has decreased both intraop and postop narcotic requirements for analgesia.[58]

Yildiz M, Tavlan A, Tuncer S, Reisli R, Yosunkaya A, Otelcioglu S in 2006 studied the effect of dexmedetomidine on the hemodynamic response to laryngoscopy in 50 patients posted for elective surgery. They have concluded that single preoperative dexmedetomidine has blunted pressor response for laryngoscopy, increased sedation score and also reduced intraop inhalational agent requirements.[59]

TanskanenPE, Kytta JV, Randell TT, Aantaa RE in 2006 performed a trial in 54 patients posted for supratentorial brain surgery to know the effects of intraop dexmedetomidine infusion on hemodynamic. The study demonstrated that dexmedetomidine infusion has significantly reduced the response to intubation and also during emergence from anaesthesia.[60]

Lee YYS, Wong SM, Hung CT in 2007 conducted a study in 60 patients posted for vitreoretinal surgery to explore the efficacy of dexmedetomidine in reducing IOP, attenuating stress response during both intubation and extubation. The study showed that dexmedetomidine provides stable hemodynamic conditions.[61]

Tufanogullari B, White PF, Peixoto MP, et al in 2008 conducted a study in 80 morbidly obese patients undergoing laparoscopic bariatric surgery to evaluate the effect of dexmedetomidine on the recovery period. They concluded that infusion rate of 0.2µg/kg/hr facilitates early recovery with stable hemodynamic along with decreased postop analgesic requirements.[62]

Turgut N, Turkmen A, Gökkaya S, Altan A, Hatiboglu MA in 2008 compared the efficacy of 0.2µg/kg/hr dexmedetomidine infusion with 0.5µg/kg/hr fentanyl infusion

in patients posted for elective spinal laminectomy. The study showed that dexmedetomidine group is hemodynamically more stable than fentanyl group with latter requiring frequent post op analgesic doses.[63]

Bekker A, Sturaitis M, Bloom M, et al in 2008 did a study in 72 patients posted for elective craniotomy using intraop dexmedetomidine infusion. The study showed stable hemodynamic throughout the surgery and also decreased length of PACU stay.[8]

Menda F, Koner O, Sayin M, Ture H, Imer P, Aykaç B in 2010 conducted a study in 30 patients to evaluate the effect of dexmedetomidine on pressor response for intubation. The study proven that a dose of 1μg/kg 15minutes blunted the hemodynamic response for laryngoscopy and intubation.[1]

Keniya VM, Ladi S, Naphade R in 2011 conducted a study in 60 patients to assess the safety and efficacy of dexmedetomidine in attenuating sympathoadrenal response to intubation. The study showed that Dexmedetomidine dose of 1μg/kg over 10mns followed by 0.2-0.7 μg/kg/hr until skin closure reduced the pressor response and alsointraop opioid requirement.[64]

Patel CR, Engineer SR, Shah BJ, Madhu S in 2012 compared the effect of dexmedetomidine with fentanyl on hemodynamic stability during surgery in 60 patients. The study demonstrated the dexmedetomidine infusion reduces the stress response and maintains hemodynamic stability.[5]

Tanuja, Shobha Purohit , Amit Kulshreshtha in 2014 conducted a study in 50 patients undergoing intracranial surgery regarding the efficacy of dexmedetomidine on IOP and sympathoadrenal response for laryngoscopy. The study showed that premedication with 0.8µg/kg over 10mns before induction blunted the response to laryngoscopy and maintained hemodynamic stability.[65]

Gaszynski T, Czarnik K, Lazinski L, Gaszynski W in 2016 , compared fentanyl and low-opioid dexmedetomidine approach in blunting intubation response in 42 morbidly obese patients posted for bariatric surgery .The study demonstrated that more than fentanyl, dexmedetomidine successfully attenuated cardiovascular response for laryngoscopy and intubation.[66]

Garg A, Kamal M, Mohammed S,Singariya G, Chouhan DS, Biyani G in 2018 conducted a study to evaluate the efficacy of dexmedetomidine in reducing emergence agitation after extubation in 72 patients undergoing nasal surgery. A bolus of 1µg/kg/hr of dexmedetomidine followed by 0.4µg/kg/hr till the end of surgery reduced the incidence of emergence agitation and also desflurane requirement during surgery.[67]

Attalla HA, Habeeb RM, Elzwedy AI in 2018 performed a trial in 60 patients posted for spine surgery to compare the effect of fentanyl and examine infusion on intraoperative hemodynamic stability and postoperative analgesia. It is seen as ketamine is more effective than fentanyl in maintaining hemodynamic along with post operative pain management.[68]

Kotak N, Mamde R, Desai PM in 2019 compared dexmedetomidine and esmolol in attenuating stress response during extubation. The study proved that 0.5µg/kg of dexmedetomidine is more effective than 1mg/kg of esmolol given 10minutes before extubation.[6]

Khanday SB, Mir AH, Sofi KP, Lone AQ, Shah AN in 2019 compared fentanyl with nalbuphine in reducing stress response to laryngoscopy and intubation in 100 patients. The study showed that 2µg/kg of fentanyl is better than nalbuphine 0.2mg/kg in blunting the pressor response.[69]

MATERIALS AND METHODS

Source of data:

90 patients undergoing elective surgeries under general anaesthesia at R L Jalappa Hospital, Department of Anaesthesia, Sri Devaraj Urs Medical College, A Constituent of SDUAHER, Tamaka, Kolar during the Academic year from January 2019-June 2020

Method of collection of data:

Inclusion criteria:

- Age group between 20 – 50 years
- ASA I and II.
- Scheduled for elective surgeries with duration of approx. 90mins like laminectomy, Oro-maxillary, ENT, Thyroid, laparotomies and laparoscopic surgeries.

Exclusion criteria:

- Patients suffering from cardiovascular diseases (uncontrolled hypertension, coronary heart disease, congestive heart failure).
- Obesity >30kg/m2
- Patients with anticipated difficult airway.
- Patients who are on sedatives and hypnotics.
- Patients who have allergy to the study drug

SAMPLING PROCEDURE:

The ethical clearance was obtained before starting the study.

A thorough preanaesthetic check-up was carried out, history was taken and systemic examination done. Vitals were noted including weight of the patient.

Investigations asked prior to surgery include

- ✓ Complete haemogram
- ✓ Serum electrolytes
- ✓ Blood urea and serum creatinine
- ✓ Random blood sugar
- ✓ Bleeding time and clotting time
- ✓ ECG and Chest x-ray
- ✓ Urine analysis for sugar, albumin and microscopy
- ✓ No other specific investigations were asked

All patients were examined 1 day prior to the surgery, investigation reports were checked, anaesthetic procedure explained and informed consent was taken.

Fasting was ensured for 8hours and patients were premedicated with Tab.Alprazolam 0.5mg and Tab.Rantac 150mg, which were repeated again on the morning of surgery.

Preparation of drug for infusion:

Dexmedetomidine 1ml ampule containing 100mcg was diluted with normal saline till 20cc so that the solution contains drug of 5µg per ml

Fentanyl 2ml containing 100µg was diluted with normal saline till 20cc so that the solution contains 5µg per ml.

The drugs were administered using a syringe pump.

Patients were randomly divided into two groups by computer generated table-

GROUP A:IV Dexmedetomidine 1µg/kg as loading dose over 10mins prior to induction followed by infusion at 0.5µg/kg/hr until 10mins prior to extubation.

GROUP B:IV Fentanyl 1µg/kg as loading dose over 10mins prior to induction followed by infusion at 0.5µg/kg/hr until 10mins prior to extubation.

Venous access was secured with 18G IVC and fluids were started at the rate of 5ml/kg/hr.

Once the patient was shifted to OT their basal HR, NIBP, SPO_2 were noted and monitoring started.

Before the induction of anaesthesia patients were premedicated with Inj.Glycopyrrolate 0.005mg/kg.

Loading dose of the study drug was started at the rate of 1µg/kg and given over 10mins. HR, SBP, DBP, MAP, RR and SPO_2 were noted before the start of infusion.

Preoxygenation was done with 100% oxygen for 3mins and anaesthesia induced with Inj.Propofol at 2mg/kg till loss of verbal commands

After the loading dose was given, the required monitoring parameters were once again recorded and the study drug infusion rate was changed to maintenance dose of 0.5µg/kg/hr till 10mins prior to extubation.

Tracheal intubation with appropriate size oral endotracheal tube is facilitated by Inj.Succinyl choline 2mg/kg. Maintenance of anaesthesia is done by 60% nitrous oxide in oxygen, isoflurane and Inj.Vecuronium 0.1mg/kg as muscle relaxant. Isoflurane concentration was titrated to maintain stable hemodynamic.

