“COMPARISON OF 0.5 µg/ kg ,0.75 µg/ kg IV DEXMEDETOMIDINE AND NORMAL SALINE FOR ATTENUATION OF HAEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION”

By

Dr. BON SEBASTIAN

DISSERTATION SUBMITTED TO
SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF MEDICINE

IN

ANAESTHESIOLOGY

Under the guidance of

Dr. ANAND .T. TALIKOTI, MD
Professor, SDUMC, KOLAR

DEPARTMENT OF ANAESTHESIOLOGY

SRI DEVARAJ URS MEDICAL COLLEGE

KOLAR-563101

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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation/thesis entitled **"COMPARISON OF 0.5µg/kg, 0.75µg/kg IV DEXMEDETOMIDINE AND NORMAL SALINE FOR ATTENUATION OF HAEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. ANAND .T .TALIKOTI, MD Professor.** Department Of Anaesthesiology and Critical Care, Sri Devaraj Urs Medical College, Tamaka, Kolar.

Date: **Dr BON SEBASTIAN**

Place : Kolar .

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Dr BON SEBASTIAN

LIST OF ABBREVIATIONS

ASA	**American Society of Anaesthesiologists.**
ATP	**Adenosine triphosphate**
BP	**Blood Pressure**
CABG	**Coronary artery bypass grafting**
CNS	**Central Nervous System.**
CT	**Computed tomography**
DBP	**Diastolic Blood Pressure**
ECG	**Electrocardiogram.**
FDA	**Food and Drug Administration**
GABA	**Gamma - aminobutyric acid**
GFR	**Glomerular filtration rate**
HR	**Heart Rate.**
ICU	**Intensive Care Unit**
IHD	**Ischaemic heart disease**
Inj.	**Injection**
IUPAC	**International Union of Pure and Applied Chemistry**
iv.	**Intravenous**
IVRA	**Intravenous Regional Anaesthesia**
Kg	**Kilogram.**
MAC	**Minimum alveolar concentration**

MAP	**Mean arterial pressure**
mg	**Milligrams**
min	**Minutes**
MRI	**Magnetic Resonance Imaging**
SBP	**Systolic Blood Pressure**
SpO2	**Percentage of Oxygen Saturation.**
TIVA	**Total intravenous anaesthesia**
α	**Alpha**
β	**Beta**
µg	**Microgram**
%	**Percentage**

ABSTRACT

INTRODUCTION

Laryngoscopic manipulation and endotracheal intubation during anaesthetic induction is a noxious stimuli mediated by proprioceptors in the supraglottic area and trachea. It can result in tachycardia, arrhythmias, hypertension and raised intracranial pressure resulting in cerebrovascular accidents which could be detrimental to patients with ischaemic heart disease or compromised myocardial function. Recently α-2 agonist like dexmedetomidine has been studied in a dose of 0.5µg/kg and 1µg/kg iv to attenuate this response. There was no study with dexmedetomidine in a dose of 0.75µg/kg iv. Hence this study was undertaken to compare the effects of dexmedetomidine in a dose of 0.5µg/kg, 0.75µg/kg iv and normal saline to attenuate the haemodynamic response to laryngoscopy and endotracheal intubation.

AIMS AND OBJECTIVES

1) To study the efficacy and compare Inj. dexmedetomidine 0.5µg/kg, 0.75µg/kg iv and normal saline for attenuation of haemodynamic response following laryngoscopy and endotracheal intubation. The magnitude of response is assessed in terms of changes in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure.

2) To assess any side effects like hypotension, bradycardia and sedation associated with the drug.

METHODOLOGY

After ethical committee clearance, ninety patients of ASA-1 grade were enrolled in the study and divided equally into 3 groups. Group A – received normal saline, Group B-received Inj. dexmedetomidine 0.5µg/kg iv and Group C-received Inj. dexmedetomidine 0.75µg/kg iv as infusion over 10 minutes. After infusion, Ramsay sedation score noted at 2, 5 and 10 minutes. Then patient was induced with Inj. propofol 2mg/kg body weight+ Inj. Fentanyl 1µg/kg + Inj. Succinylcholine 2mg /kg body weight iv. Intubation response was assessed by heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure recorded at 1, 3 and 5 minutes after intubation . The data collected were statistically analysed.

SUMMARY OF RESULTS

The groups were well-matched for their demographic data. The basal readings of heart rate, SBP, DBP and MAP were similar in all the three groups. Maximum intubation response was seen at 1' post intubation. The group A had statistically higher values of HR, SBP, DBP and MAP at all time intervals post intubation when compared to group B and group C. The haemodynamic variables never reached the baseline by 5 minutes in case of group A. In group B they approached near the baseline by 3 minutes. In group C the variables fell below the baseline by 3 minutes. Group B and group C obtunded the intubation response better when compared with Group A.

Though bradycardia and hypotension have been reported in other studies, neither bradycardia nor hypotension were observed in the patients. The mean sedation scores were more in group B and group C when compared to group A.

CONCLUSION

Dexmedetomidine in a dose of 0.5µg/kg and 0.75µg/kg iv attenuates laryngoscopy and endotracheal intubation when compared to normal saline while maintaining a state of arousable sedation.

Key Words: Laryngoscopy, Intubation, Dexmedetomidine, General Anaesthesia.

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INTRODUCTION

Anaesthetic practice has evolved from a need for pain relief and altered consciousness to allow surgery. In general anaesthesia a reversible state of unconsciousness is achieved. Inorder to safeguard the airway in such occasions, endotracheal intubation is essential. Endotracheal intubation involves the translaryngeal placement of the tube into the trachea via the nose or mouth. Laryngoscopy and intubation are noxious stimuli capable of stimulating the sympathoadrenal system and producing heightened cardiorespiratory and neurological reflexes such as tachycardia, hypertension, bronchospasm, increased intracranial pressure and increased intraocular pressure.[1]

The response although transient can prove to be detrimental for patients with ischaemic heart disease (IHD) or compromised myocardial function. Various drug regimens and techniques have been used from time to time for blunting the stress response like opioids, barbiturates, benzodiazepines, β blockers, calcium channel blockers, vasodilators like nitroglycerine.[2] The above drugs though were effective in attenuating laryngoscopy and intubation response, were required to be used in high doses and were associated with much adverse effects.

None of them were ideal, so a continued quest was there by the clinicians for obtunding the sympathoadrenal response. This led to the use of α-2 adrenergic agonists like clonidine and dexmedetomidine. The useful properties of dexmedetomidine like sedation, anxiolysis, sympatholysis and analgesic sparing properties make it an ideal drug for attenuating the haemodynamic stress response.[3] Dexmedetomidine is a newer α-2 agonist when compared to clonidine and is gaining popularity among the clinicians. It has 8 times highly selective α-2 adrenergic agonistic activity than clonidine.[4]

Dexmedetomidine has been studied by many authors in a dose of 1μg/kg as an infusion for attenuating haemodynamic response to laryngoscopy and intubation. They found it to be very effective but was associated with increased sedation scores and bradycardia.[5,6] One study with dexmedetomidine in a dose of 0.5μg/kg has been shown to attenuate stress response to laryngoscopy and intubation.[7]

There are no studies with dexmedetomidine in a dose of 0.75μg/kg being used to attenuate intubation response. Hence this study is undertaken in order to compare dexmedetomidine in a dose of 0.5μg/kg , 0.75μg/kg and a placebo (normal saline) for attenuation of stress response to laryngoscopy and endotracheal intubation.

OBJECTIVES

1) To study the efficacy and compare Inj. dexmedetomidine 0.5µg/kg, 0.75µg/kg iv and normal saline for attenuation of haemodynamic response following laryngoscopy and endotracheal intubation. The magnitude of response is assessed in terms of changes in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure.

2) To assess any side effects like hypotension, bradycardia and sedation associated with the drug.

REVIEW OF THE ANATOMY OF THE UPPER AIRWAY [8]

The stress response during laryngoscopy and endotracheal intubation is brought about by the nerve supply of the upper airway.

The upper airway includes the nasal cavity, oral cavity, pharynx and larynx.

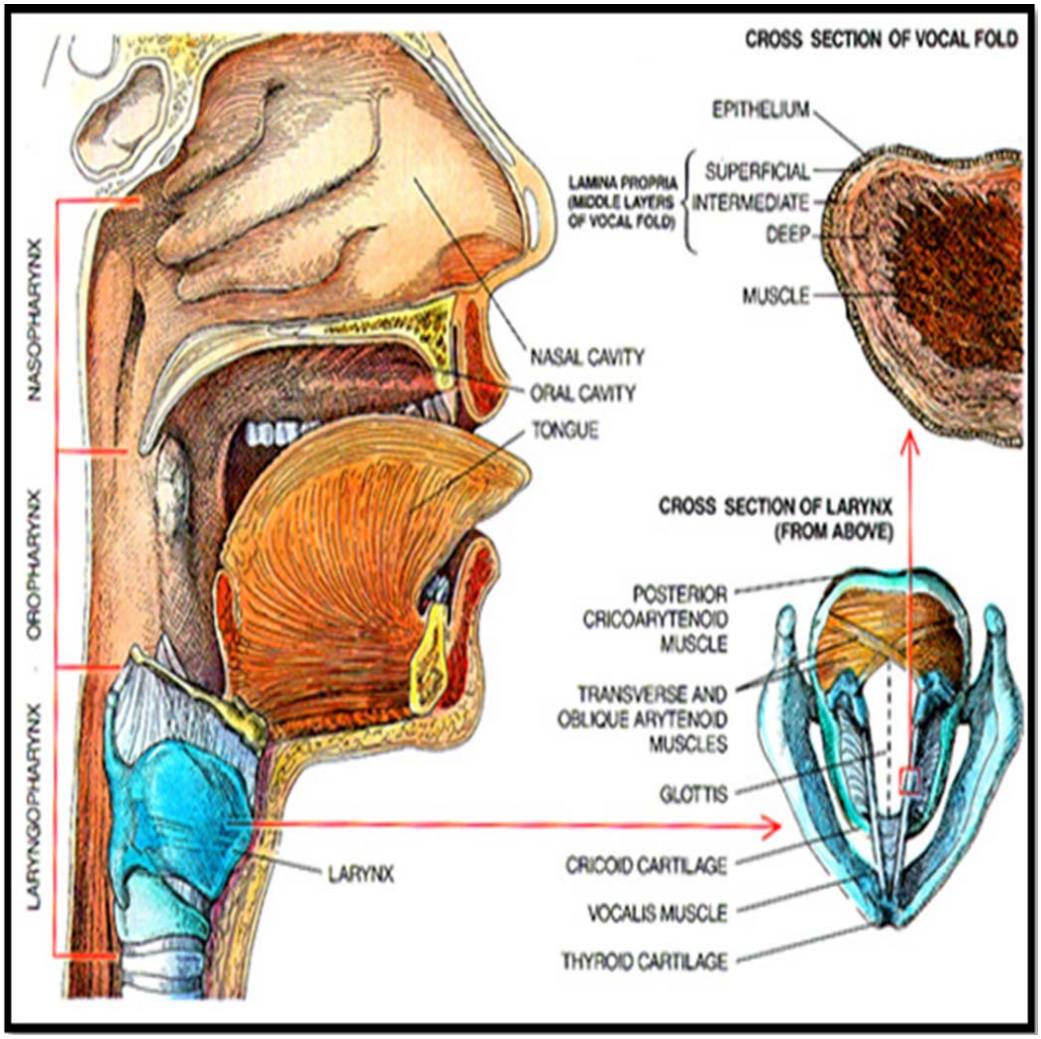

Figure 1: Anatomy of Larynx

SENSORY NERVE SUPPLY OF UPPER AIRWAY

NASAL CAVITY

- Olfactory nerves which arise from special olfactory cells are present in the olfactory mucus membrane and relay in the olfactory bulb. They are the special sensory nerves.
- Nerves of ordinary sensation arise from branches of nasociliary nerve, a branch of ophthalmic division (V1) of trigeminal nerve and branches of maxillary division (V2) of trigeminal nerve.
- Sympathetic post ganglionic vasoconstrictor fibres arise from superior cervical ganglion.
- Para sympathetic post ganglionic secretomotor fibres from the pterygopalatine ganglion supply the nasal glands.

MUCOUS MEMBRANE OF ORAL CAVITY

- Roof of the mouth is supplied by the greater palatine and nasopalatine nerves, branches of maxillary division of trigeminal nerve.
- Floor is supplied by the lingual nerve, branch of mandibular division of trigeminal nerve.
- Cheek is supplied by the buccal nerve, branch of mandibular division of trigeminal nerve.

TONGUE

- In anterior 2/3rd general sensation is carried by lingual nerve and chorda tympani carries the taste sensation.
- In posterior 1/3rd glossopharyngeal nerve carries both general and taste sensation.

PALATE

- Hard and soft palates are innervated by greater and lesser palatine nerves, nasopalatine and glossopharyngeal nerves.

PHARYNX

- Nasal part is supplied by maxillary nerve (V2).
- Oral part is supplied by glossopharyngeal nerve.
- Laryngeal part is supplied by internal laryngeal branch of vagus nerve.

EPIGLOTTIS

- Anterior surface is innervated by glossopharyngeal nerve.
- Posterior surface is innervated by vagus nerve.

LARYNX

- Mucus membrane above the vocal cords are supplied by internal laryngeal nerve.
- Mucus membrane below the vocal cords receive supply from recurrent laryngeal nerve.

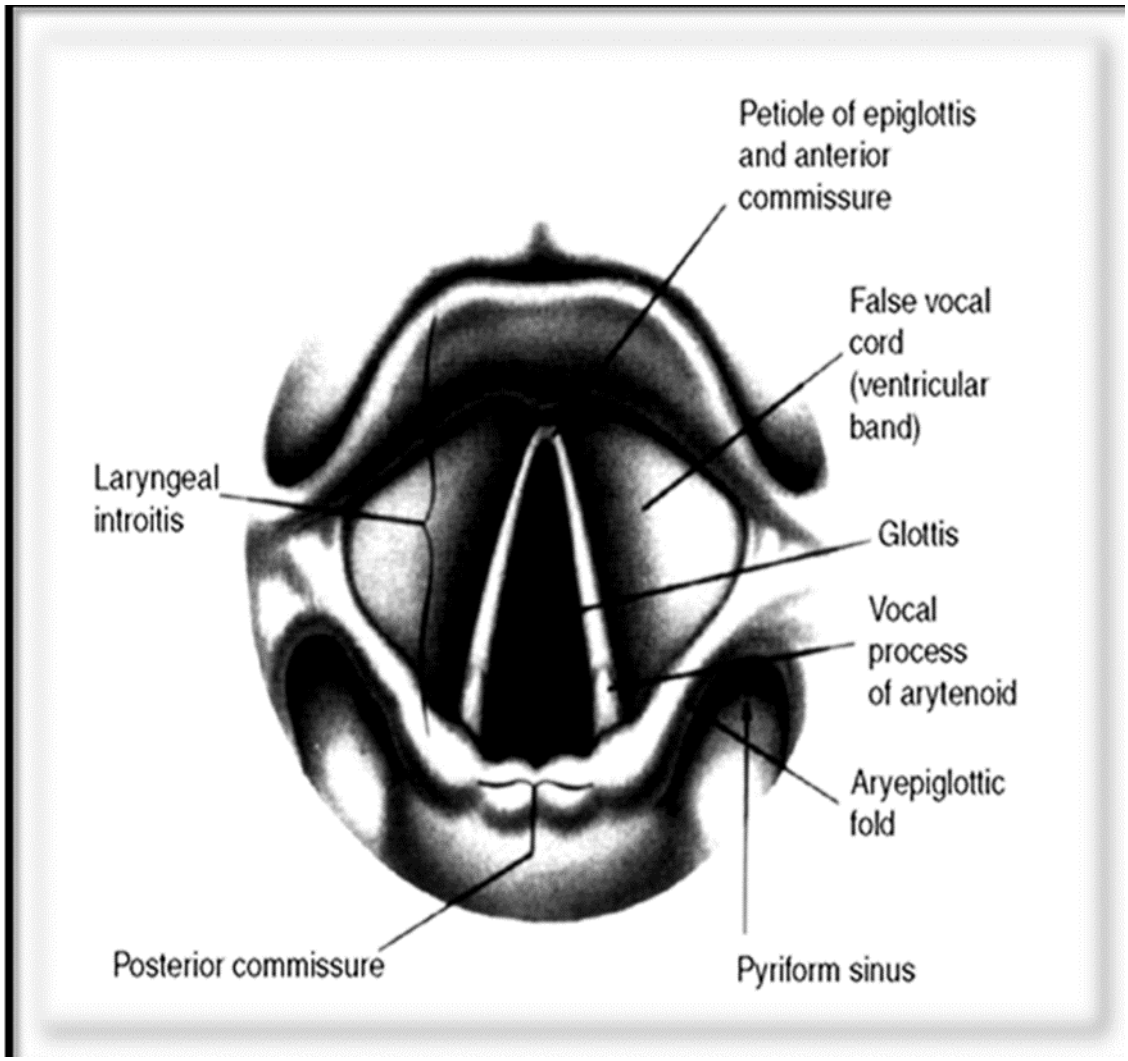

Figure 2: Laryngoscopic view of larynx

PHYSIOLOGICAL AND PATHOLOGICAL RESPONSES TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION [9]

Laryngoscopy, endotracheal intubation, and other airway manipulations are noxious stimuli capable of inducing profound changes in the cardiovascular physiology, primarily through reflex responses. The cardiovascular responses are initiated by proprioceptors located superficially in the airway mucosa. These proprioceptors consist of mechanoreceptors with small-diameter myelinated fibres, slowly adapting stretch receptors with large-diameter myelinated fibres and polymodal endings of nonmyelinated nerve fibres. They respond to tissue irritation in the supraglottic region and trachea.