Patient was mechanically ventilated to maintain $ETCO_2$ between 30-35mm of Hg.

HR, SBP, DBP, MAP, RR, SPO_2 were recorded 1min after intubation and then at 3min, 5min followed by at every 15 min interval till extubation.

Bradycardia will be treated by IV Atropine at 0.02mg/kg and hypotension will be treated by titrating isoflurane concentration or by rate of infusion of intravenous fluids.

Infusion of the study drug was stopped and isoflurane was discontinued 10mins prior to reversal.

The residual neuromuscular blockade was reversed with Inj.Neostigmine 0.05mg/kg and Inj.Glycopyrrolate 0.01mg/kg.

After observing the motor recovery and spontaneous breathing efforts, patient was extubated after thorough oral suctioning. Vitals were noted 1, 3 ,5, and 15min after extubation to check for extubation response.

Patient was transferred to post anaesthesia care unit for observation of any nausea or drug induced side effects.

For first 24 hrs patient was monitored for pain using VAS score and the number of analgesics used were noted.

STATISTICAL ANALYSIS

Study design: Randomised Control Study

Statistical analysis:

Collected data was coded into Microsoft excel spread sheet and statistically analysed using SPSS 22. 0. All the quantitative measures like HR, SBP, DBP were presented by mean, standard deviation and confidence intervals. Categorical data was indicated in %. The significance of the difference in quantitative measures was done by using student‘t’ test. ‘Chi’ square test was used to compare the difference in proportion. $P<0.05$ was considered as statistically significant.

Sample size:

Sample size has been selected based on the differences in major outcome variables like heart rate, systolic blood pressure, diastolic blood pressure to assess hemodynamic response in patients.

$$n = \frac{2Sp^2[Z_{1-\alpha/2} + Z_{1-\beta}]^2}{\mu^2 d}$$

$$S^2_p = \frac{S_1^2 + S_2^2}{2}$$

- S_1^2 = standard deviation in first group
- S_2^2 = standard deviation in second group

μ^2 = mean difference between sample

- α = significance level
- $1-\beta$ = power

In a study of Jayashree P Vaswani et al, they observed an average variance estimate of 144 in diastolic blood pressure between two groups (Dexmedetomidine and Fentanyl)[10] .

To detect a mean difference of 7.16mm of Hg (Effect size with 95% confidence interval with 80% power) the required sample size per group estimated as 45.

RESULTS

Table 1: Age distribution of patients studied between two groups

Age in years	Group A	Group B	P Value
Mean ± SD	36.29±9.93	37.44±8.98	0.564

The Mean age of subjects in the study was 36.29 ± 9.93 years and in group B was 36.87± 9.43 years. There was no significant difference in mean age between two groups with p value 0.564.

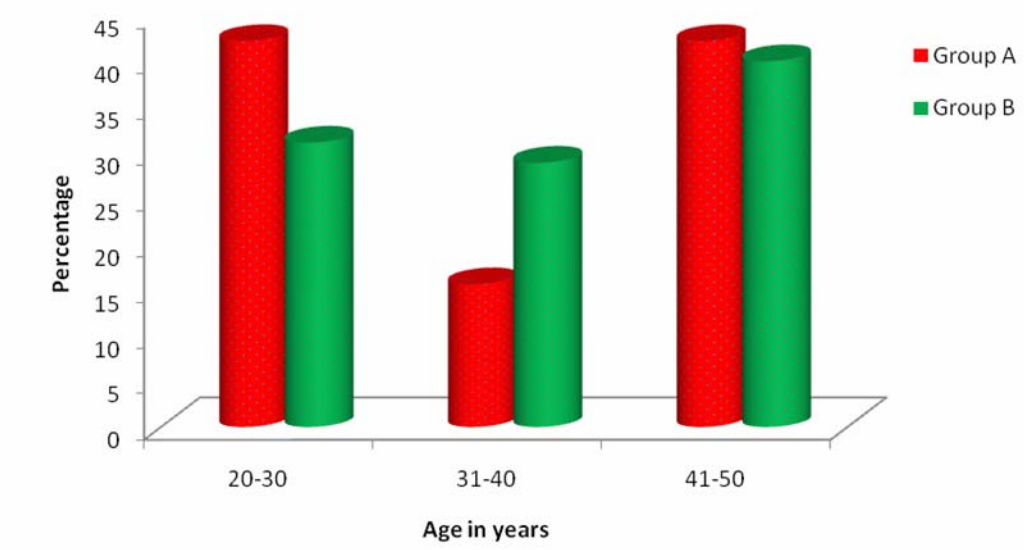

FIGURE NO 7: BAR DIAGRAM SHOWING AGE DISTRIBUTION OF SUBJECTS BETWEEN TWO GROUPS

Table 2: Gender distribution of patients studied

Gender	Group A	Group B	Total
Female	25(55.6%)	21(46.7%)	46(51.1%)
Male	20(44.4%)	24(53.3%)	44(48.9%)
Total	45(100%)	45(100%)	90(100%)

Samples are gender matched with P=0.399, Chi-Square test

In this study, 51% were females and 48.9% were males. There was no significant difference in gender between two groups.

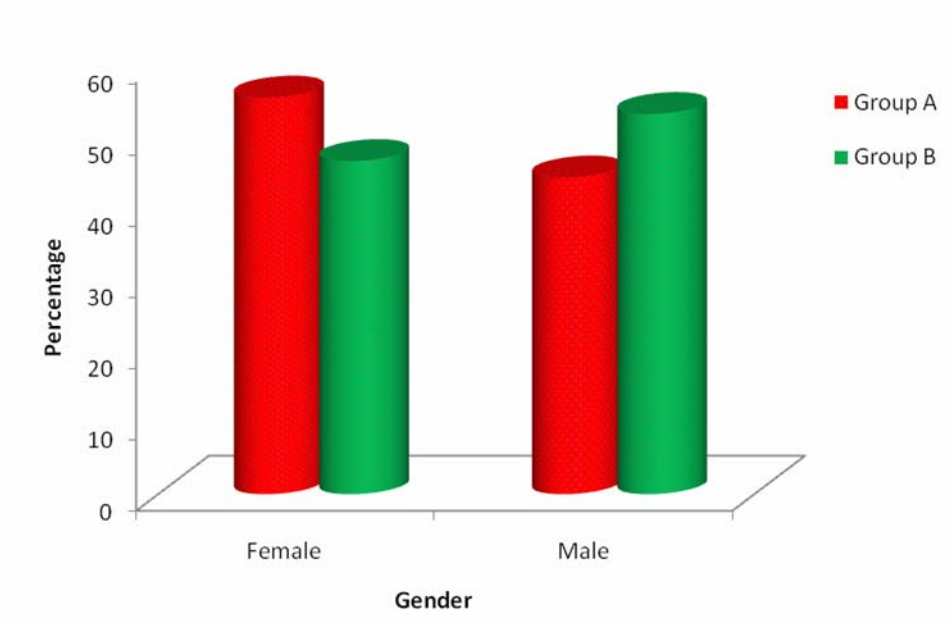

FIGURE NO 8: BAR DIAGRAM SHOWING GENDER DISTRIBUTION BETWEEN TWO GROUPS

Table 3: Weight (kg) distribution in two groups of patients studied

Weight in kgs	Group A	Group B	P Value
Mean ± SD	59.51±10.49	61.11±9.84	0.458

Mean weight of subjects in Group A was 59.51±10.49 kgs and in Group B was 61.11 ± 9.84 kgs. There was no significant difference in mean weight between two groups.

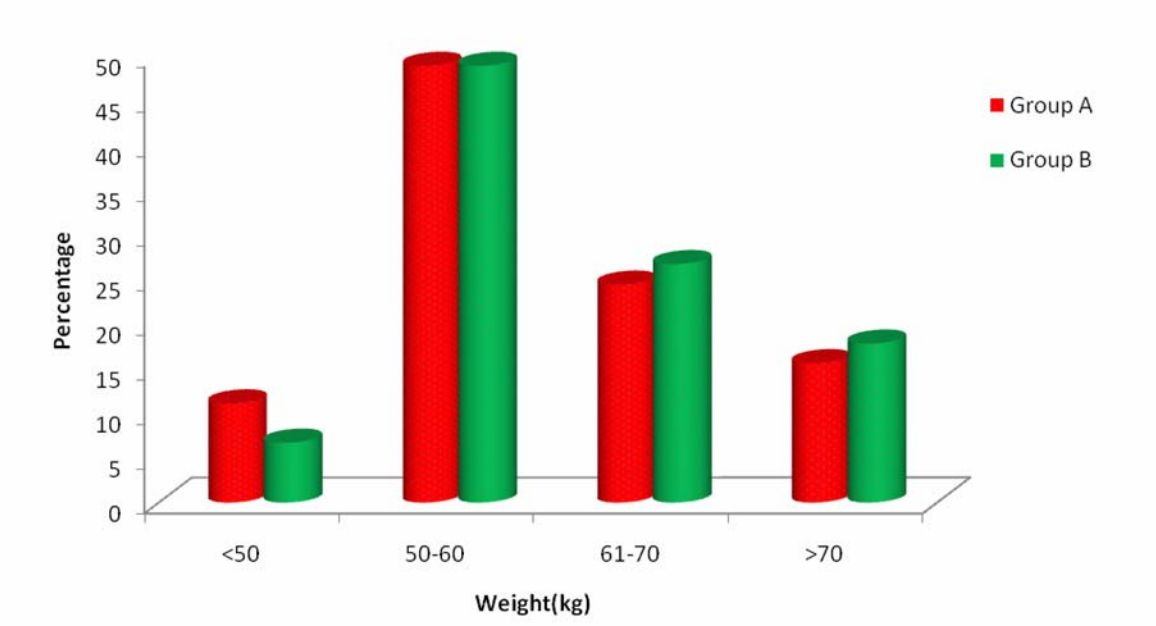

FIGURE NO 9: BAR DIAGRAM SHOWING WEIGHT DISTRIBUTION BETWEEN TWO GROUPS

Table 4: ASA Grade distribution in two groups of patients studied

ASA Grade	Group A	Group B	Total
1	33(73.3%)	31(68.9%)	64(71.1%)
2	12(26.7%)	14(31.1%)	26(28.9%)
Total	45(100%)	45(100%)	90(100%)

In the study, 64% of patients belonged to ASA I and 26% of patients belonged to ASA II. There was no significant difference in ASA grading between two groups.[p value is 0.642]

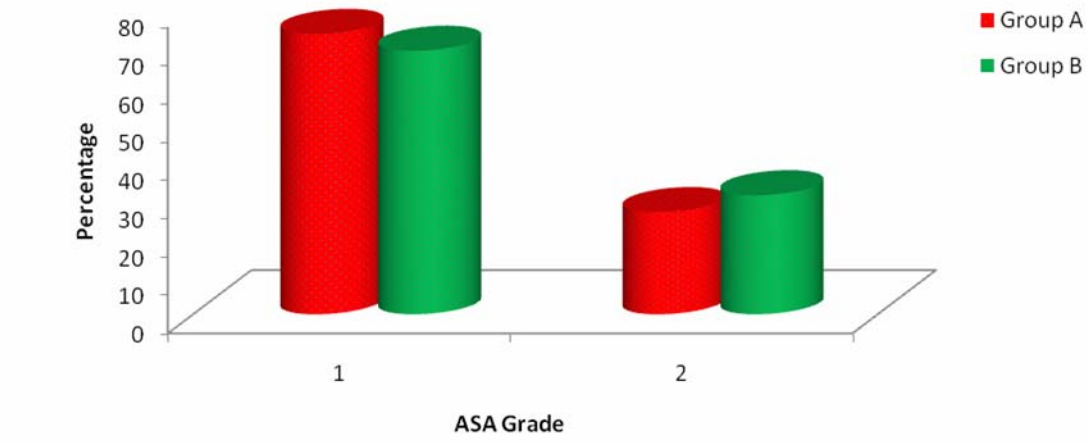

FIGURE NO 10: BAR DIAGRAM SHOWING ASA GRADING DISTRIBUTION BETWEEN TWO GROUPS

Table 5: Heart rate (bpm)-A Comparison in two groups of patients studied

Heart rate (bpm)	Group A	Group B	Total	P value
Baseline	83.98±9.15	82.71±9.72	83.34±9.41	0.526
After infusion	78.53±9.10	82.73±7.32	80.63±8.48	0.018*
After Intubation				
• 1	80.73±8.57	95±7.63	87.87±10.79	<0.001**
• 3	76.93±8.68	92.4±8.89	84.67±11.7	<0.001**
• 5	73.27±7.94	88.09±8.41	80.68±11.03	<0.001**
• 10	71.31±7.54	84.56±9.13	77.93±10.66	<0.001**
• 15	68.53±6.65	81.56±10.22	75.04±10.79	<0.001**
• 30	66.91±7.04	78.87±11.53	72.89±11.24	<0.001**
• 45	64.98±7.3	75.38±11.76	70.18±11.05	<0.001**
• 60	64.16±6.34	73.29±11.44	68.72±10.28	<0.001**
• 75	62.47±6.31	72.00±12.23	67.23±10.79	<0.001**
• 90	62.40±6.72	72.60±12.07	67.5±10.99	<0.001**
After Extubation				
• 1	69.56±6.46	87.38±8.47	78.47±11.68	<0.001**
• 3	67.89±7.04	82.96±10.56	75.42±11.70	<0.001**
• 5	64.87±6.33	77.36±13.86	71.11±12.42	<0.001**
• 10	63.76±6.35	75.49±13.05	69.62±11.79	<0.001**
• 15	62.62±6.24	75.20±12.51	68.91±11.69	<0.001**

Baseline HR (bpm) was comparable in both the groups, which was 83.98±9.15 and 82.71±9.72 in group A and Group B respectively.

After start of dexmedetomidine infusion, HR decreased to 78.53±9.10 bpm in Group A. After intubation in 1st minute, there was slight increase in HR of about 80.73±8.57, which settled down to below the baseline 10mins after intubation. In the 1st minute after extubation, HR increased, which was 69.56±6.46 but still was lower than the baseline level.

In Group B, after start of fentanyl infusion, HR maintained at 82.73±7.32 which was same as baseline level (82.71±9.72). In the 1st minute after intubation, there was significant increase in HR which was 95±7.63. The increase in HR settled down to baseline level 15mins after intubation. In the 1st minute after extubation, there was again significant increase in HR of 87.38±8.47, which settled down to 77.36±13.86 after 5mins of extubation.