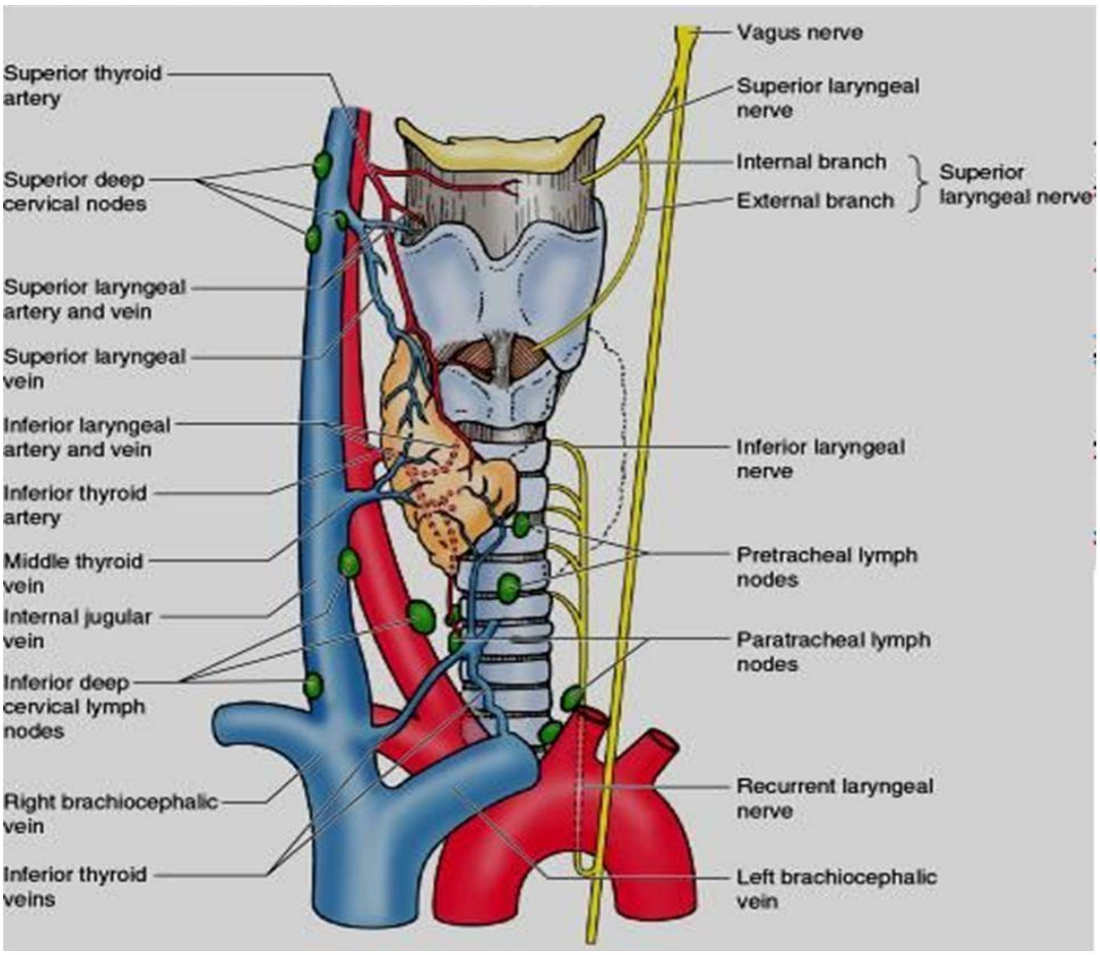

Figure 3: Nerve Supply of Larynx

The afferent pathway of the response is carried by glossopharyngeal and vagal nerves which transmit these impulses to the brain stem. It causes autonomic activation through both the sympathetic and parasympathetic nervous systems. Bradycardia is often seen in infants and small children and is the autonomic equivalent of the laryngospasm response. This reflex results from an increase in vagal tone at the sinoatrial node. It is a monosynaptic response to a noxious stimulus in the airway.

In adults the response to airway manipulation is hypertension and tachycardia. They are mediated by the cardioaccelerator nerves and sympathetic chain ganglia. This response is brought about by the release of norepinephrine from adrenergic nerve terminals and secretion of epinephrine from the adrenal medulla. Some of the response occur due to activation of the renin-angiotensin system, with release of renin from the renal juxtaglomerular apparatus, which is innervated by β-adrenergic nerve terminals.

Stimulation of the central nervous system results in increased electroencephalographic activity, cerebral metabolic rate, and cerebral blood flow. The increase in cerebral blood flow in turn results in elevated intracranial pressure, herniation of brain contents and severe neurological compromise.

REVIEW OF LITERATURE – CLINICAL STUDIES

A double blind randomised control study was done comparing the effects of dexmedetomidine 1µg/kg, remifentanil 1µg/kg and normal saline in 90 patients. The patients received the drugs as infusion over ten minutes. They were induced with propofol and relaxation was achieved by rocuronium 0.6 mg/kg. The parameters noted were heart rate, systolic blood pressure and diastolic blood pressure until 5 minutes after intubation. They found that maximum response was seen in the saline group followed by remifentanil group and the least was seen in dexmedetomidine. Thus it was concluded that both remifentanil and dexmedetomidine were effective in reducing the stress response with dexmedetomidine exhibiting a better efficacy. [10]

Another prospective study which was carried out evaluated dexmedetomidine 1µg/ kg, fentanyl 2µg/kg and esmolol 2 mg/kg. The infusions were administered 2 minutes before induction. The subjects were intubated after inducing with thiopentone 6mg/kg and relaxation with vecuronium 0.1mg/kg. They found out that esmolol was superior than the other two medications in attenuating systolic, diastolic and mean arterial pressures. On the other hand, dexmedetomidine proved to be superior in preventing rise of heart rate. [11]

In yet another study dexmedetomidine 1µg/kg, clonidine 2µg/kg and normal saline were analysed. The haemodynamic variables were noted at 1' , 3' 5' and 10' after intubation. They concluded that dexmedetomidine blunted the haemodynamic response better than clonidine and normal saline. [12]

Few authors initiated a prospective randomised control trial to compare the efficacy of dexmedetomidine in a dose of 0.6µg/kg to reduce the intubation response. It was evaluated in comparison with normal saline as a placebo. The groups were analysed in

terms of haemodynamic response, raise of intraocular pressure and dose of propofol required for induction. It was demonstrated that dexmedetomidine premedication provided a higher grade control of the haemodynamic parameters , decreased intraocular pressures and reduced the requirement for propofol. [13]

Dexmedetomidine in a dose of 1µg/kg was compared with fentanyl 1µg/kg by some authors in eighty patients. They demonstrated that both fentanyl and dexmedetomidine partially obtunded the intubation response. Dexmedetomidine proving to be better than fentanyl. They also noted some complications like hypotension and bradycardia in both the groups which was not statistically significant. [14]

A prospective randomised study was carried out in a tertiary care teaching hospital. A total of 100 patients posted for elective surgery under general anaesthesia were enrolled in the study. They were randomly divided into two groups, group L (lignocaine group) receiving 1.5mg/kg and group D (dexmedetomidine group) receiving 1µg/kg as an infusion. Thiopentone was given for induction and intubation was facilitated with succinylcholine. They demonstrated the efficacy of dexmedetomidine over lignocaine in decreasing the intubation response without any deleterious effects. Furthermore, dexmedetomidine decreases the dose of thiopentone required for induction of anaesthesia. [15]

Yet another study was done with the objective of studying the clinical effects of dexmedetomidine with esmolol and a control group in attenuating the presser response during laryngoscopy. The patients were randomly divided into three groups. Group C received placebo, Group E received 2 mg/kg of esmolol and Group D received 1µg/kg of dexmedetomidine intravenously over 10 min and 3 min before

induction of general anaesthesia. All patients were premedicated, induced and intubated using thiopentone and succinylcholine as per standard protocol. Both the study drugs attenuated the pressure response. Of the two drugs administered, dexmedetomidine 1μg/kg provided a consistent, reliable and effective attenuation of pressure responses when compared to esmolol 2 mg/kg. [16]

A study with the aim of studying the efficacy of 0.6 μg/kg dexmedetomidine, given 10 minutes (min) before induction to obtund the pressor response of laryngoscopy and tracheal intubation was conducted. Normal saline was chosen as the placebo. The study arrived at a conclusion that dexmedetomidine at a dose of 0.6μg/kg was able to attenuate the haemodynamic stress response to intubation in adults and pediatric patients. It was also found out that dexmedetomidine had the ability to reduce the requirement of thiopentone and vecuronium without significant side effects. [17]

A prospective, double-blinded, parallel group randomised clinical trial was initiated to evaluate the haemodynamic response to laryngoscopy and endotracheal intubation with a single preinduction infusion of dexmedetomidine 1 μg/kg over a 10 min period**.** The trial was done in 60 adult patients undergoing elective off pump coronary arterial bypass grafting. The patients received either dexmedetomidine or normal saline. Heart rate, systolic BP, diastolic BP, MAP and pulmonary artery pressures were significantly lower in those who received dexmedetomidine. There was no case of hypotension or bradycardia reported during the study. [18]

In a study conducted in a tertiary hospital in India, patients were given a loading dose of dexmedetomidine 1 μg/kg, followed by a continuous infusion of 0.5 μg/kg/hour. It was supplemented with end-tidal sevoflurane 1-2% when heart rate and mean arterial pressure exceeded 20% of baseline values. After surgery, the time taken to

discontinue dexmedetomidine infusion and the extubation time were also noted. The study demonstrated significant reduction in heart rate and systolic blood pressure following the loading dose of dexmedetomidine in the intraoperative period and during intubation and extubation. None required supplementary doses of analgesics in the intraoperative period. Thus they arrived at the conclusion that dexmedetomidine provided a stable haemodynamic profile in the perioperative period and blunted the pressor response to intubation and extubation with an acceptable recovery profile. [19]

A study was undertaken with the aim of comparing dexmedetomidine with an ultra-short acting beta blocker, esmolol to see which among the two is better in attenuating the haemodynamic response to laryngoscopy and tracheal intubation. Patients received dexmedetomidine 0.5µg/kg and esmolol 0.5mg/kg as intravenous premedication over five minutes before a rapid sequence induction and tracheal intubation. Systolic, diastolic and mean arterial pressures along with heart rate were measured using invasive arterial line at various time points. The percentage change of all the haemodynamic parameters from base line were less in the dexmedetomidine group than in the esmolol group at all time points of measurement. There was a statistically significant difference at various time points within 1 minute after tracheal intubation. This again proved the superior efficacy of dexmedetomine over esmolol in attenuating the pressor response. [20]

Yet another study compared the efficacy of esmolol and dexmedetomidine. Patients of either sex scheduled for elective neurosurgical procedures were included in this study. Patients were randomly administered 0.9% saline, dexmedetomidine 1µg/kg and esmolol 1.5mg/kg. All the drugs were infused over a period of 10 minutes. Data analysis revealed better stress response control for dexmedetomidine than esmolol. [21]

DEXMEDETOMIDINE PHARMACOLOGY [22,23]

Dexmedetomidine is a newer second generation α-2 agonist that was synthesised in the late 1980's. It is the pharmacologically active d- isomer of medetomidine. It got the approval of FDA in 1999 for use as a short term sedative analgesic in ICU. It was also certified for use in non-intubated patients (both adult and paediatric) that require sedation prior to and / or during surgical and other procedures in 2008.

CHEMICAL STRUCTURE:

Chemical Formula: $C_{13}H_{16}N_2$

IUPAC Name: 4-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1H-imidazole.

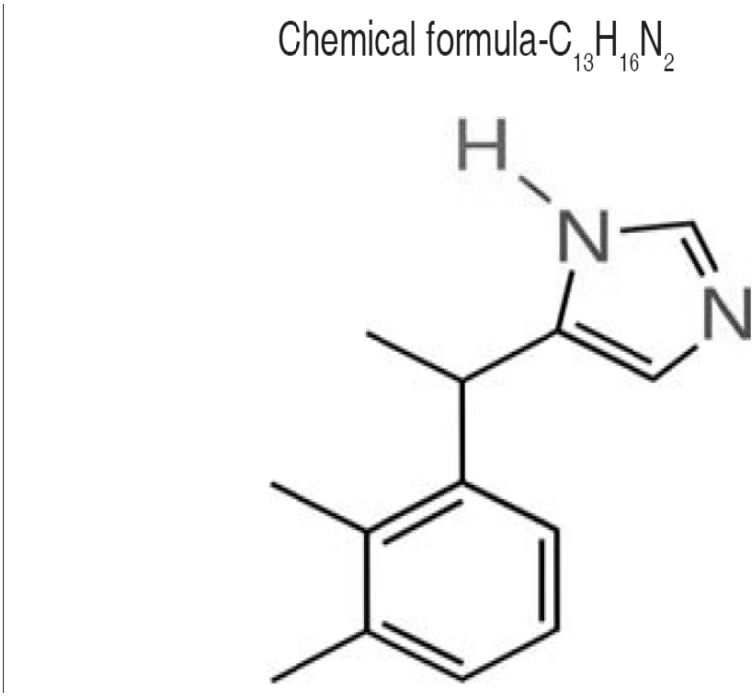

Figure 4: Chemical Structure of dexmedetomidine

MECHANISM OF ACTION:

PHYSIOLOGY OF α ADRENERGIC RECEPTORS

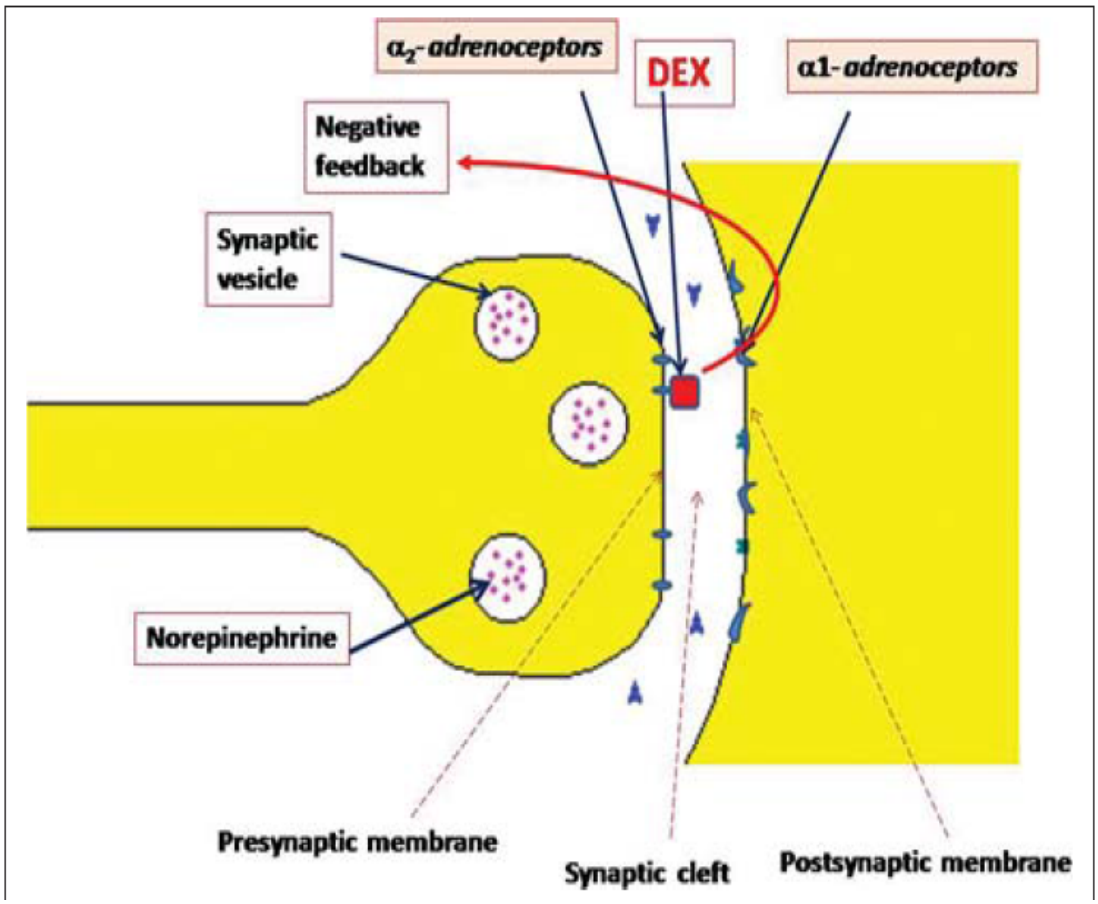

Figure 5: Physiology of α adrenergic receptors

Subtypes: α-adrenergic receptors

Receptor	Potency order	Specific actions	Mechanism	Net effect
α-2A	Epinephrine> Norepinephrine	decrease sympathetic outflow and blood pressure	$G_{i\ protein\ coupled}$: adenyl cyclase inactivation,	Biphasic response to BP
α-2B	Epinephrine> Norepinephrine	increases blood pressure	cAMP reduction,	Hypotension, Bradycardia
α-2C	Epinephrine> Norepinephrine	regulates neurotransmitter release from adrenergic nerves	release of Substance P in spinal cord: Inhibition	Analgesia, sedation

Table 1: Types of α-2 receptors

α-2 receptors are found at many sites in the CNS. The highest densities are found in locus ceruleus which is the predominant noradrenergic nuclei of the brainstem and an important modulator of vigilance. The presynaptic activation of the α-2 receptors will inhibit the release of norepinephrine and this brings about the sedative and hypnotic effects of dexmedetomidine.

It produces analgesia by central, spinal and peripheral mechanisms. The pre-synaptic α-2 receptors regulate the release of nor-adrenaline and adenosine tri phosphate (ATP), through negative feedback mechanism. The supraspinal level of analgesia is due to modulation of descending medullospinal noradrenergic pathway originating in the locus ceruleus. This supraspinal action explains the prolongation of spinal analgesia after intravenous administration of dexmedetomidine. At the spinal level the antinociceptive action is through the substantia gelatinosa (Lamina II of Rexed in grey matter of spinal cord). It closes the gate at the dorsal horn to stimuli coming from

peripheral Aδ and C fibers and also inhibits release of nociceptive humoral transmitters like substance P.

Activation of postsynaptic α-2 adrenoceptors is responsible for peripheral actions of the drug. Activation of α-2 receptors lead to dose dependent reduction in the level of plasma catecholamines, bradycardia and hypotension secondary to sympathetic inhibition of medullary vasomotor center.

After administering it rapidly, a biphasic response on blood pressure is observed: an initial short hypertensive phase which is followed by hypotensive phase. α-2B adrenergic receptors are responsible for the initial short hypertensive phase while subsequent hypotension is mediated by α-2A adrenergic receptors.

PHARMACODYNAMICS:

CARDIOVASCULAR SYSTEM

Dexmedetomidine produces a biphasic response on blood pressure with an initial transient rise with a reflex fall in heart rate brought about by stimulation of α-2B subtypes of receptors present in vascular smooth muscles. This is followed by fall in blood pressure and heart rate due to inhibition of central sympathetic outflow and stimulation of presynaptic α-2A receptors causing decreased release of noradrenaline leading to further fall in the blood pressure. It also produces a dose dependent increase in coronary vascular resistance and oxygen extraction without altering the supply demand ratio.

CENTRAL NERVOUS SYSTEM

Dexmedetomidine causes a reduction in cerebral blood flow and cerebral metabolic demand of oxygen and thereby reduces the intracranial pressure. The neuroprotective effects are a result of reduced circulating and cerebral catecholamines. This improves the blood supply to ischaemic cerebral tissues. It has been found to reduce the levels of glutamate, which enhances the cellular brain injury especially in subarachnoid haemorrhage. It has properties of sedation, hypnosis, anxiolysis and analgesia. The sedation caused by dexmedetomidine is termed as “cooperative” or “arousable” .

RESPIRATORY SYSTEM

Dexmedetomidine has no active role in the respiratory centre and therefore it has minimal effects on the respiratory system even over a broad range of plasma concentration. There is no impairment of ventilation or gas exchange.

ENDOCRINE SYSTEM

Dexmedetomidine causes inhibition of renin-angiotensin system and inhibit the release of renin. Dexmedetomidine causes suppression of stress response to surgery by activation of peripheral α-2 receptors and reducing the release of catecholamines. It also produces decreased insulin release from pancreas. It is found to have no inhibitory effects on steroidogenesis when used for short term sedation by intravenous infusion.[24]

RENAL SYSTEM

It is associated with increased glomerular filtration rate (GFR), increased excretion of sodium, water and thus diuresis.

HAEMATOLOGY

Dexmedetomidine causes decreased platelet aggregation.

EYES

It reduces the intraocular pressures.

MISCELLANEOUS

There occurs decreased gastrointestinal secretions and decreased gastrointestinal motility. It is capable of producing constriction of vascular and other smooth muscles. Dexmedetomidine also reduces the threshold of shivering by approximately two degree celsius.

PHARMACOKINETICS:

Dexmedetomidine has poor bioavailability due to extensive first pass metabolism. The sublingual route has a bioavailability of about 84%. It exhibits linear pharmacokinetics over a dose range of 0.2 – 0.7μg/kg/hr intravenous infusion. Pharmacokinetics does not change with age, sex or in patients with renal failure. It is rapidly distributed with a distribution half life of 6 minutes. The volume of distribution being 118 litres and has an elimination half life of 2 hours. It is 94% protein bound and does not displace most of the protein bound drugs used commonly in anaesthesia and intensive care. The context sensitive half life varies from 4 minutes for a 10 minute infusion to 250 minutes for an 8 hour infusion. Dexmedetomidine undergoes almost complete biotransformation (>95%) by glucoronidation and by cytochrome P 450 mediated aliphatic hydroxylation to inactive metabolites. These

metabolites are excreted in the urine (95%) and in faeces (4%). It is necessary to decrease the typical dose in patients with hepatic failure.

INDICATIONS:

1) PERIOPERATIVE USES:

a) Dexmedetomidine can be used as an adjunct to general anaesthetics to attenuate stress response to endotracheal intubation or extubation.

b) As an adjuvant to general anaesthesia it has minimum alveolar concentration (MAC) reducing and opiate sparing properties, which helps in decreasing the inhalational and intravenous anaesthetics and opioid requirements. It also has a strong synergistic effect with other sedatives

c) The analgesic-sparing effect can be observed which can last up to 24 hours in the post operative period.

d) Dexmedetomidine when given as a premedication, decreases the oxygen consumption and subsequent myocardial ischaemia and infarction in the intraoperative and post-operative period.

e) Intraoperative uses of dexmedetomidine include its use as adjunct to general anaesthesia, as adjunct to regional anaesthesia, in monitored anaesthesia care, or as a sole agent for total intravenous anaesthesia (TIVA).

f) Dexmedetomidine provides an ideal condition for facilitation of awake fibreoptic intubation in patients with compromised airway. It provides a good

sedation, analgesia with little or no respiratory depression as well as no effect on airway reflexes.

g) Dexmedetomidine is ideal for induction and maintenance of controlled hypotension in various surgeries to minimise the blood loss as well as providing optimal conditions for surgery like spinal fusion surgery, endoscopic nasal, and sinus surgery and maxillofacial surgery.

h) As an adjunct in neuraxial anaesthesia. Dexmedetomidine produces a dose-dependent increase in the duration of the motor and sensory blocks induced by local anaesthetics regardless of the neuraxial route of administration (epidural, caudal, or spinal) without any neurotoxicity

i) As adjuvant to regional anaesthesia: As an adjuvant in peripheral nerve block and intravenous regional anaesthesia (IVRA). Dexmedetomidine when added to local anaesthetics or given through intravenous route prolongs the duration of sensory block of local anaesthetic during peripheral nerve block. It also improves the quality of the block.

j) Dexmedetomidine is effective in reducing the postoperative nausea and vomiting. It is also capable of reducing the shivering and associated morbidity in the postoperative period.

2) Intensive care unit sedation: The sedation produced mimics that of normal sleep pattern. The patients remain calm, quiet, arousable and cooperative. It was initially approved for use for less than 24 hours as an intravenous infusion, but recently studies have demonstrated its efficacy for use beyond 24 hours.

3) Treatment of substance withdrawal: Dexmedetomidine has been shown to be effective in opioid or benzodiazepine withdrawal by reducing the sympathetic outflow and noradrenergic stimulation caused by the withdrawal. This is mainly attributed to their blocking of α−2A receptors situated in the locus ceruleus. It has been found to be helpful in controlling the agitation in alcoholics after traumatic brain injury and thus helps in monitoring and allows serial neuro testing in these patients.

4) As an opioid substitute: Dexmedetomidine may be used as an alternative in patients developing tolerance to opioids or in those forms of pain with poor response to opioid analgesics, like sympathetically maintained neuropathic pain.

5) Treatment of delirium: Studies have demonstrated a reduction in the duration and incidence of delirium following dexmedetomidine. Dexmedetomidine is better than midazolam for attenuating the cardiostimulatory and postanaesthetic delirium effects of ketamine.

6) As an end of life medication: Recently approved by the FDA for treating cancer patients at the end of life who are suffering from intractable pain, agitation or delirium. It is used both intravenous and intrathecally in cancer pain refractory to multiple treatment modalities.

7) In paediatrics: Dexmedetomidine may be administered by noninvasive route like intranasal and buccal to substitute narcotics causing respiratory depression. In children, it has various applications like procedural sedation, sedation during mechanical ventilation, prevention of emergence agitation,

prevention of withdrawal symptoms following prolonged use of opioids and benzodiazepines and sedation during MRI and CT scan.

8) Obstetric analgesia: Dexmedetomidine is highly lipophilic in nature. Hence it is retained in the placental tissue and has a decreased incidence of fetal bradycardia. The drug also possesses attractive properties such as maternal haemodynamic stability, anxiolysis, and stimulation of uterine contractions.

9) Newer potential uses: In animals it has been shown to have a diuretic effect by inhibition of antidiuretic action of vasopressin at the collecting duct. It has been found to attenuate radio contrast nephropathy by preserving cortical blood flow. It is effective in controlling supraventricular and junctional tachyarrhythmias

CONTRAINDICATIONS:

a) Dexmedetomidine is not recommended for microvascular free flap procedures, as α-2 agonists cause direct vasoconstriction and reduction in flap blood flow. Also in neurovascular patients or in those where high risk of vasospasm is not recommended.

b) It is not indicated in recent acute epilepsy or uncontrolled seizure activity.

c) The teratogenic effects of dexmedetomidine have not been adequately studied. The drug does cross the placenta and should be used during pregnancy or breast feeding only if the benefits justify the risk to the fetus.

d) Should be used cautiously in patients with hypotension, bradycardia and heart blocks.

ADVERSE EFFECTS:

a) Hypotension or hypertension

b) Bradycardia

c) First or second degree heart block

d) Sedation

e) Apnea at a higher loading dose.

f) Cardiac arrest.

ANTIDOTE:

Atipamezole is found to be an effective antagonist for reversing the psychomotor impairment produced by dexmedetomidine. It acts by increasing the central turnover of norepinephrine. Antagonism is dose dependent. Ratios in the range of 40:1 to 100:1 for atipamezole: dexmedetomidine were found to be effective. [25]

DOSAGE AND ADMINISTRATION:

Intravenous infusion of dexmedetomidine is commonly initiated with a 1 μg /kg loading dose, administered over 10 minutes, followed by a maintenance infusion of 0.2–1.0 μg /kg/h.[22]

Doses varying from 3 to 15 μg have been used as adjuvant to bupivacaine for spinal anaesthesia. There has been dose-dependant prolongation of analgesia.[26]

Dexmedetomidine has been successfully used in children as adjuvant in caudal epidural. Dexmedetomidine in a dose of 1–2μg/kg used along with bupivacaine provided prolonged analgesia without significant side effects. [26]

MATERIALS AND METHODS

After Ethical Committee clearance, the study was conducted at R.L Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College from December 2013 to June 2015. Ninety patients admitted for elective surgeries to be done under general anaesthesia were included in the study.

INCLUSION CRITERIA

Patients of ASA physical status 1 in the age group of 18 years to 50 years of either sex, posted for elective surgeries under general anaesthesia were enrolled for the study.

EXCLUSION CRITERIA

1) Patients physically dependant on narcotics.
2) Any predicted difficult airway.
3) History of bronchial asthma.
4) History of drug or alcohol abuse.
5) Laryngoscopy time exceeding 15 seconds.
6) Patients with history of known drug allergy to either clonidine or dexmedetomidine.
7) History of cerebrovascular, neurologic, respiratory or ischemic heart disease (history of angina, previous myocardial infarction).
8) Renal and hepatic dysfunction.
9) Patients with hypertension, diabetes mellitus and pheochromocytoma.
10) Patients on beta blockers, antidepressants, antianxiety, anticonvulsant or antipsychotics.

After obtaining informed written consent, patients were randomly divided into 3 groups of 30 each. Randomisation was done using computer generated random number table.

Group A: received 20 mL normal saline iv as infusion over 10 minutes.

Group B: received Inj. dexmedetomidine 0.5µg/kg diluted to 20 mL with normal saline as iv infusion over 10 minutes.

Group C: received Inj. dexmedetomidine 0.75µg/kg diluted to 20 mL with normal saline as iv infusion over 10 minutes.