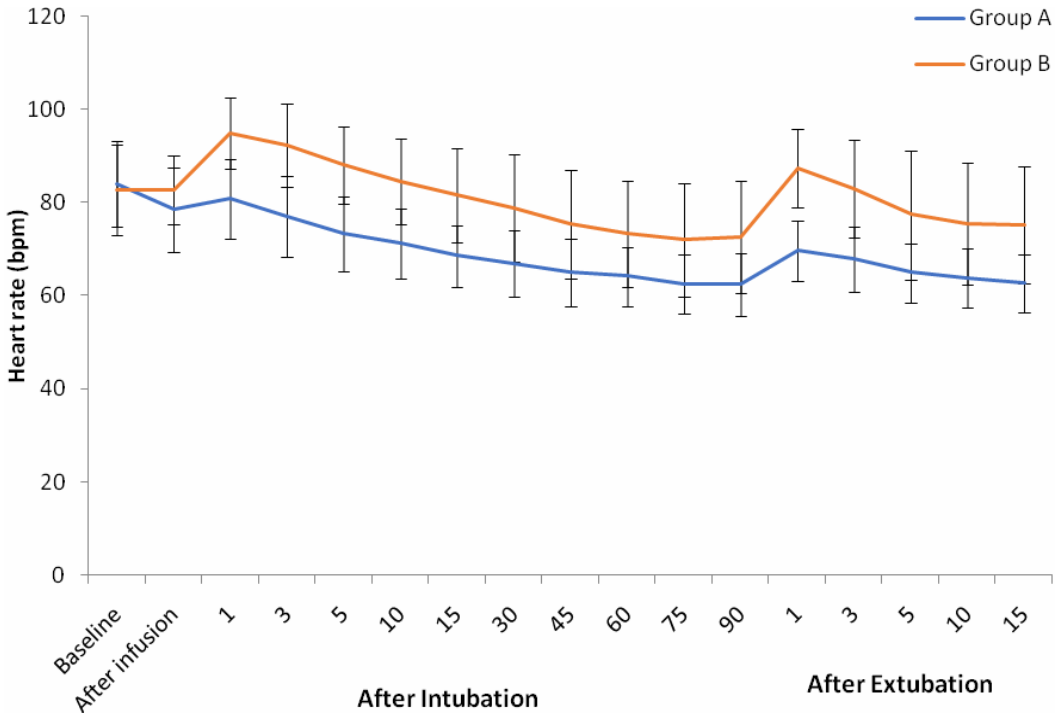

FIGURE NO 11: LINE DIAGRAM SHOWING HEART RATE COMPARISON BETWEEN TWO GROUPS

Table 6: Systolic blood pressure-A Comparison in two groups of patients studied

SBP (mm Hg)	Group A	Group B	Total	P value
Baseline	129.02±11.98	128.91±12.49	128.97±12.17	0.966
After infusion	124.82±11.97	127.73±12.4	126.28±12.21	0.260
After Intubation				
• 1	122.27±13.07	139.73±10.07	131.00±14.55	<0.001**
• 3	117.82±12.66	137.42±12.52	127.62±15.93	<0.001**
• 5	112.91±13.21	133.00±13.03	122.96±16.50	<0.001**
• 10	109.38±12.73	131.22±9.10	120.30±15.55	<0.001**
• 15	107.24±12.63	129.31±9.67	118.28±15.75	<0.001**
• 30	106.00±12.43	128.67±9.70	117.33±15.90	<0.001**
• 45	105.33±11.13	125.84±11.24	115.59±15.17	<0.001**
• 60	104.56±9.65	124.53±10.59	114.54±14.23	<0.001**
• 75	103.93±9.53	123.24±10.82	113.59±14.04	<0.001**
• 90	104.73±9.15	125.62±12.02	115.18±14.94	<0.001**
After Extubation				
• 1	109.36±8.80	137.87±9.45	123.61±16.97	<0.001**
• 3	107.44±8.91	136.13±8.02	121.79±16.71	<0.001**
• 5	104.51±8.74	132.60±8.35	118.56±16.48	<0.001**
• 10	103.51±7.55	129.73±8.09	116.62±15.31	<0.001**
• 15	103.49±7.12	128.11±8.16	115.8±14.53	<0.001**

SBP (in mm Hg) is comparable in both the groups with 129.02±11.98 in group A and 128.91±12.49 in group B.

After infusion of dexmedetomidine, SBP decreased to 124.82±11.97, which further reduced in the 1st minute after intubation to 122.27±13.07. SBP was maintained around 106.00±12.43 which was below the baseline throughout the surgery with slight increase in the 1st minute after extubation to 109.36±8.80.

After fentanyl infusion, SBP remained same as baseline and there was significant increase in the 1st minute after intubation to 131.00±14.55. Throughout the procedure it was maintained same as baseline which significantly increased in the 1st minute after extubation to 137.87±9.45.

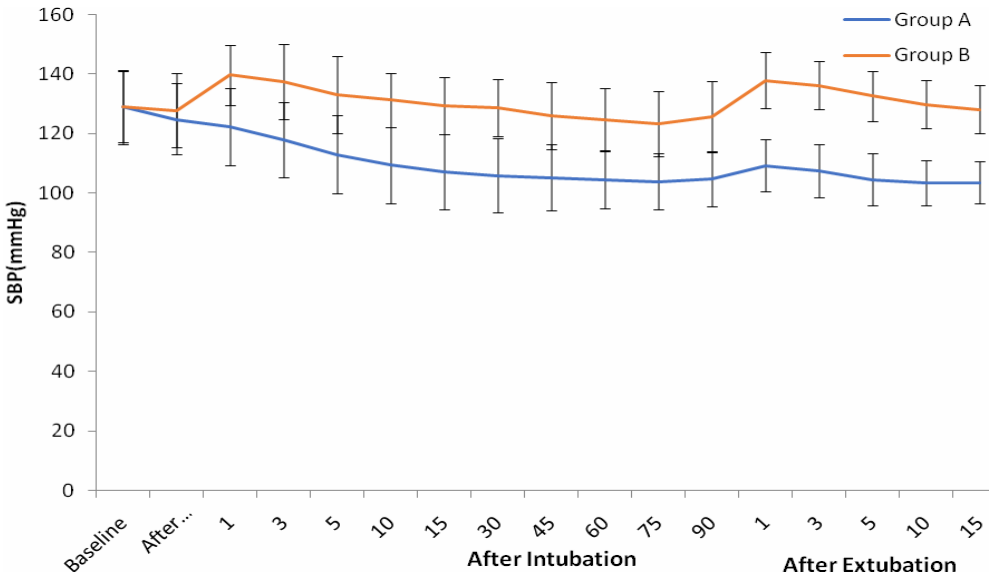

FIGURE NO 12: LINE DIAGRAM SHOWING SYSTOLIC BLOOD PRESSURE COMPARISON BETWEEN TWO GROUPS

Table 7: DBP (mm Hg)- A Comparison in two groups of patients studied

DBP (mm Hg)	Group A	Group B	Total	P value
Baseline	82.44±6.43	83.09±8.59	82.77±7.55	0.688
After infusion	78.44±6.66	81.16±8.31	79.80±7.61	0.091+
After Intubation				
• 1	76.98±8.91	91.13±9.07	84.06±11.43	<0.001**
• 3	72.91±9.29	88.89±9.63	80.9±12.37	<0.001**
• 5	68.73±8.85	85.09±9.81	76.91±12.41	<0.001**
• 10	66.07±8.77	83.04±7.27	74.56±11.71	<0.001**
• 15	63.62±9.05	79.89±7.78	71.76±11.72	<0.001**
• 30	62.33±8.72	78.96±8.24	70.64±11.87	<0.001**
• 45	61.71±8.38	76.8±7.76	69.26±11.05	<0.001**
• 60	61.51±7.2	75.84±8.55	68.68±10.66	<0.001**
• 75	60.76±7.52	74.11±9.28	67.43±10.75	<0.001**
• 90	61.38±7.79	75.67±10.13	68.52±11.50	<0.001**
After Extubation				
• 1	65.98±9.51	85.60±8.38	75.79±13.29	<0.001**
• 3	63.64±8.33	83.84±9.08	73.74±13.35	<0.001**
• 5	62.00±8.04	81.42±9.18	71.71±13.00	<0.001**
• 10	61.02±7.25	77.82±7.76	69.42±11.28	<0.001**
• 15	61.84±7.70	75.33±8.01	68.59±10.35	<0.001**

At baseline, diastolic blood pressure is comparable between two groups.

After dexmedetomidine infusion, DBP dropped below the baseline i.e., from 82.44±6.43 to 78.44±6.66, which is further reduced to 76.98±8.91 after 1st minute after intubation. There was also only slight increase in DBP in the 1st minute after extubation(61.38±7.79 to 65.98±9.51).

After fentanyl infusion, DBP dropped from 83.09±8.59 to 81.16±8.31. In the 1st minute after intubation, DBP significantly increased to 91.13±9.07. There was significant increase in the 1st minute after extubation from 75.67±10.13 to 85.60±8.38.

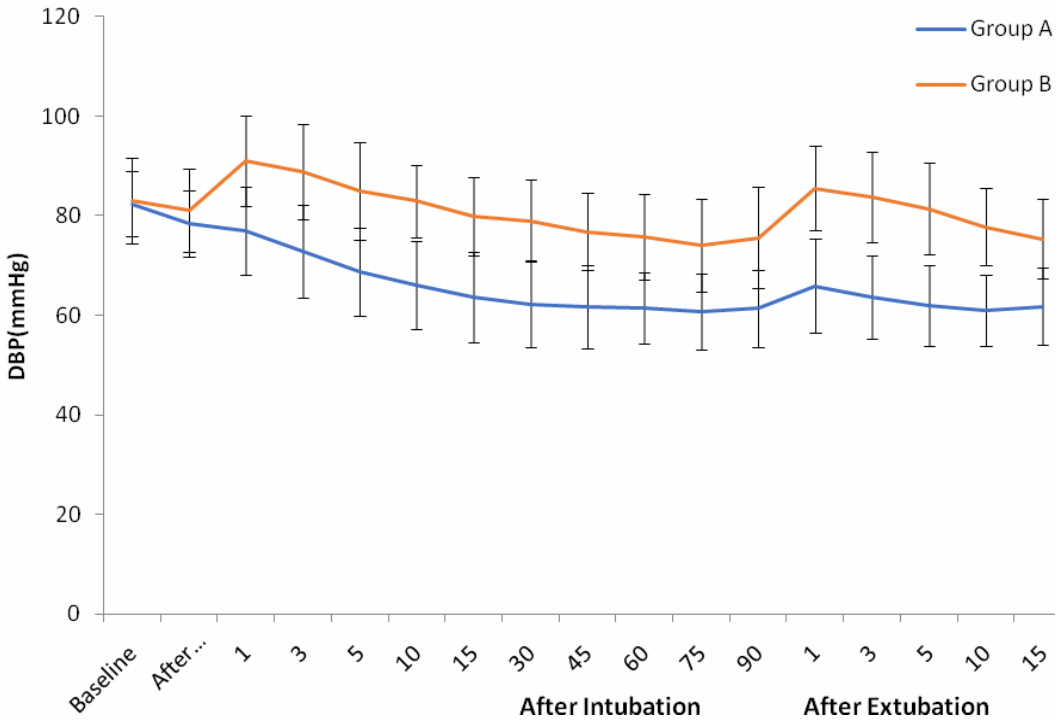

FIGURE NO 13: LINE DIAGRAM SHOWING DIASTOLIC BLOOD PRESSURE COMPARISON BETWEEN TWO GROUPS

Table 8: MAP (mm Hg)- A Comparison in two groups of patients studied

MAP (mm Hg)	Group A	Group B	Total	P value
Baseline	98.00±7.82	98.40±9.08	98.20±8.43	0.823
After infusion	93.98±7.80	96.71±8.99	95.34±8.48	0.127
After Intubation				
• 1	92.09±9.47	107.31±8.69	99.7±11.84	<0.001**
• 3	87.93±9.75	105.09±10.16	96.51±13.13	<0.001**
• 5	83.56±9.72	101.04±10.52	92.30±13.37	<0.001**
• 10	80.51±9.63	99.16±7.13	89.83±12.60	<0.001**
• 15	78.20±9.64	96.31±7.60	87.26±12.55	<0.001**
• 30	76.87±9.34	95.56±7.83	86.21±12.72	<0.001**
• 45	76.24±8.51	93.13±8.16	84.69±11.87	<0.001**
• 60	75.89±7.05	92.07±8.56	83.98±11.27	<0.001**
• 75	75.20±7.01	90.47±9.36	82.83±11.25	<0.001**
• 90	75.89±7.08	92.29±10.21	84.09±12.02	<0.001**
After Extubation				
• 1	80.42±8.01	103.04±8.03	91.73±13.89	<0.001**
• 3	78.27±7.16	101.22±7.91	89.74±13.77	<0.001**
• 5	76.18±6.79	98.49±8.31	87.33±13.52	<0.001**
• 10	75.24±6.20	95.07±7.37	85.16±12.05	<0.001**
• 15	75.69±6.19	92.91±7.65	84.30±11.08	<0.001**

There was no significant difference in Mean arterial pressure (MAP) between two groups at baseline and also after the infusion of the study drugs.

Patients who received fentanyl had shown significant increase in MAP in the 1st minute after intubation from 96.71±8.99 to 107.31±8.69 and also in the 1st minute after extubation from 92.29±10.21 to 103.04±8.03.

Patients who received dexmedetomidine had shown no increase in MAP after intubation and also only mild increase in MAP in the 1st minute after extubation from 75.89±7.08 to 80.42±8.01.

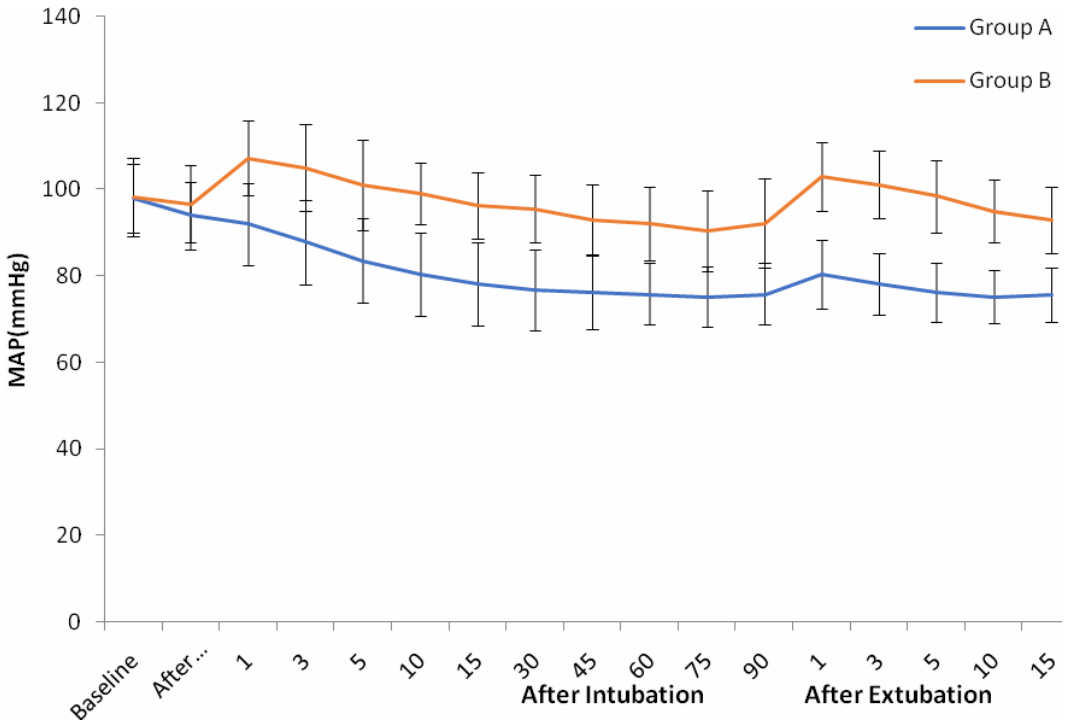

FIGURE NO 14: LINE DIAGRAM SHOWING MEAN ARTERIAL BLOOD PRESSURE COMPARISON BETWEEN TWO GROUPS

Table 9: Respiratory rate breaths per minute

Respiratory rate breaths per minute	Group A	Group B	Total	P value
Baseline	16.53±2.83	16.84±2.81	16.69±2.81	0.602
After infusion	15.82±2.42	16.22±2.68	16.02±2.55	0.460
After Extubation				
• 1	17.84±1.88	17.98±2.04	17.91±1.95	0.748
• 3	17.38±2.24	17.24±2.73	17.31±2.48	0.801
• 5	17.47±2.49	17.31±2.74	17.39±2.60	0.779
• 10	16.78±2.94	16.71±3.17	16.74±3.04	0.918
• 15	17.07±3.46	18.44±12.48	17.76±9.13	0.477

There was insignificant difference between in respiratory rate between two groups