All patients were examined a day before surgery. The patients were kept fasting overnight after 10:00pm and they received Tab. ranitidine 150mg orally and Tab. alprazolam 0.5mg orally as premedication at night before surgery. All patients were monitored with electrocardiography, pulse oximetry and noninvasive blood pressure. An intravenous line was secured and the patients were given intravenous fluids Ringer Lactate. Inj. glycopyrrolate 0.2 mg iv + Inj. ondansetron 50µg/kg iv was given half an hour prior to surgery. Baseline heart rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and SpO2 were measured after premedication. After 10 min, appropriate study drug infusion was given over ten minutes. Any hypotension (systolic blood pressure less than 20% of the baseline) was treated with increments of Inj. mephentermine 3mg iv and incidence of bradycardia (heart rate less than 50 beats) was treated with Inj. Atropine 0.6mg iv.[21] After completion of drug infusion, sedation was assessed at 2, 5, and 10 min using Ramsay sedation score as noted below. [27] After noting the sedation scores for ten minutes, the anaesthetic procedure was initiated. General anaesthesia technique was standardized for all the three groups. Then patients were induced with Inj. propofol 2mg/kg bodyweight and Inj. xylocard in conc. of 0.1%+ Inj. fentanyl 1µg/kg+ Inj. succinylcholine 2mg /kg

body weight iv. Following laryngoscopy and endotracheal intubation the parameters recorded were heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure at 1', 3', 5'after intubation. Anaesthesia was maintained with O_2+N_2O in a ratio of 50% each and isoflurane 0.4 %. Muscle relaxation was maintained with Inj. vecuronium 0.1mg/kg iv with top ups of 0.04 mg/kg. After surgery, reversal was achieved with Inj. neostigmine 0.05 mg/kg + Inj. glycopyrrolate 0.01 mg/kg iv. After adequate recovery patients were shifted to post anaesthesia care unit and monitored for 12 hours and later shifted to ward.

RAMSAY sedation score-

Score 1- Anxious or restless or both.

Score 2-Cooperative, oriented and tranquil.

Score 3-Responding to commands.

Score 4-Brisk response to stimulus.

Score 5-Sluggish response to stimulus.

Score 6-No response to stimulus

The study required the following investigations:

Complete haemogram.

Bleeding time and clotting time.

Random blood sugar.

Blood urea and serum creatinine.

Serum electrolytes.

Urine analysis for sugar, albumin and microscopy.

ECG and chest X-ray

Statistical Methods: Data was entered into Microsoft excel data sheet. Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented as Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients. Post-Hoc Tukey test has been used to find the Pairwise significance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Significant figures :

Statistically significant (P value: $p< 0.05$)

** Strongly significant (P value : $P<0.01$)

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS

AGE DISTRIBUTION OF PATIENTS

Table 2: Age distribution of patients

Age in years	Group A	Group B	Group C	Total
<30	14 (46.7%)	11 (36.7%)	17 (56.7%)	41
31-40	10 (33.3%)	6 (20%)	7 (23.3%)	23
41-50	6 (20%)	13 (43.3%)	6 (20%)	25
Total	30	30	30	90
Mean ± SD	24.43 ±3.75	35.74 ± 2.81	46.24 ±1.87	

p = 0.175

The mean age and standard deviation of Group A, Group B and Group C were 24.43±3.75, 35.74±2.81 and 46.24 ±1.87 respectively. In the study it was observed that there was no significant difference in age groups among the three groups. This can be attributed to age matching in the study subjects.

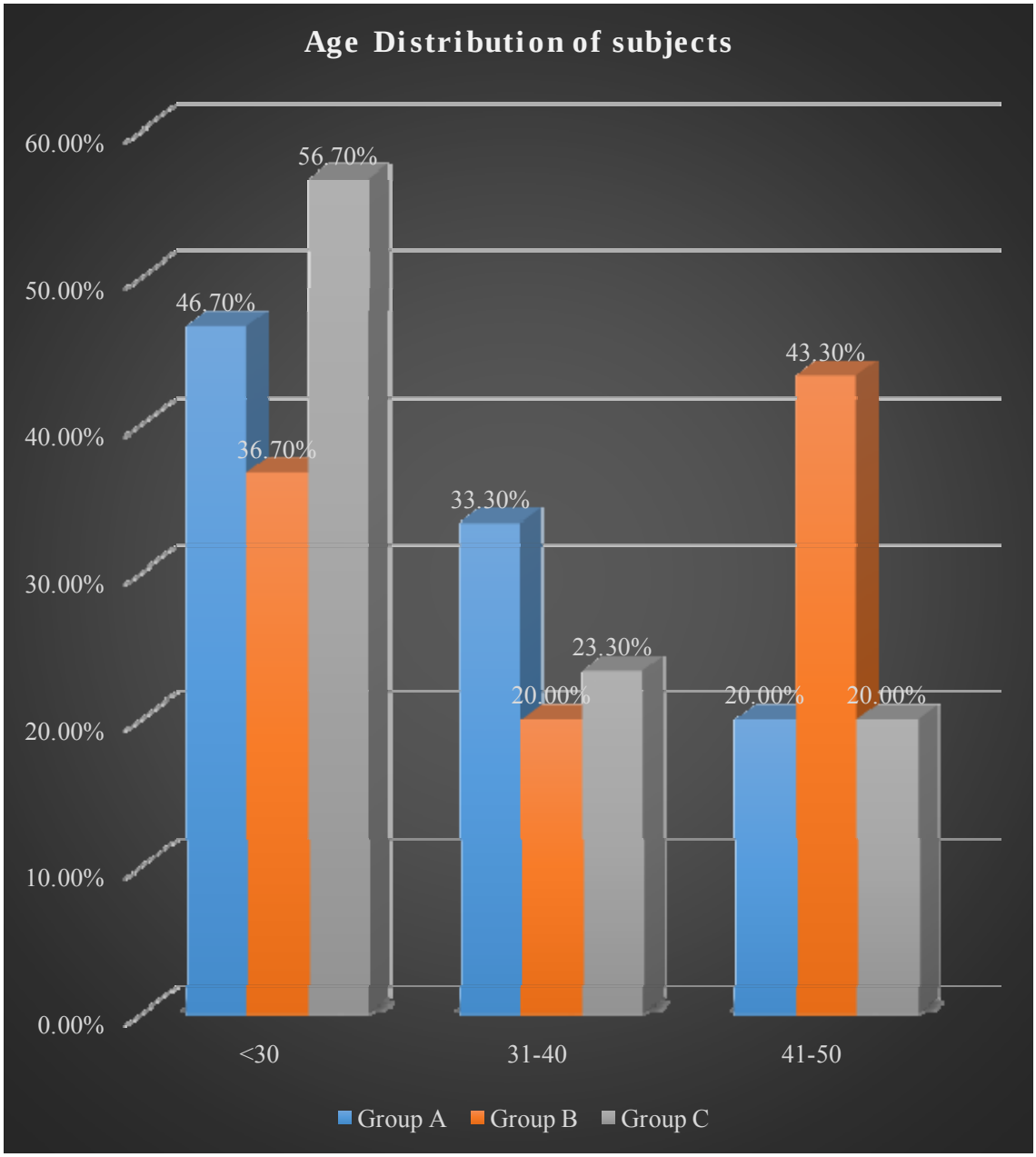

Figure 6: Bar diagram showing age distribution of subjects

GENDER DISTRIBUTION OF PATIENTS

Table 3: Gender distribution of patients

Gender	Group A	Group B	Group C	Total
Female	15 (50%)	13 (43.3%)	16 (53.3%)	44
Male	15 (50%)	17 (56.7%)	14 (46.7%)	46
Total	30	30	30	90

p = 0.733

In the study it was observed that there was no significant difference in gender among the three groups. This can be attributed to gender matching in the study subjects.

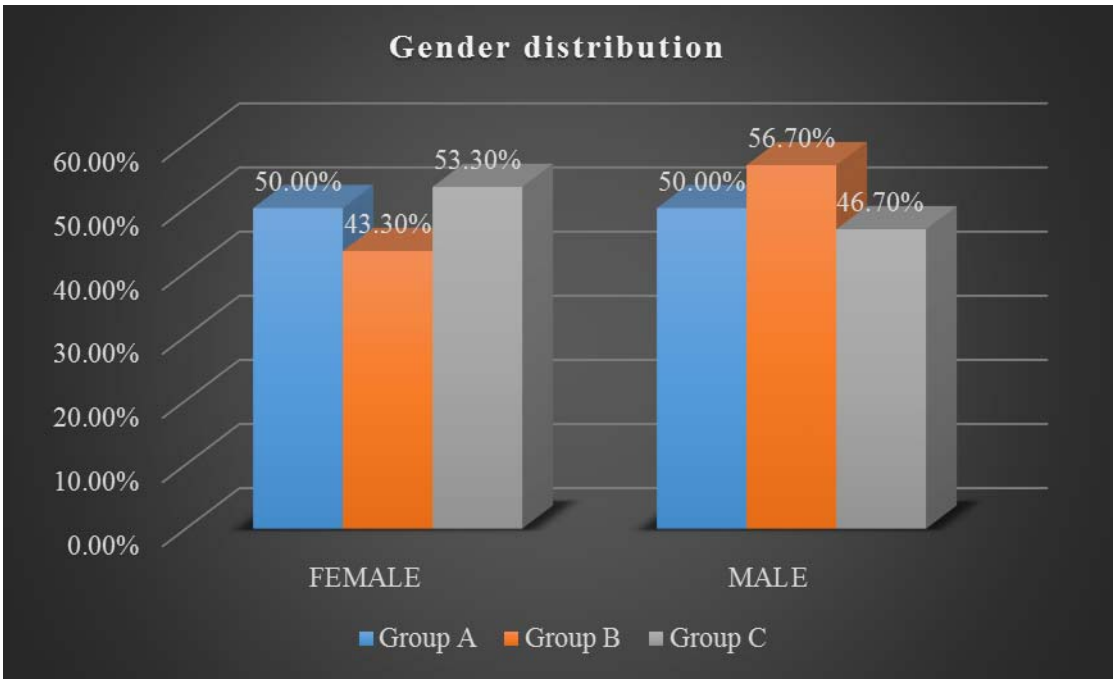

Figure 7: Bar diagram showing Gender distribution of subjects

COMPARISON OF HEART RATE

Table 4: Comparison of Heart Rate (bpm) between three groups

Heart rate (bpm)	Group A	Group B	Group C	p value	Pair wise significance		
					Group A Vs Group B	Group A Vs Group C	Group B Vs Group C
Baseline	80.40± 5.67	81.50± 5.30	81.47± 5.28	0.672	0.712	0.727	1.399
1 min	112.23 ±5.8	85.57± 5.41	84.37± 5.51	<0.001**	<0.001**	<0.001**	1.439
3 min	104.03 ±4.63	83.73± 4.95	80.83± 5.40	<0.001**	<0.001**	<0.001**	1.293
5 min	92.87± 5.08	79.47± 4.65	75.03± 5.8	<0.001**	<0.001**	<0.001**	1.343

It was observed that at baseline the mean heart rate was comparable between the three groups and that there was no statistical significance among the three groups. From the above table, it can be observed that heart rate increased significantly in Group A when compared to the other two groups- Group B and Group C at all times post intubation. There was no statistically significant difference between Group B and C. The heart rate never reached baseline in case of Group A. The heart rate went below the baseline values at 3' and 5' in case of Group C. In case of Group B the heart rate value was below baseline at 5'.

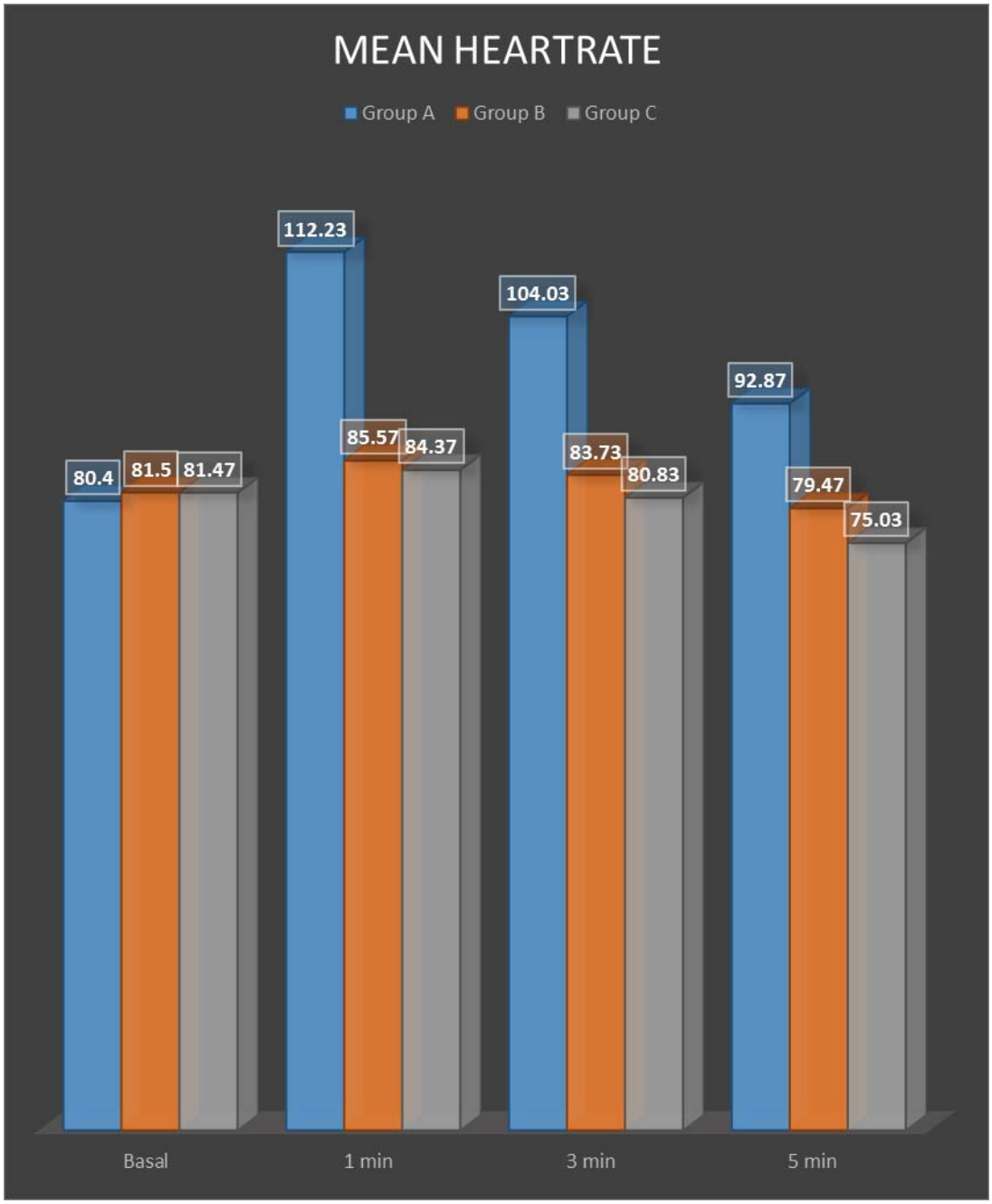

Figure 8: Bar diagram showing Mean Heart rate variation

COMPARISON OF SYSTOLIC BLOOD PRESSURE (SBP)

Table 5: Comparison of Systolic Blood Pressure (SBP) between three groups

SBP mm Hg	Group A	Group B	Group C	p value	Pair wise significance		
					Group A vs Group B	Group A vs Group C	Group B vs Group C
Base line	128.07 ±7.90	128.73± 9.82	130.07± 8.04	0.660	0.952	0.643	0.821
1 min	160.13 ±6.08	134.60± 9.74	133.27± 7.75	<0.001**	<0.001**	<0.001**	2.065
3 min	148.33 ±5.87	129.87± 9.75	124.67± 8.41	<0.001**	<0.001**	<0.001**	2.110
5 min	139.60 ±4.94	126.07± 9.78	117.80± 7.49	<0.001**	<0.001**	<0.001**	1.978

It was observed that at baseline there was no significant difference in mean SBP between three groups. The basal SBP was comparable in the three groups. Whereas there was significant difference in mean SBP at 1 min, 3 min and 5 min between the groups. From the above table it can observed that SBP increased significantly in Group A when compared to Group B and Group C. Comparison between Group B and Group C did not reveal significant difference. The baseline values were not

achieved in Group A patients even after 5’ post intubation. Baseline values were attained at 5’ in case of Group B and at 3’ and 5’ in case of Group C.