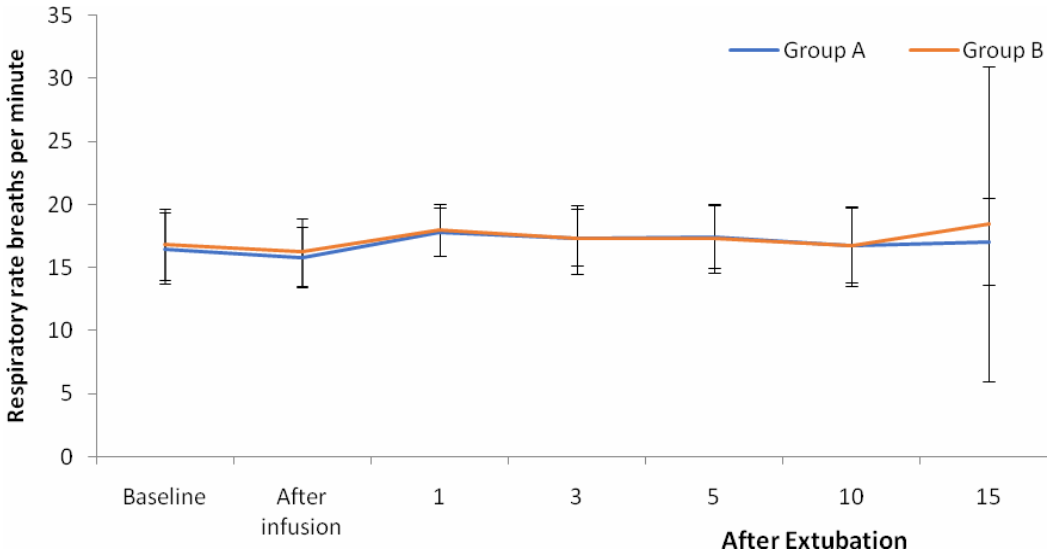

FIGURE NO 15: LINE DIAGRAM SHOWING RESPIRATORY RATE COMPARISON BETWEEN TWO GROUPS

Table 10: SPO2%- A Comparison in two groups of patients studied

SPO2%	Group A	Group B	Total	P value
Baseline	98.36±1.30	98.38±1.23	98.37±1.26	0.934
After infusion	98.53±0.99	98.60±1.05	98.57±1.02	0.758
After Intubation				
• 1	98.47±0.89	98.44±1.08	98.46±0.98	0.915
• 3	98.73±0.96	98.69±0.79	98.71±0.88	0.812
• 5	98.78±0.90	98.73±0.91	98.76±0.90	0.817
• 10	98.80±0.76	98.98±0.99	98.89±0.88	0.341
• 15	98.87±0.89	98.87±0.97	98.87±0.93	1.000
• 30	98.89±0.83	98.89±0.88	98.89±0.85	1.000
• 45	99.04±0.77	98.96±0.77	99.00±0.76	0.584
• 60	98.91±0.9	98.71±0.87	98.81±0.89	0.287
• 75	98.8±0.97	98.87±0.84	98.83±0.90	0.728
• 90	98.89±0.78	98.96±0.82	98.92±0.80	0.694
After Extubation				
• 1	98.64±0.83	98.69±0.97	98.67±0.90	0.816
• 3	98.71±0.97	98.60±1.10	98.66±1.03	0.611
• 5	98.53±1.04	98.62±0.91	98.58±0.97	0.667
• 10	98.71±0.89	98.56±0.92	98.63±0.91	0.418
• 15	98.69±0.92	98.98±0.89	98.83±0.91	0.135

There was insignificant difference in SPO_2 % between two groups

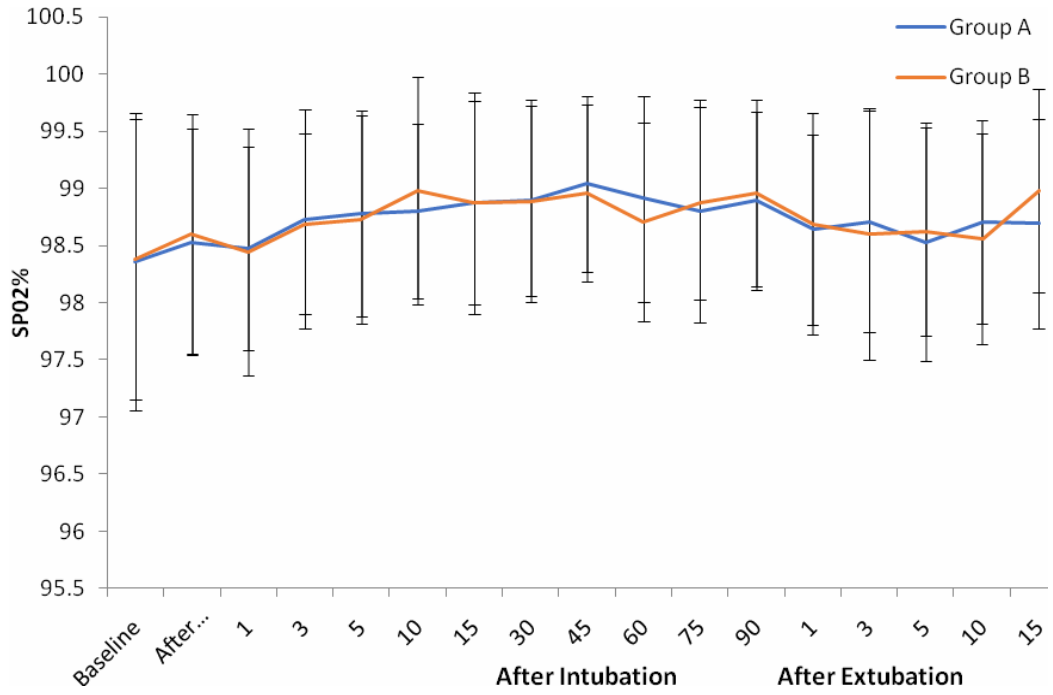

FIGURE NO 16: LINE DIAGRAM SHOWING SPO_2% COMPARISON BETWEEN TWO GROUPS

Table 11: VAS Score- A Comparison in two groups of patients studied

VAS Score	Group A	Group B	Total	P value
0hr	1.44±0.50	2.64±0.48	2.04±0.78	<0.001**
6 hr	3.07±0.54	5.09±0.47	4.08±1.13	<0.001**
12 hr	5.07±0.62	6.38±0.53	5.72±0.87	<0.001**
24 hr	6.11±0.78	6.84±0.42	6.48±0.72	<0.001**

VAS scores are significantly higher in fentanyl group when compared to dexmedetomidine at 0hr, 6hr, 12hr and 24hrs post-surgery.

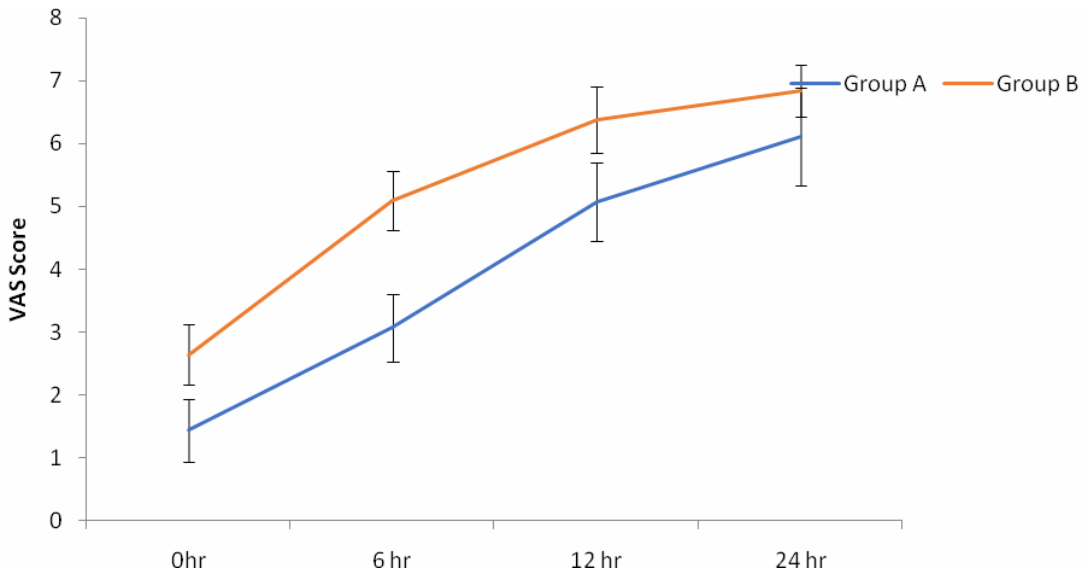

FIGURE NO 17: LINE DIAGRAM SHOWING VAS SCORES COMPARISON BETWEEN TWO GROUPS

Table 12: No. of Rescue analgesic doses in first 24hrs

No. of Rescue analgesic doses in first 24hrs	Group A	Group B	Total
1	11(24.4%)	0(0%)	11(12.2%)
2	28(62.2%)	2(4.4%)	30(33.3%)
3	6(13.3%)	28(62.2%)	34(37.8%)
4	0(0%)	15(33.3%)	15(16.7%)
Total	45(100%)	45(100%)	90(100%)

There was significant difference in the requirement of rescue analgesics in the first 24hrs between the two groups.

62.2% of patients from Group A required only 2 rescue analgesics while 62.2% of patients from Group B required 3 rescue analgesics in the first 24hrs following surgery. [p value <0.001, significant]

Significant figures:

+ Suggestive significance (P value: $0.05<P<0.10$)

* Moderately significant (P value:$0.01<P \leq 0.05$)

** Strongly significant (P value : $P \leq 0.01$)

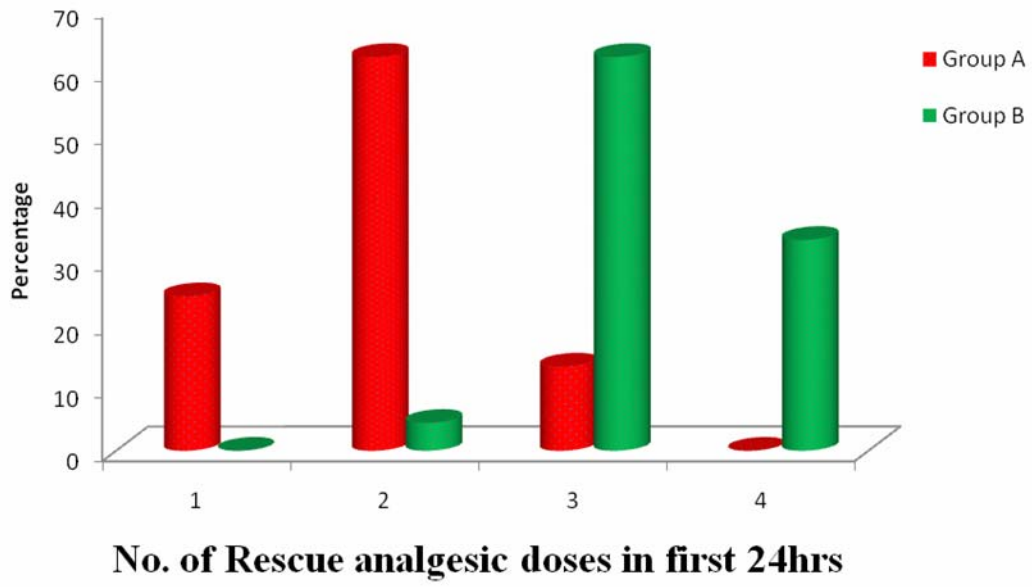

FIGURE NO 18: BAR DIAGRAM SHOWING RESCUE ANALGESICS

COMPARISON BETWEEN TWO GROUPS

DISCUSSION

During general anaesthesia, the critical events include laryngoscopy, tracheal intubation and extubation. These events are associated with significant sympathetic stimulation. To mitigate the hemodynamic changes associated with sympathetic response, various techniques have been tried. These techniques range from application of local anaesthtetics, nerve blocks infiltration to various drugs. Short acting beta blockers like esmolol was tried initially to treat hypertensive episodes. But beta blockers are associated with side effects like bradycardia and conduction delays. Other drugs include calcium channel blockers, vasodilators, opioids and adrenergic blocking agents.

Dexmedetomidine is a highly selective α_2 agonist.[11] It maintains hemodynamic stability through its central sympatholytic action. Dexmedetomidine has been extensively used as an adjuvant to general anaesthesia owing to its anaesthetic sparing and sedative properties. Fentanyl is synthetic potent μ receptor agonist.It controls both heart rate and blood pressure responses during intubation and extubation.[13]

This was a prospective double blinded randomized controlled study carried out at R L Jalappa Hospital and Research, Tamaka, Kolar, during the Academic year from January 2019-June 2020. Ninety patients of age group 20-50years with ASA grade I, II of either sex undergoing elective surgeries with duration of approx. 90mins like laminectomy, Oro-maxillary, ENT, Thyroid, laparotomies and laparoscopic surgeries under general anaesthesia were included. Patients were randomly divided into two groups each of 45 after obtaining the informed consent. Baseline vitals like HR, SBP,

DBP and MAP were recorded. Loading dose of the study drug was started at the rate of 1µg/kg and given over 10mins. After the loading dose is given, the required monitoring parameters were once again recorded and the study drug infusion rate was changed to maintenance dose of 0.5µg/kg/hr Preoxygenation was done with 100% oxygen for 3minutes and premedicated with glycopyrrolate and induced with propofol. till 10mins prior to extubation. Group A received dexmedetomidine and Group B received fentanyl. The infusion of study drug was stopped 10mins prior to extubation. HR, SBP, DBP and MAP were again recorded until 15mins post extubation. VAS scores were recorded for first 24hrs post-operative period. The requirement of rescue analgesics was also compared between two groups.

Both the groups were comparable in terms of age, weight, gender and ASA grading in our study. In our study, we observed that there was significant difference in the heart rate after the intubation with less increase in dexmedetomidine group when compared to fentanyl group as in accordance with the study conducted by Tanuja et al. [65]

From our study, we observed a significant increase in SBP, DBP and MAP after intubation with fentanyl group than dexmedetomidine group with p value less than 0.05. Our results were consistent with the study conducted by Patel CR et al, which has shown similar fluctuations in blood pressure after intubation implying the attenuating effect of dexmedetomidine on laryngoscopic response.[5]

From Our study, we found out that intraoperative hemodynamic were better maintained with dexmedetomidine infusion with MAP 20% less than baseline than fentanyl infusion. Bekker et alfrom his study concluded that dexmedetomidine infusion was able to blunt the perioperative blood pressure changes.[8]

By observing the significant increase in HR and MAP in our study after extubation in fentanyl group than dexmedetomidine group, we conclude that dexmedetomidine is better in attenuating the stress response during extubation. Kotak N et alfrom his study concluded that 0.5μg/kg of dexmedetomidine over 10mins prior to extubation is effective in attenuating stress response to extubation.[6] Aksu et alfrom his study concluded that 0.5μg/kg of dexmedetomidine is effective in mitigating airway reflexes during extubation better than fentanyl 1μg/kg[7]. Study done by Garg A et aldemonstrated that intraop infusion of dexmedetomidine at 1 μg/kg over 10 min followed by 0.4 μg/kg/h reduces the emergence agitation after nasal surgery[67].

Post-operative analgesia is important for anaesthesiologist as it impairs the recovery of the patient. Our study demonstrated that patients who received intraop dexmedetomidine had less VAS scores when compared to fentanyl group with p value less than 0.05.

Our results were consistent with the study done by Vaswani JP et al, where they concluded that postoperative analgesia was higher in dexmedetomidine group.[10] Study done by Turgat N et aldemonstrated that fentanyl group required earlier rescue analgesic than dexmedetomidine group.[63]

In our study there is insignificant difference in RR and SPO_2 between two groups.

Dexmedetomidine has side effects such as bradycardia and hypotension. We did not encounter any such episodes in our study.

CONCLUSION

We hereby conclude from our study that, dexmedetomidine at 1μg/kg over 10mins followed by 0.5μg/kg/hr of infusion is better in attenuating the stress response to intubation, in maintaining the intraoperative hemodynamic and in attenuating extubation response. Dexmedetomidine also provides better post-operative analgesia when compared to fentanyl.

SUMMARY

A randomized double blinded prospective control study was conducted at R L Jalappa Hospital and Research Centre, Tamaka, Kolar from January 2019-June 2020. Ninety patients of either sex belonging to ASA I/II grade and of age group between 20-50years, undergoing elective surgeries of duration approx. 90mins under general anaesthesia were included in this study.

Patients were allotted into two groups after informed consent has been taken based on computer generated table. Baseline vitals like HR, SBP, DBP, MAP, RR, SPO_2 were noted before and after the loading dose of study drug was given. The loading dose was changed to maintenance dose and preoxygenation was done for 3mins. Patient was then premedicated with Inj. Glycopyrrolate and induced with propofol.

Group A received Dexmedetomidine at 1µg/kg over 10mins followed by 0.5µg/kg/hr and Group B received Fentanyl at 1µg/kg over 10mins followed by 0.5µg/kg/hr till 10mins prior to extubation.

Vitals were noted starting from intubation till 15mins post extubation. Vas scores were assessed and no. of recue analgesics required in the first 24hrs in each group were also noted.

There was no significant difference between both groups in terms of age, gender, ASA grading, RR and SPO_2.

There was significant decrease in HR, SBP, DBP and MAP in dexmedetomidine group after intubation and extubation. Post-operative analgesia was better in dexmedetomidine group than fentanyl group.

Thus, Dexmedetomidine is better in attenuating the pressor response during both intubation and extubation. It also provides stable perioperative hemodynamic and good postoperative analgesia.