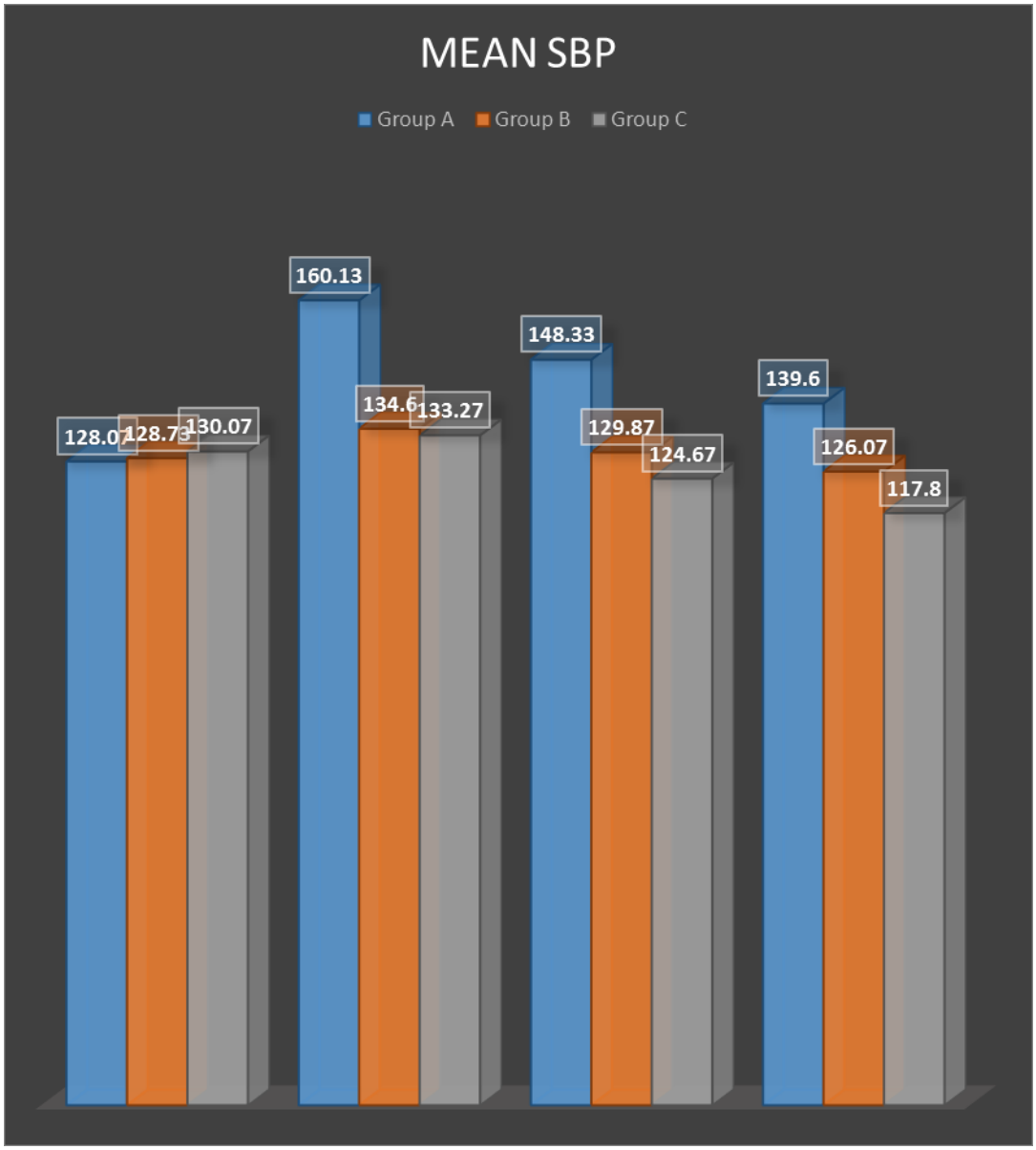

Figure 9: Bar diagram showing Mean SBP variation in three groups

COMPARISON OF DIASTOLIC BLOOD PRESSURE (DBP)

Table 6: Comparison of Diastolic Blood Pressure (DBP) between three groups

DBP mm Hg	Group A	Group B	Group C	Overall P value	Pair wise significance		
					Group A vs Group B	Group A vs Group C	Group B vs Group C
Baseline	76.40± 6.94	77.27± 4.91	74.87± 5.16	0.266	0.829	0.557	0.243
1 min	91.27± 6.02	81.67± 4.52	77.33± 5.26	<0.001**	<0.001**	<0.001**	1.369
3 min	88.13± 5.63	76.67± 4.62	72.47± 5.16	<0.001**	<0.001**	<0.001**	1.331
5 min	84.67± 5.21	74.33± 4.52	69.53± 4.66	<0.001**	<0.001**	<0.001**	1.241

The baseline DBP was similar among the three groups with no significant difference in mean DBP between the three groups. The peak response was obtained at 1'. From the above table, we can infer that DBP increased significantly in Group A than the other two groups. The DBP values went below the baseline at 3' and 5' following intubation in Group B and C. The comparison among Group B and C did not reveal any significant difference. The response brought about were very minimal in these two groups.

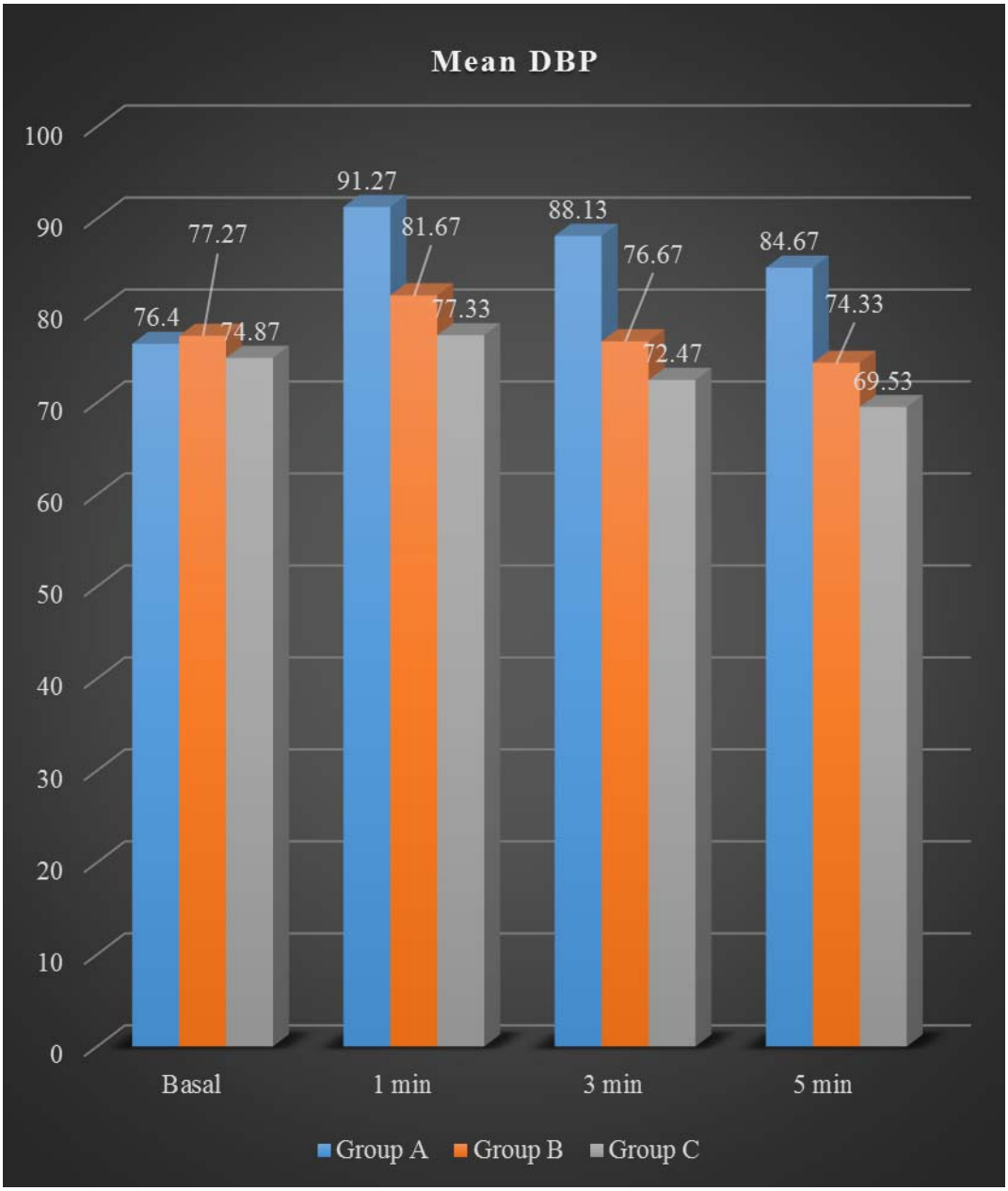

Figure 10: Bar diagram showing Mean DBP variation in three groups

COMPARISON OF MEAN ARTERIAL PRESSURE (MAP)

Table 7:Comparison of Mean Arterial Pressure (MAP) between three groups

MAP (mm Hg)	Group A	Group B	Group C	p value	Pair wise significance		
					Group A Vs Group B	Group A Vs Group C	Group B Vs Group C
Basal	93.83±6.36	94.70±5.75	93.27±5.53	0.639	0.836	0.926	0.615
1 min	114.57±5.14	98.87±5.86	96.33±5.40	<0.001**	<0.001**	<0.001**	1.414
3 min	108.47±4.97	94.83±5.13	90.27±5.49	<0.001**	<0.001**	<0.001**	1.343
5 min	103.37±4.51	91.80±5.48	85.47±5.08	<0.001**	<0.001**	<0.001**	1.301

It was observed that at baseline, there was no significant difference in mean MAP between the three groups. Whereas there was significant difference in mean MAP at 1', 3' and 5'between the groups. From the above table it can observed that MAP was increased significantly in Group A when compared to other two groups. The increase in MAP was parallelto that in SBP and DBP. The intergroup comparison between Group B and Group C revealed insignificant changes.

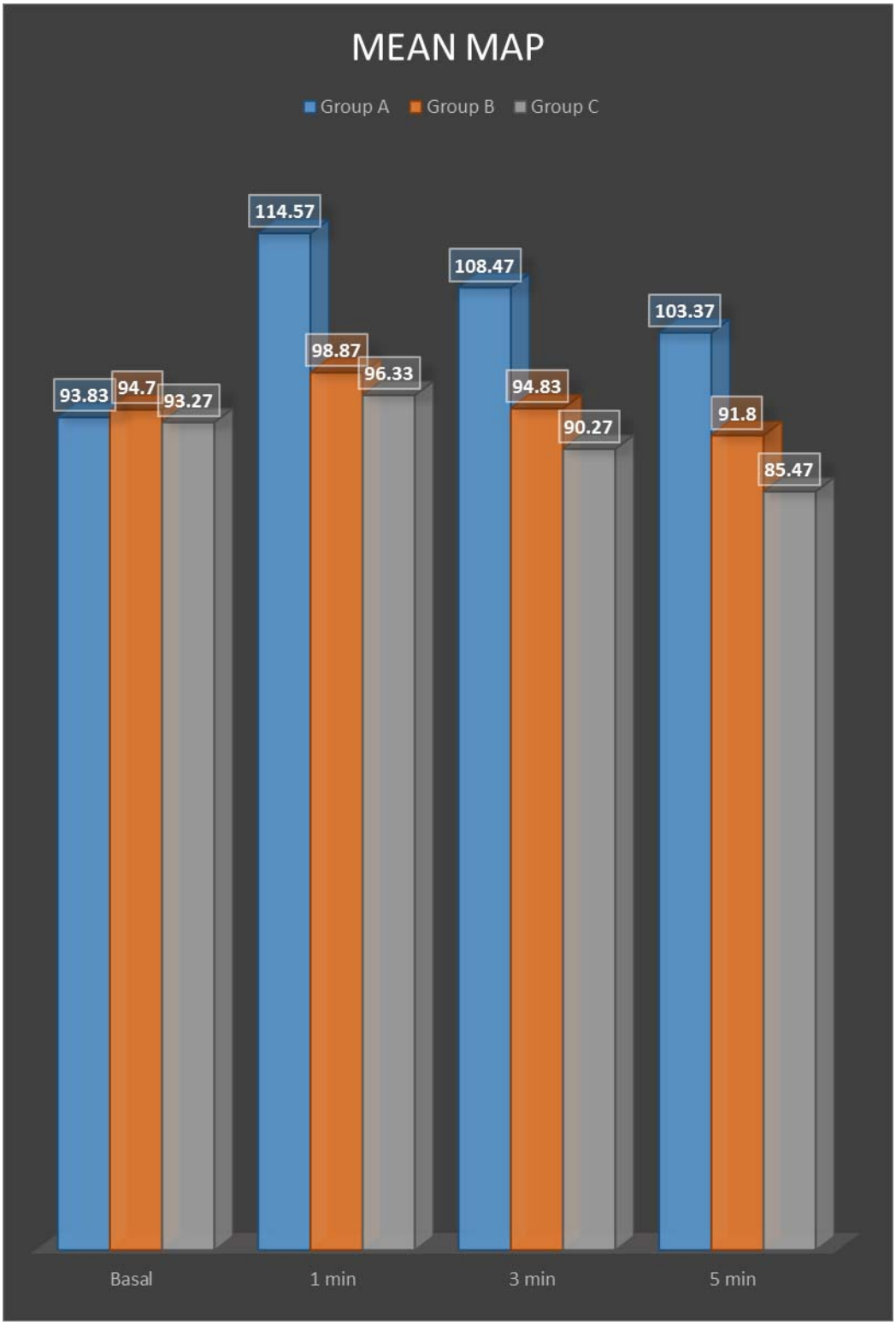

Figure 11: Bar diagram showing Mean MAP variation in three groups

COMPARISON OF SEDATION SCORE BETWEEN THREE GROUPS

Table 8: Comparison of Sedation score between three groups at 2 minute

Sedation Score	Group A	Group B	Group C
1	6 (20%)	0 (0%)	0 (0%)
2	21 (70%)	16(53.33%)	13 (43.33%)
3	3 (10%)	14(46.67%)	17 (56.67%)
4	0 (0%)	0 (0%)	0 (0%)
5	0 (0%)	0 (0%)	0 (0%)
6	0 (0%)	0 (0%)	0 (0%)

At 2 minutes after the drug infusion, maximum patients in Group A had a sedation score of 2 which was 70% of the group population. While 20% had score of 1, 10% had a score of 3. In Group B, majority had score 2(53.33%) while 46.67% had score 3. Group C had 17 persons (56.67%) with a sedation score of 3 and 43.33% had a score of 2.

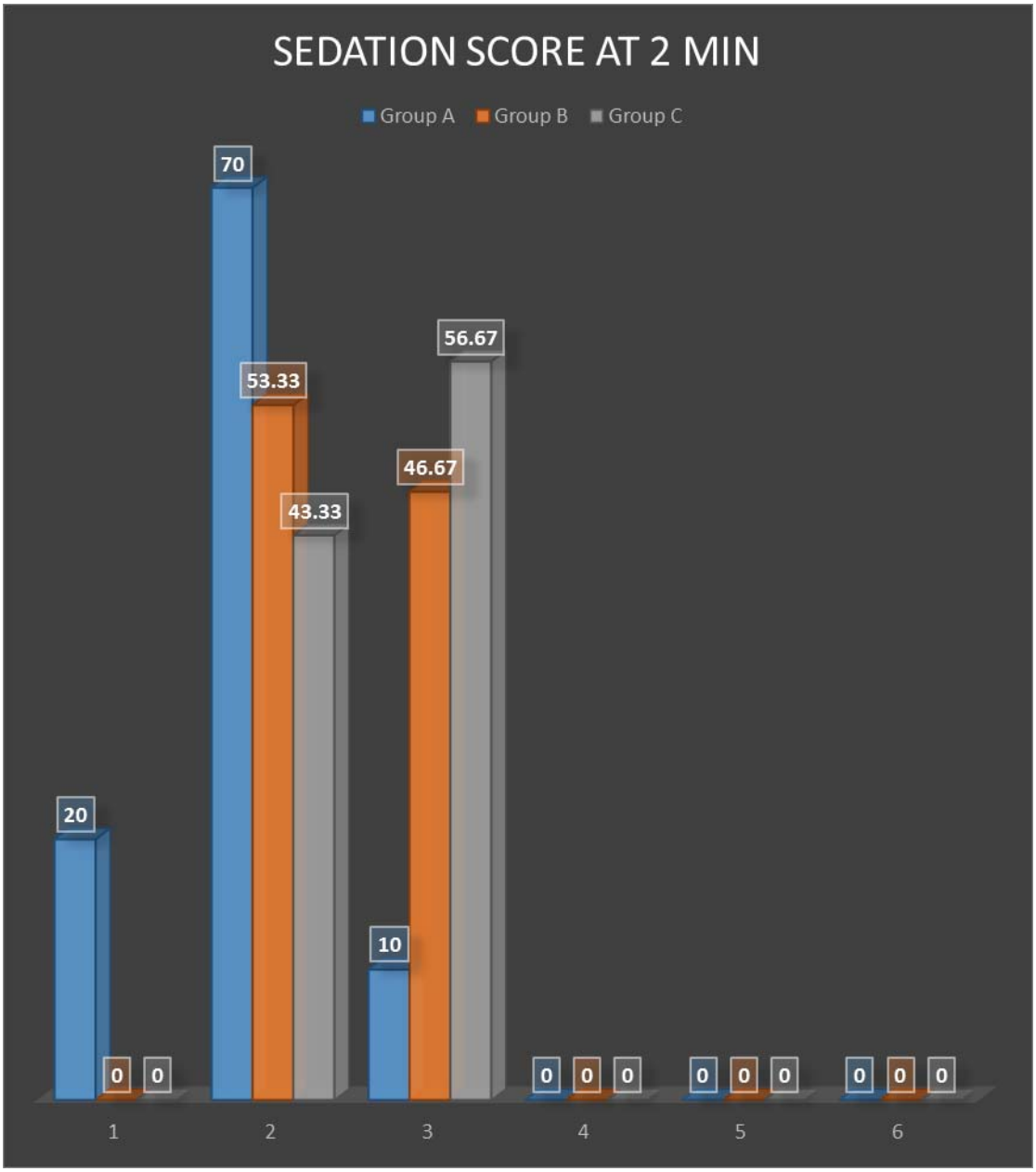

Figure 12: Bar diagram showing Sedation score at 2 min

Table 9: Comparison of Sedation score between three groups at 5 minute

Sedation Score	Group A	Group B	Group C
1	4 (13.33%)	0 (0%)	0 (0%)
2	23 (76.67%)	13 (43.33%)	8 (26.67%)
3	3 (10%)	15 (50%)	18 (60%)
4	0 (0%)	2 (6.67%)	4 (13.33%)
5	0 (0%)	0 (0%)	0 (0%)
6	0 (0%)	0 (0%)	0 (0%)

After 5 minutes, Group A maintained its results with maximum number of them having a sedation score of 2 (76.67%). In Group B, there was a slight increase in patients with sedation score of 3 to 15 (50%).2 patients (6.67%) had a score of 4. In Group C majority of them (60%) had score of 3. There was an increase in the number of people having a score of 4 to 13.33%.

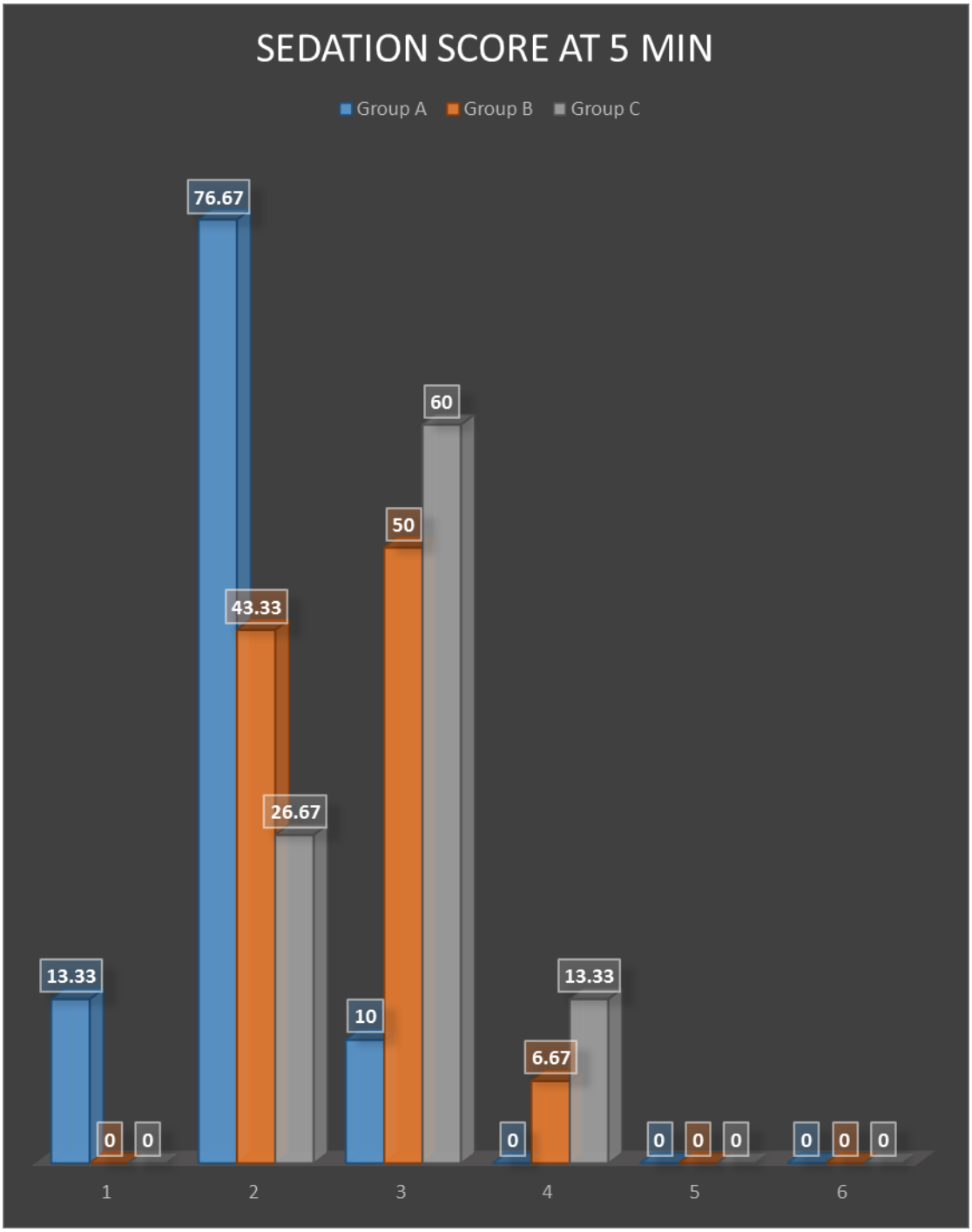

Figure 13: Bar diagram showing Sedation score at 5 min

Table 10: Comparison of Sedation score between three groups at 10 minute

Sedation Score	Group A	Group B	Group C
1	3 (10%)	0 (0%)	0 (0%)
2	24 (80%)	11 (36.67%)	2 (6.67%)
3	3 (10%)	19 (63.33%)	22 (73.33%)
4	0 (0%)	0 (0%)	6 (20%)
5	0 (0%)	0 (0%)	0 (0%)
6	0 (0%)	0 (0%)	0 (0%)

After 10 minutes, the results of Group A was the same with 80% having a score of 2. In Group B the majority of them (63.33%) had a sedation score of 3 and 36.67% had a score of 2. In Group C there was a rising trend in the people having a sedation score of 3 and 4 -73.33% and 20% respectively.

Thus it was clear that at any point of time, Group C had a higher number of patients with a higher sedation score than Group B.

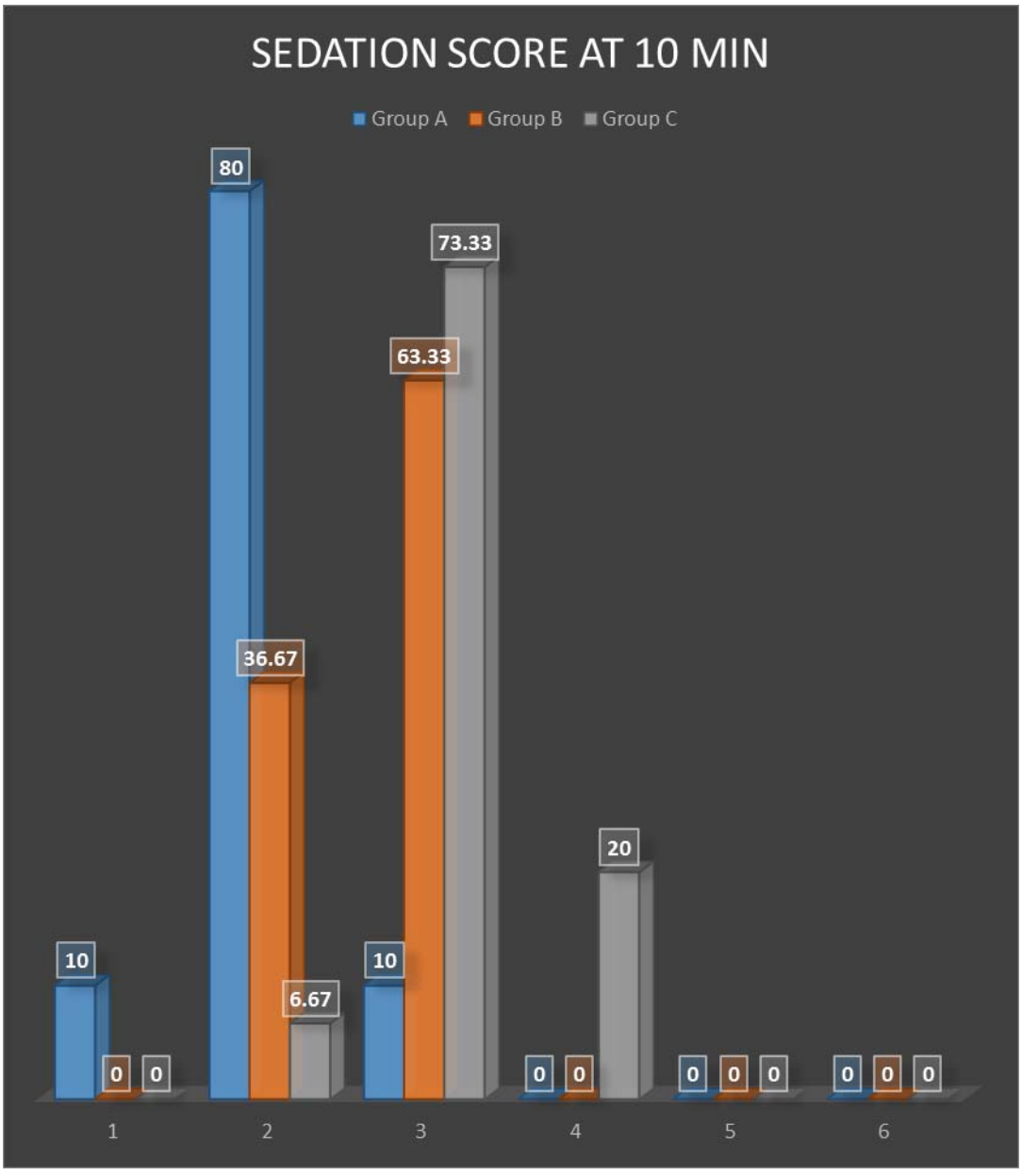

Figure 14: Bar diagram showing sedation score at 10min

DISCUSSION

The administration of anaesthesia before surgery was not scientifically practiced until the middle of the 19th century and the patients were required to withstand the pain of the surgery. With the introduction of general anaesthesia it was possible to render the patient unconscious and thus insensitive to pain and oblivious to the events occurring during the procedure. Throughout the 20th century, the technique of delivering and monitoring anaesthesia were improved. The technique of balanced anaesthesia achieves the tripartite goals of anaesthesia: hypnosis, analgesia and muscle relaxation. General anaesthesia has become very safe with an incidence of less than 1 death per 2,00,000 procedures solely attributable to anaesthesia. [28]

The anaesthetized patients are unable to maintain an adequate airway on their own and there arises the need to employ artificial airway maintenance devices like endotracheal tube. Traditionally, laryngoscopy and endotracheal intubation has been the mainstay in safeguarding the airway in such patients. Though intubation has its own advantages like a safe and secured airway, prevention of aspiration and delivery of anaesthetic gases, it is not without complications. Laryngoscopy and endotracheal intubation are noxious stimuli capable of producing a huge spectrum of stress responses like tachycardia, hypertension, laryngospasm, bronchospasm, raised intracranial pressure and intraocular pressure. [1]

The haemodynamic changes brought about by laryngoscopy and intubation was first described by Reid and Brace. [29] The haemodynamic response is initiated within seconds of direct laryngoscopy and further increases with the passage of the endotracheal tube. The response starts within 5 seconds of laryngoscopy, peaks in 1 – 2 minutes and returns to normal levels within 5 minutes.[30] These changes are usually

short lived and well tolerated by normal patients. In patients with cardiovascular disease, it can incite harmful effects like myocardial ischaemia, ventricular dysrhythmias, ventricular failure and pulmonary edema. It can also lead to cerebral haemorrhage in cerebrovascular disease patients. [17]

Various drug regimens and techniques have been tried from time to time by the clinicians for obtunding the stress response. Opioids like fentanyl [31] and remifentanil[32] provided good haemodynamic stability following intubation. Lidocaine topically and through the intravenous route were tried with some efficacy. [30] Studies have shown that vasodilators like nitroglycerine[33] , nitroprusside[34] and calcium channel blockers like diltiazem[35] were also capable of decreasing the stress response. Esmolol which is a β blocker is capable of attenuating cardiovascular response to laryngoscopy and intubation. [36] Barbiturates and benzodiazepines which are commonly used as premedication agents has the potential to attenuate haemodynamic response to a certain extent. [37] Structural analogues of GABA like gabapentin and pregabalin were studied by some authors and proven to be effective. [38, 39] Increasing the depth of anaesthesia by using volatile anesthetics was another theory, but changes in the concentration of anaesthetic agents in blood and at the effector sites occur slowly in relation to the onset and offset of noxious airway stimuli and haemodynamic responses. [30]

As none of them were ideal, the quest continued and α-2 receptor agonists began to be used. They mediate their action via α-2A receptors located in locus ceruleus, the predominant noradrenergic nuclei of upper brainstem. The presynaptic activation of α-2A receptors in the locus ceruleus inhibits the noradrenaline release and brings about sedation and hypnosis. Post synaptic activation of α-2 receptors in CNS brings about decreased sympathetic activity leading to bradycardia and hypotension. [22]

Clonidine was the first α-2 receptor agonist that was developed while dexmedetomidine being a newer potent α-2 agonist. Clonidine is considered to be a partial α-2 agonist as its α2/ α1 selectivity is 200:1. Dexmedetomidine has an α2/ α1 selectivity of 1620:1. Hence dexmedetomidine is eight times more potent α-2 receptor agonist than clonidine. The duration of clonidine is longer with an elimination half time of 6- 24 hours. The action of dexmedetomidine is short lived with elimination half time of 2 hours. Dexmedetomidine has a reversal drug for its sedative effect called as atipamezole. Atipamezole acts by increasing the central turnover of norepinephrine. These factors make dexmedetomidine superior to clonidine. [25]

This study was undertaken to study the haemodynamic changes brought about by laryngoscopy and endotracheal intubation following the administration of intravenous dexmedetomidine 0.5µg/kg, 0.75µg/kg and normal saline as placebo. The parameters studied were heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure. The incidence of hypotension, bradycardia and sedation scores were also noted. Dexmedetomidine in a dose of 0.5µg/kg and 1µg/kg have been studied by many authors previously. No study has been done to see the efficacy of dexmedetomidine in a dose of 0.75µg/kg for attenuation of laryngoscopy and intubation response. Hence in this study, we chose to include and compare normal saline with Inj. dexmedetomidine in a dose of 0.5µg/kg and 0.75µg/kg for attenuation of laryngoscopy and intubation response.