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ANNEXURE I

PROFORMA

INVESTIGATORS: Dr G N S Sravanthi, Dr Ravi M

NAME: AGE: SEX: WT:

HOSPITAL NO:

DEPT: ASA GRADE:

DIAGNOSIS AND OPERATION:

PREANAESTHETIC EVALUATION:

GENERAL PHYSICAL EXAMINATION

PALLOR: CLUBBING: ICTERUS:

OEDEMA:

LYMPHADENOPATHY: MALLAMPATI CLASS:

PR: BP: RR:

SYSTEMIC EXAMINATION:

CVS: RS: CNS: PA:

INVESTIGATIONS

Hb%: BT/CT: BLOOD UREA: Sr Cr:

RBS:

Na^+: K^+: ECG:

CHEST XRAY:

PROTOCOL:

PREMEDICATION: At 10:00 PM-Tab Rantac 150mg+ Tab Alprazolam-0.5mg

Inj.Glycopyrrolate 0.2mg followed by pre-oxygenation for 3mins

INDUCTION: Inj.Propofol 2 mg/kg, Inj.Suxamethonium 2mg/kg

MAINTENANCE: With Vecuronium 0.02 mg/kg (every 30-40 min); Isoflurane (0.8 – 1.0 MAC) Nitrous Oxide 60% with Oxygen

MONITORING: Heart rate, Systolic Blood Pressure, Diastolic Blood Pressure, Mean arterial pressure, Respiratory rate, SpO2

REVERSAL: Inj.Neostigmine 0.05 mg/kg, Inj.Glycopyrrolate 0.01mg/kg IV

STUDY DRUG:

Group D: Dexmedetomidine 1 µg/kg as a bolus dose slowly over 10minsprior to induction followed by 0.5µg/kg/hr as an infusion

Group F: Fentanyl 1µg/kg as a bolus dose over 10mins prior to induction followed by 0.5 µg/kg/hr as an infusion

	Baseline	After infusion	After intubation 1min	3 min	5 min	10 min	15 min	30 min	45 min	60 min	75 min	90 min	After extubation 1 min	3 min	5 min	10 min	15 min
HR Beats/ min																	
SBP																	
DBP																	
MAP																	
RR																	
SpO2																	

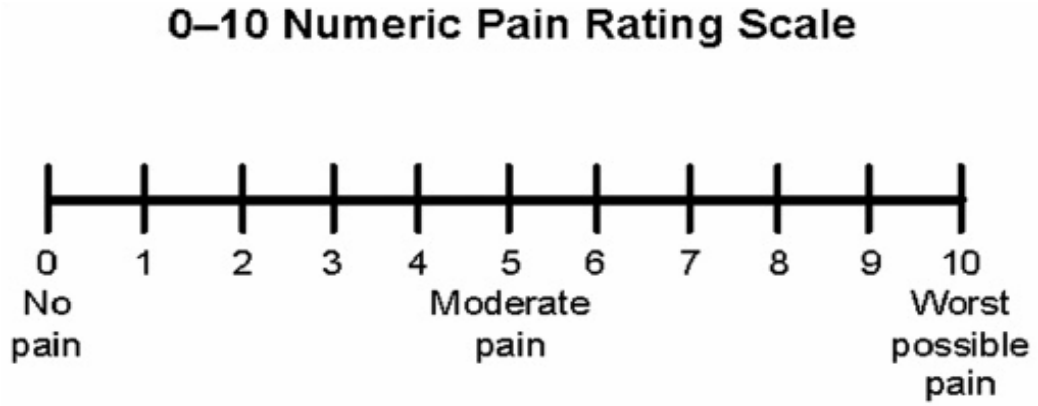
POST OPERATIVE PAIN: **VISUAL ANALOG SCALE**

0 – No Pain

1-3 – Mild Pain

4-6 – Moderate Pain

7-10 – Severe Pain



ANNEXURE II

PATIENT INFORMATION SHEET

TITLE OF THE STUDY: COMPARATIVE EVALUATION OF DEXMEDETOMIDINE AND FENTANYL INFUSION ON HAEMODYNAMIC RESPONSE IN PATIENTS UNDERGOING ELECTIVE SURGERY UNDER GENERAL ANAESTHESIA

The main objective of the study is to compare and evaluate dexmedetomidine and fentanyl on hemodynamic response in patients during intubation and extubation.

Purpose of the research: The procedures like laryngoscopy and intubation evoke stress response in patients undergoing elective surgeries under general anaesthesia. Due to the activation of sympathetic system, there will be increase in heart rate, mean arterial blood pressure and increased systemic vascular resistance. These hemodynamic changes can be tolerated by healthy individuals but not by patients who have hypertension or coronary artery disease. Therefore, there is a constant need of a drug that attenuates this presser response with fewer side effects in patients undergoing elective surgeries.

Procedures and Protocol:

This is a randomized prospective study. 90 patients undergoing elective surgeries under general anaesthesia at R L Jalappa Hospital, Tamaka, Kolar during the Academic year from January 2019-January 2020 will be included in the study.

After obtaining informed consent, 90 patients will randomly be divided into two (2) groups of 45 each. Randomization will be done by computer generated table.

GROUP D: IV Dexmedetomidine 1µg/kg will be given as loading dose over 10mns prior to inductionfollowed by 0.5µg/kg/hr as an infusion.

GROUP F: IV Fentanyl 1µg/kg will be given as a loading dose over 10mns prior to inductionfollowed by 0.5µg/kg/hr as an infusion.

Reimbursements: You will not be given money or gifts to take part in this research.

Confidentiality: We will not be sharing the identity of the participant. The information we collect from you will be kept confidential and only researchers involved in this project will have access to it.

Right to Refuse or Withdraw: You do not have to take part in this research, if you do not wish to do so and you can refuse to participate.

Whom to Contact: If you have any questions, you may ask us now or later. Even after the study has started, you may contact the following person:

For more information:

Dr. G N S Sravanthi	Dr. Ravi M
Postgraduate in Anaesthesiology	Professor of Anaesthesiology
Sri Devaraj Urs Medical College, Tamaka, Kolar	Sri Devaraj Urs Medical College, Tamaka, Kolar
Mobile – 8472090239	Mobile - 9845287591
Email: sravanthigns@gmail.com	Email: ravijaggu@gmail.com

ANNEXURE III

INFORMED CONSENT FORM

Name of the institution: Sri Devaraj Urs academy of higher education and research.

TITLE OF THE STUDY

COMPARATIVE EVALUATION OF DEXMEDETOMIDINE AND FENTANYL INFUSION ON HAEMODYNAMIC RESPONSE IN PATIENTS UNDERGOING ELECTIVE SURGERY UNDER GENERAL ANAESTHESIA

Name of the principal investigator: **Dr. G N S SRAVANTHI, DR. RAVI MADHUSUDHANA**

I have been explained in a language understandable to me regarding the procedure i.e., increase in hemodynamic response during intubation and extubation under general anaesthesia and the treatment protocol for it.

I have also been explained the need of attenuating hemodynamic responses during intubation and extubation by combination of drugs like dexmedetomidine and fentanyl.

The associated side effects of study drugs such as hypotension and bradycardia have been enlisted to me and the way it is treated.

Bradycardia: Less than 60bpm- Inj. Atropine 0.6 mg (I.V)

Hypotension: Less than 30% of baseline systolic blood pressure- Inj.Mephenteramine 6 mg (I.V).

I have read the information and I have had the opportunity to ask questions regarding various aspects of the study and my questions have been answered to my satisfaction.

I am aware that I am entitled to refrain/withdraw from study at any point.

I, the undersigned agree to participate in this study and authorize the collection and disclosure of my personal information as outlined in this consent form.

Subject's/guardian's name and signature/thumb impression:

Date:

Name and signature of witness:

Date:

Name and signature of principal investigator

Date:

For any clarification you are free to contact the Investigator:

Principal Investigators

Dr. G N S SRAVANTHI (Mobile - 8472090239)

Dr. Ravi Madhusudhana (Mobile - 9845287591)

A copy of this informed consent form has been provided to the participant.

KEY TO MASTER CHART

M	Male
F	Female
KGS	Kilograms
ASA PS	American society of Anaesthesiologists Physical Status
HR	Heart Rate
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
MAP	Mean Arterial Pressure
mmHG	Millimetre of Mercury
SPO_2	Peripheral Capillary Oxygen Saturation
VAS	Visual Analogue Scale
MINS	Minutes
B/L	Bilateral
FESS	Functional Endoscopic Sinus Surgery
CSOM	Chronic Suppurative Otitis Media
MNG	Multinodular Goitre
SDH	Subdural Haemorrhage
L	Lumbar
S	Sacral
ORIF	Open Reduction and Internal Fixation
DNS	Deviated Nasal Septum
DCR	Dacrocystorhinostomy
LCP	Locking Compression Plate

MASTER CHART

| GROUP | AGE IN YEARS | GENDER | WEIGHT IN KGS | ASA- PHYSICAL STATUS | DIAGNOSIS | OPERATION | IN-PATIENT NUMBER | HEART RATE IN BEATS PER MINUTE | | | | | | | | | | | | | | | | | | | | | | | | | | | | SYSTOLIC BLOOD PRESSURE IN MM HG | | | | | | | | | | | | | | | | | | | | | | DIASTOLIC BLOOD PRESSURE IN MM HG | | | | | | | | | | | | | | | | | | | | | | MEAN ARTERIAL PRESSURE IN MMHG | | | | | | | | | | | | | | | | | | | | | | RESPIRATORY RATE BREATHS PER MINUTE | | | | | | | | | | SPO2 | | | | | | | | | | | | | | | | | | | | | | VAS Score | | | | |
|---|---|---

MASTER CHART

| | | |