DEMOGRAPHIC DATA:

Ninety patients who were posted for elective surgeries under general anaesthesia were enrolled in the study. They were divided equally into 3 groups. The two groups were comparable in patient characteristics with respect to age and gender. The mean age of

group A was 24.43 years, group B was 35.74 years and group C was 46.24 years. The total number of females were 44 and males were 46. They were found to be statistically not significant. This can be attributed to the gender and age matching in the study subjects.

HEART RATE:

In this study we have used heart rate as one of the parameters. It was measured 1',3'and 5' post intubation. The mean basal heart rate was similar in all the 3 groups. The increase of heart rate was maximum at 1' post intubation in all the three groups. The increase was maximum in group A and least in group C. The increase of heart rate was statistically significant when we compared group A with group B and group C. Hence dexmedetomidine in doses of 0.5µg/kg and 0.75µg/kg were found to attenuate tachycardia response when compared with normal saline. Raval et al did a study comparing the efficacy of dexmedetomidine in a dose of 0.5µg/kg and 1µg/kg. The results of our study correlated with them in that dexmedetomidine provided a better haemodynamic stability following laryngoscopy and intubation. [40] The study by Smitha et al compared the effect of 0.5µg/kg and 1µg/kg of dexmedetomidine with normal saline in attenuating stress response. The intergroup comparison revealed a statistically significant reduction in heart rate by dexmedetomidine than normal saline. [41]The data obtained during our study also showed similar results.

SYSTOLIC BLOOD PRESSURE:

The means of basal systolic blood pressure were 128.07, 128.73 and 130.07 in Group A, Group B and Group C respectively. The basal systolic blood pressures were comparable among the three groups as there was no statistical difference between them. The systolic blood pressure increased the maximum at 1' following

laryngoscopy and intubation in all the groups. The maximum increase in blood pressure was recorded in Group A and least in Group C. There was a statistically significant increase in systolic blood pressure in Group A on comparison with Group B and Group C. A study was done by Menda and his colleagues on ischaemic heart disease patients undergoing fast-track CABG. They had compared dexmedetomidine 1μg/kg and placebo. In the placebo group, the systolic arterial pressure increased significantly after the intubation when compared to pre-intubation period whereas it did not change significantly in the dexmedetomidine group. [42] In another study, Fayaz et al studied the effects of preoperative infusion of dexmedetomidine in a dose of 1μg/kg and normal saline for attenuation of hypertensive response following laryngoscopy. An increase in systolic pressure of 33.81% occurred in saline group as compared to 8.18% in dexmedetomidine group ($p<0.05$). [43] Thus observations made in our study corroborated with the previous studies.

DIASTOLIC BLOOD PRESSURE:

The variation in the diastolic blood pressure at different instances of time revealed an elevation of diastolic blood pressure in Group A more than Group B and Group C. The maximum elevation occurred at 1' after laryngoscopy. The comparisons revealed a statistically significant elevation in group A when compared with group B and group C. These results correlated with the previous studies by Jakkola et al and Gulabani et al. Jakkola et al studied dexmedetomidine in a dose of 0.6μg/kg and normal saline in patients undergoing cataract surgery. They demonstrated that maximum diastolic arterial pressures were significantly lower in the dexmedetomidine group. Dexmedetomidine also reduced the intraocular pressures following intubation. [44] Dexmedetomidine 1 μg/kg and 0.5μg/kg were compared with lignocaine 1.5 mg/kg by Gulabani et al to maintain haemodynamic stability

associated with intubation. Dexmedetomidine 1 μg/kg was found to be more effective than dexmedetomidine 0.5 μg/kg and lignocaine without any side effect and hence beneficial for cardiac patients where the stress response to laryngoscopy and intubation is highly undesirable. [45]

MEAN ARTERIAL PRESSURE:

The variation in mean arterial pressures were parallel to the magnitude of change in systolic and diastoloic blood pressure. The pressor response was found to be significantly higher in Group A than in Group B and Group C at all times post intubation. The study by Smitha et al compared dexmedetomidine 1 μg/kg,0.5μg/kg and normal saline in a manner almost similar to our study. SBP, DBP, MAP and HR levels were used as the parameters for assessing intubation response. At 1 minute after laryngoscopy and intubation, these levels increased in all the three groups. The amount of increase in the vital parameters level was less in 1μg/kg when compared to 0.5 μg/kg and very much less than the control group. [41] Hence, it was found that dexmedetomidine is very effective in suppressing the haemodynamic response to laryngoscopy and intubation. These data obtained matched with our study results.

RAMSAY SEDATION SCORE:

Ramsay sedation score was used in the study. The sedation score was assessed at 2' 5' and 10' after the drug infusion.

After 2' of drug infusion, 10% of patients in Group A had a sedation score of 3 while in Group B and C it was 46.67% and 56.67%. After 5' of drug infusion Group A had a maximum sedation score of 3 for 10% of its patients. In Group B the highest sedation score of 4 was found in 6.67%. In Group C 13.33% had a score of 4. By 10' Group A continued to have a maximum score of 3 for 10% of the patients. Group B

had 63.33% of patients with a score of 3 and Group C had 20% with a score of 4. The sedation scores of dexmedetomidine were higher when compared to normal saline. The sedation scores matched those obtained by Gourishankar et al in their study of effects of low dose dexmedetomidine infusion on haemodynamic stress response, sedation and post-operative analgesia requirement in patients undergoing laparoscopic cholecystectomy. [46]

ADVERSE EFFECTS:

No adverse effects were noted in any of the groups. In this study no hypotension or bradycardia were seen and no medical intervention was required in any of the groups. Also no significant respiratory depression, apnea, muscle rigidity or decrease in SpO2 was seen in any patient. Other studies have shown such similar results in the past. [40, 41]

CONCLUSION

Based on our present comparative study the following conclusions were drawn:

- Dexmedetomidine in a dose of 0.5µg/kg was more effective than normal saline for attenuation of haemodynamic response to laryngoscopy and intubation.
- Dexmedetomidine in a dose of 0.75µg/kg as a premedication agent obtunded the responses to laryngoscopy and intubation better than normal saline.
- Sedation scores were more for dexmedetomidine when compared with normal saline, but a state of "arousable sedation" was maintained.
- Dexmedetomidine in a dose of 0.75µg/kg caused more sedation when compared to dexmedetomidine in a dose of 0.5µg/kg and normal saline.
- There were no adverse effects like hypotension, bradycardia, respiratory depression and apnea with any of the drugs.

SUMMARY

The sequence of laryngoscopy and tracheal intubation is associated with marked haemodynamic changes and autonomic reflex activity in the form of tachycardia and hypertension which may be a cause of concern in many high risk patients. The response starts within 5 seconds of laryngoscopy, peaks in 1 – 2 minutes and returns to normal levels within 5 minutes. Though various methods were employed to attenuate this stress response, each had its own limitations. The newer agents tried were α-2 agonists like clonidine and dexmedetomidine. In this randomised clinical comparative study, we compared the effects of iv dexmedetomidine in a dose of 0.5µg/kg, 0.75µg/kg and normal saline for attenuating haemodynamic responses to laryngoscopy and tracheal intubation.

Ninety patients of ASA grade 1 in the age group of 18 years to 50 years, of either sex, posted for elective surgeries under general anaesthesia were selected for the study. Patients were randomly divided into three groups of 30 each.

Group A: received 20 mL normal saline as iv infusion.

Group B: received Inj. dexmedetomidine 0.5µg/kg diluted to 20 mL with normal saline as iv infusion.

Group C: received Inj. dexmedetomidine 0.75µg/ kg diluted to 20 mL with normal saline as iv infusion.

On the morning of surgery Inj. glycopyrrolate 0.2 mg iv + Inj. ondansetron 50µg/kg iv were given half an hour prior to surgery. Baseline heart rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and SpO2 were measured after premedication. After 10 min, appropriate study drug infusion was given over ten

minutes. After completion of drug infusion, sedation was assessed at 2, 5, and 10 min using Ramsay sedation score as noted below. After noting the sedation scores for ten minutes, the anaesthetic procedure was administered. General anaesthesia technique was standardised for all the three groups. Then patients were induced with Inj. propofol 2mg/kg body weight and Inj. xylocard in conc. of 0.1%+ Inj. fentanyl 1µg/kg + Inj. succinylcholine 2mg /kg body weight iv. Following laryngoscopy and endotracheal intubation the parameters recorded were heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure at 1', 3', 5' after intubation . Anaesthesia was maintained with O_2+N_2O in a ratio of 50% each and isoflurane 0.4 %. Muscle relaxation was maintained with Inj. vecuronium 0.1mg/kg iv with top ups of 0.04 mg/kg iv. After surgery, reversal was achieved with Inj neostigmine 0.05 mg/kg + Inj. glycopyrrolate 0.01 mg/kg iv. After adequate recovery patients were shifted to post anaesthesia care unit and monitored for 12 hours and later shifted to ward.

RAMSAY sedation score-

Score 1- Anxious or restless or both.

Score 2-Cooperative, oriented and tranquil.

Score 3-Responding to commands.

Score 4-Brisk response to stimulus.

Score 5-Sluggish response to stimulus.

Score 6-No response to stimulus

The groups were well-matched for their demographic data. The basal readings of heart rate, SBP, DBP and MAP were similar in all the three groups. Maximum intubation response was seen at 1' post intubation. The group A had statistically higher values of HR, SBP, DBP and MAP at all time intervals post intubation when compared to group B and group C. The haemodynamic variables never reached the baseline by 5 minutes in case of group A. In group B they approached near the baseline by 3 minutes. In group C the variables fell below the baseline by 3 minutes.

Though bradycardia and hypotension have been reported in other studies, neither bradycardia nor hypotension were observed in the patients. The mean sedation scores were more in group B and group C when compared to group A.

Hence from our study, we conclude that dexmedetomidine in a dose of 0.5 µg/kg and 0.75µg/kg were effective in attenuating haemodynamic response to laryngoscopy and intubation when compared to normal saline as a placebo without any adverse effects.

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ANNEXURES

PROFORMA

NAME: HOSPITAL NO:

AGE: DIAGNOSIS:

SEX: SURGERY:

WEIGHT:

GROUP A	20 mL of Inj.NORMAL SALINE AS INFUSION	
GROUP B	20 mL of Inj.DEXMEDETOMIDINE 0.5µg/kg iv AS INFUSION	
GROUP C	20 mL of Inj.DEXMEDETOMIDINE 0.75µg/kg AS INFUSION	

Premedication with Inj. glycopyrrolate 0.2mg and Inj. ondansetron 50µg/kg iv is given.

TIMING OF RECORDING THE PARAMETERS	HR	SBP	DBP	MAP	SpO2
BEFORE PREMEDICATION					
AFTER PREMEDICATION					

INFUSION OF THE APPROPRIATE DRUG OVER 10 MINUTES

TIMING OF RECORDING THE PARAMETERS	HR	SBP	DBP	MAP	SPO2
2’ AFTER INFUSION					

4’ AFTER INFUSION					
6’ AFTER INFUSION					
8’ AFTER INFUSION					
10’ AFTER INFUSION					

Intubation with Inj propofol 2mg/kg ,with xylocard in a conc. of 0.1% + Inj. Fentanyl 1µg/kg and Inj. succinyl choline 2 mg/kg iv.

TIMING OF RECORDING THE PARAMETERS	HR	SBP	DBP	MAP	SPO2
1’ AFTER INTUBATION					
3’ AFTER INTUBATION					
5’ AFTER INTUBATION					

SEDATION SCORE: RAMSAY SEDATION SCORE

AFTER INFUSION:

2’ :

5’ :

10’ :

ADVERSE EFFECTS :

PATIENT INFORMATION SHEET

Title: COMPARISON OF 0.5µg/kg, 0.75µg/kg IV DEXMEDETOMIDINE AND NORMAL SALINE FOR ATTENUATION OF HAEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION

We are carrying out a study on use of dexmedetomidine to attenuate haemodynamic response to endotracheal intubation. The study has been reviewed by the local ethical review board and has been started only after their formal approval.

Laryngoscopic manipulation and endotracheal intubation can result in tachycardia, arrhythmias, hypertension and raised intracranial pressure resulting in cerebrovascular accidents which could be detrimental to patients with ischaemic heart disease or compromised myocardial function. Dexmedetomidine has been studied in a dose of 0.5µg/kg and 1µg/kg to attenuate this response. There was no study with dexmedetomidine in a dose of 0.75µg/kg. Hence this study was undertaken.

Dexmedetomidine has been proven to be a safe drug without any significant adverse effects.

Participation in this study doesn't involve any cost for the patient.

All the information collected from the patient will be strictly confidential and will not be disclosed to any outsider unless compelled by law. This information collected will be used only for research.

I request you to kindly give consent for the study.

There is no compulsion to participate in this study. You will be no way affected if you don't wish to participate in this study. You are required to sign only if you voluntarily agree to participate in this study. Further, you are at a liberty to withdraw from the study at any time, if you wish to do so. Be assured that your withdrawal will not affect your treatment in any way. It is up to you to decide whether to participate. This document will be stored in the safe locker in the department of Anaesthesia in the college and a copy is given to you for information.

INFORMED CONSENT

Sl. no:

Title of the study: COMPARISON OF 0.5µg/kg, 0.75µg/kg IV DEXMEDETOMIDINE AND NORMAL SALINE FOR ATTENUATION OF HAEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION

I, the undersigned, agree to participate in this study as outlined in this consent form.

I have been read out/ explained in my local language i.e. in _____ and understand the purpose of this study and the confidential nature of the information that will be collected and disclosed during the study. I have had the opportunity to ask questions regarding the various aspects of this study and my questions have been answered to my full satisfaction. The information collected will be used only for research.

I understand that I remain free to withdraw from this study at any time. Participation in this study is under my sole discretion and does not involve any cost to me.

Subject's name and signature /thumb impression

Name and signature of the witness:

1) Date:

2) Date:

Name and signature of the interviewer:

1) Date:

MASTER CHART

		A:Normal saline B:0.5µg/kg C:0.75µg/kg				BASAL	HEART RATE			BASAL	SYSTOLIC BLOOD PRESSURE			BASAL	DIASTOLIC BLOOD PRESSURE			BASAL	MEAN ARTERIAL PRESSURE			RAMSAY SEDATION SCALE		
SL NO	HOSPITAL NUMBER	Group	Age	Gender	SURGERY		1 MIN	3 MIN	5MIN		1MIN	3MIN	5MIN		1 MIN	3 MIN	5 MIN		1MIN	3MIN	5MIN	2 MIN	5 MIN	10 MIN
						a1	a2	a3	a4	b1	b2	b3	b4	c1	c2	c3	c4	d1	d2	d3	d4			
1	100750	A	33 YEARS	MALE	TYMPANOMASTOID EXPLORATION	76	110	102	89	138	166	154	146	70	84	82	80	90	112	106	102	2	2	2
2	89489	A	20 YEARS	MALE	SEPTOPLASTY	78	114	106	92	134	168	154	144	68	82	80	76	90	111	102	99	2	3	2
3	99063	A	20 YEARS	FEMALE	TOTAL MAXILLECTOMY	79	112	105	93	126	158	146	138	62	80	78	78	84	106	101	98	1	2	2
4	12176	A	35 YEARS	MALE	CORTICAL MASTOIDECTOMY WITH TYMPANOPLASTY	85	119	108	98	130	162	154	142	66	82	78	76	88	109	104	98	2	2	2
5	113443	A	45 YEARS	MALE	LAPROSCOPIC APPENDICECTOMY	80	116	106	94	132	164	152	142	74	88	84	80	94	114	107	101	3	2	2
6	113611	A	38 YEARS	FEMALE	LAPROSCOPIC APPENDICECTOMY	82	110	107	96	128	162	150	138	76	90	86	82	94	114	108	101	2	2	1
7	64154	A	23 YEARS	FEMALE	LAPROSCOPIC TUBECTOMY	84	118	104	96	128	158	148	140	78	92	90	86	95	114	110	104	2	2	2
8	116660	A	46 YEARS	FEMALE	LAPROSCOPIC CHOLECYSTECTOMY	82	116	110	96	140	172	160	152	88	102	98	96	106	126	119	115	2	1	2
9	102256	A	22 YEARS	MALE	SEPTOPLASTY	78	106	104	92	138	166	156	148	84	98	94	90	102	121	115	110	2	2	2
10	118003	A	25 YEARS	MALE	TYMPANOPLASTY	86	115	108	90	124	160	148	136	72	88	86	84	90	112	107	102	3	1	2
11	118498	A	30 YEARS	FEMALE	EXCISION	74	106	98	87	118	154	142	136	74	90	88	84	89	112	106	102	2	2	2
12	116474	A	30 YEARS	FEMALE	DIAGNOSTIC LAPROSCOPY	92	123	114	103	120	154	144	132	78	94	90	86	92	114	108	105	2	2	2
13	122091	A	27 YEARS	FEMALE	EXCISION	81	108	106	94	136	162	150	142	82	98	96	90	100	120	114	108	1	1	1
14	122180	A	40 YEARS	FEMALE	EXCISION	77	110	102	90	134	166	152	144	84	98	94	92	101	121	114	110	2	2	2
15	123381	A	36 YEARS	FEMALE	LAPROSCOPIC APPENDICECTOMY	85	117	107	97	122	156	148	134	76	92	90	86	92	114	110	102	1	2	2
16	116182	A	45 YEARS	FEMALE	TOTAL THYROIDECTOMY	79	105	98	90	114	152	140	136	70	86	86	82	85	108	104	100	2	2	2
17	125778	A	21 YEARS	MALE	RADIUS AND ULNA PLATING	68	102	94	81	130	160	148	140	80	94	90	88	97	116	110	106	2	2	2
18	130698	A	45 YEARS	MALE	EXPLORATION	89	122	108	99	142	174	160	144	82	94	92	86	102	121	115	106	2	2	1
19	130223	A	40 YEARS	MALE	MICROLUMBAR DISCECTOMY	75	109	99	88	112	146	138	130	66	82	78	74	82	104	98	93	3	3	3
20	131228	A	28 YEARS	MALE	TENDON TRANSFER	84	110	104	96	126	162	150	142	76	92	90	86	93	116	110	105	2	2	3
21	130365	A	21 YEARS	FEMALE	ORIF WITH LCP	82	111	103	94	130	158	146	138	80	92	88	88	97	114	108	105	2	2	2
22	133047	A	40 YEARS	MALE	ORIF WITH LCP	79	108	99	91	132	164	152	140	90	102	96	92	104	123	115	108	1	2	2
23	133471	A	20 YEARS	MALE	LAPROSCOPIC APPENDICECTOMY	66	98	93	80	116	150	136	132	72	90	84	84	87	110	102	100	2	2	2
24	133994	A	45 YEARS	MALE	PLATING FOR FEMUR,K-WIRE FOR CALCANEUM,ULNA PLATING	87	120	109	98	118	154	142	136	76	92	90	84	90	113	108	102	2	1	2
25	133006	A	34 YEARS	FEMALE	SEPTOPLASTY	74	112	101	88	128	158	144	138	80	94	90	84	96	116	108	102	2	2	3
26	131999	A	36 YEARS	MALE	TYMPANOPLASTY	78	114	104	90	138	160	146	138	84	98	94	88	102	119	112	105	1	2	2
27	149881	A	29 YEARS	MALE	FESS	84	115	106	96	122	158	146	136	68	86	84	82	86	110	105	100	2	2	2
28	144107	A	20 YEARS	FEMALE	TYMPANOPLASTY	82	109	103	95	130	162	154	146	86	100	96	92	101	121	116	110	2	2	2
29	153646	A	44 YEARS	FEMALE	TYMPANOPLASTY	80	114	105	94	124	158	144	140	74	88	84	80	91	112	104	100	1	2	2
30	145907	A	37 YEARS	FEMALE	TYMPANOPLASTY	86	118	108	99	132	160	146	138	76	90	88	84	95	114	108	102	2	3	2
31	854305	B	39 YEARS	MALE	R- TYMPANOPLASTY	86	91	88	84	136	144	138	134	78	82	80	74	98	103	100	94	3	3	3
32	61333	B	29 YEARS	MALE	SEPTOPLASTY & FESS	81	85	82	80	128	136	134	128	66	74	68	64	87	95	89	86	2	3	3
33	55317	B	35 YEARS	MALE	FESS	83	88	85	84	140	146	142	136	80	86	84	80	100	106	104	99	3	3	2
34	63702	B	27 YEARS	MALE	SEPTOPLASTY	78	84	80	77	122	126	122	118	76	80	78	74	92	96	93	89	2	2	3
35	51655	B	48 YEARS	FEMALE	MODIFIED RADICAL MASTECTOMY	85	87	85	82	134	140	136	132	72	82	76	72	93	102	96	92	3	3	3
36	62775	B	20 YEARS	FEMALE	CRIF WITH SCREW FIXATION	82	88	85	81	136	144	140	132	78	84	78	72	88	104	99	92	2	2	2
37	1018943	B	48 YEARS	FEMALE	SSG WITH WOUND DEBRIDEMENT	87	91	89	84	118	128	124	112	70	76	72	68	86	94	90	83	2	3	3
38	61034	B	45 YEARS	MALE	ANTERIOR TRANSPOSITION OF NERVE	79	82	80	75	114	122	116	114	72	74	70	68	96	90	86	87	2	2	2
39	62675	B	38 YEARS	FEMALE	HEMITHYROIDECTOMY	94	100	96	88	124	134	128	120	80	86	80	76	95	102	96	91	3	2	3
40	63662	B	46 YEARS	MALE	FESS	88	91	90	87	138	144	138	132	82	84	78	74	99	104	98	84	3	2	3
41	65081	B	23 YEARS	MALE	ORIF WITH LCP FIXATION	73	78	77	74	108	116	112	106	76	82	78	72	87	94	90	87	3	3	2
42	404632	B	23 YEARS	FEMALE	OSSICULOPLASTY	78	83	81	77	126	132	126	120	80	82	76	74	96	99	93	90	3	3	3
43	1019455	B	50 YEARS	MALE	TOTAL THYROIDECTOMY	86	90	89	82	130	134	128	126	82	84	78	78	98	91	95	94	2	2	2
44	1019824	B	45 YEARS	FEMALE	TOTAL THYROIDECTOMY	80	84	84	79	134	140	134	132	82	86	78	76	100	94	97	95	3	3	3
45	1019859	B	48 YEARS	MALE	FESS	81	84	83	79	140	144	136	134	86	90	82	80	104	108	100	98	3	2	3
46	23609	B	43 YEARS	MALE	SEPTOPLASTY & FESS	79	85	83	74	138	144	142	136	80	86	80	80	100	106	101	99	2	3	2
47	54059	B	20 YEARS	FEMALE	ADENOTONSILLECTOMY	84	86	85	80	132	136	128	128	74	80	76	74	94	99	94	92	3	3	3
48	176653	B	34 YEARS	FEMALE	ADENOTONSILLECTOMY	76	80	79	79	110	114	110	110	72	74	66	64	85	88	91	80	2	3	3
49	1019906	B	50 YEARS	MALE	ENDOSCOPIC DCR	80	84	82	78	116	124	118	114	76	84	80	78	90	98	93	90	2	2	2
50	1019888	B	45 YEARS	FEMALE	ENDOSCOPIC DCR	86	89	87	85	128	136	132	126	74	80	76	74	92	99	95	92	3	3	3
51	85028	B	30 YEARS	FEMALE	ORIF WITH DCP	84	86	86	84	130	134	124	122	78	80	74	72	96	98	91	91	3	3	3
52	83801	B	32 YEARS	MALE	NAILING OF FEMUR AND PLATING OF HUMERUS	88	92	89	82	132	136	132	134	72	74	70	74	92	92	88	94	2	2	3
53	77707	B	28 YEARS	FEMALE	FESS	68	70	70	66	106	108	106	104	70	74	68	68	82	86	81	80	2	4	3
54	78556	B	21 YEARS	MALE	SEPTOPLASTY WITH ADENOIDECTOMY	76	81	79	75	136	142	136	132	80	84	80	78	99	104	96	96	2	2	3
55	54254	B	28 YEARS	MALE	SEPTOPLASTY WITH TURBINECTOMY	78	82	81	77	134	138	138	136	82	84	78	76	100	102	98	96	2	2	2
56	86970	B	25 YEARS	MALE	TYMPANOPLASTY	74	79	77	76	128	134	130	128	74	78	74	74	92	97	93	92	2	4	3
57	79753	B	44 YEARS	MALE	SUPERFICIAL PAROTIDECTOMY	80	84	82	73	132	136	130	128	76	82	80	78	95	100	97	95	3	3	2
58	20198	B	48 YEARS	FEMALE	FESS	86	90	87	82	138	144	138	134	82	84	80	78	101	104	100	97	3	3	3
59	68574	B	33 YEARS	FEMALE	MASTOID EXPLORATION	81	85	84	80	136	142	140	138	84	86	78	80	102	105	99	100	2	2	2
60	103309	B	48 YEARS	MALE	SEPTOPLASTY WITH FESS	84	88	87	80	138	140	138	136	84	88	84	80	102	106	102	99	2	2	2
61	58298	C	30 YEARS	MALE	SUPERFICIAL PAROTIDECTOMY	83	87	84	77	134	136	132	124	76	78	74	72	96	98	94	90	2	3	3
62	93688	C	23 YEARS	FEMALE	LAPROSCOPIC APPENDICECTOMY	80	82	80	74	136	140	132	122	78	80	76	72	98	100	95	89	3	3	3
63	93459	C	25 YEARS	FEMALE	CRANIOPLASTY	88	91	87	84	140	142	134	128	80	84	78	76	100	104	97	93	3	3	3
64	68395	C	30 YEARS	FEMALE	CRANIOPLASTY	81	85	81	75	132	134	126	118	70	72	68	66	91	93	88	84	3	4	3
65	92306	C	20 YEARS	MALE	RECON LOCKING AND PLATING	76	79	74	68	128	132	124	116	66	68	64	62	87	90	84	80	2	2	3
66	1018751	C	35 YEARS	FEMALE	LAPROSCOPIC CHOLECYSTECTOMY	79	81	78	73	132	136	128	118	68	72	64	64	90	94	86	82	2	3	4
67	32948	C	26 YEARS	MALE	MICROLARYNGEAL SURGERY	84	87	84	78	136	140	130	124	76	78	72	70	96	99	92	88	3	4	2
68	27514	C	25 YEARS	MALE	ENDOSCOPIC DCR	86	88	85	80	144	146	140	132	84	86	80	78	104	106	100	96	2	2	4
69	40064	C	19 YEARS	FEMALE	DIAGNOSTIC LAPROSCOPY	78	82	79	70	126	128	120	112	68	70	68	64	88	90	86	80	3	3	3
70	56767	C	24 YEARS	MALE	SEPTOPLASTY , PARTIAL TURBINECTOMY,MIDDLE MEATAL ANTROSTOMY	76	78	76	66	130	134	122	116	74	78	74	70	93	97	90	86	2	3	3
71	62630	C	30 YEARS	MALE	ORIF WITH DCP - HUMERUS, CRIF WITH NAILING-TIBIA	82	85	82	74	128	132	122	114	72	74	70	66	91	94	88	86	2	3	2
72	62096	C	32 YEARS	MALE	LAPROSCOPIC CHOLECYSTECTOMY	84	86	82	75	134	136	128	120	78	82	76	72	97	100	94	88	2	3	3
73	91453	C	35 YEARS	FEMALE	CORTICAL MASTOIDECTOMY AND TYMPANOPLASTY	72	74	70	64	114	118	110	104	72	74	68	66	86	89	82	79	3	3	3
74	95909	C	48 YEARS	MALE	ORIF WITH LCP PLATING	92	95	92	86	140	142	136	126	80	82	76	74	100	102	96	82	2	2	4
75	84610	C	46 YEARS	FEMALE	CORTICAL MASTOIDECTOMY AND TYMPANOPLASTY	86	89	85	80	136	138	132	126	82	84	78	74	100	102	96	82	3	4	4
76	68437	C	45 YEARS	MALE	MICROVASCULAR DECOMPRESSION	84	86	83	79	134	138	128	120	78	80	76	74	97	100	94	90	2	2	3
77	75945	C	32 YEARS	FEMALE	TOTAL THYROIDECTOMY	77	80	78	72	130	132	124	120	74	76	72	70	93	95	90	87	3	3	3
78	98963	C	48 YEARS	MALE	HEMITHYROIDECTOMY	88	91	85	81	138	140	130	124	80	84	80	76	100	103	97	92	2	2	3
79	95133	C	20 YEARS	FEMALE	TYMPANOPLASTY	68	70	66	60	116	118	108	102	70	72	68	64	86	88	82	79	3	3	3
80	10078	C	25 YEARS	MALE	ORIF WITH CLAVICULAR PLATING	74	76	72	68	110	114	104	102	68	70	66	62	82	88	79	76	2	3	4
81	100385	C	20 YEARS	FEMALE	LAPROSCOPIC APPENDICECTOMY	85	89	85	78	122	126	116	110	72	74	68	66	89	92	84	81	3	3	3
82	95688	C	40 YEARS	FEMALE	WERTHEIMS HYSTERECTOMY	81	84	80	76	126	130	122	114	74	78	70	68	92	96	87	87	2	2	3
83	94189	C	45 YEARS	MALE	TYMPANOPLASTY	89	92	86	80	140	144	136	126	84	86	82	78	103	106	100	94	3	3	3
84	98158	C	36 YEARS	MALE	TOTAL THYROIDECTOMY	78	81	78	72	120	124	114	110	82	84	80	74	95	98	92	76	3	2	3
85	103249	C	24 YEARS	FEMALE	EXCISION AND BIOPSY	82	86	83	78	130	134	122	116	78	80	76	70	96	98	92	86	2	2	3
86	94958	C	30 YEARS	FEMALE	TOTAL THYROIDECTOMY	84	87	84	76	126	130	122	114	72	76	72	68	90	94	91	87	3	3	3
87	101020	C	22 YEARS	FEMALE	LAPROSCOPIC APPENDICECTOMY	85	88	84	80	132	134	128	122	68	70	66	64	90	88	87	84	3	4	4
88	102304	C	23 YEARS	FEMALE	EXCISION	80	85	82	76	128	132	122	116	74	76	72	70	92	95	89	86	3	3	3
89	104326	C	32 YEARS	FEMALE	EXCISION	78	81	77	73	124	128	120	114	70	72	66	66	88	91	84	86	3	3	3
90	107009	C	46 YEARS	MALE	LAPROSCOPIC APPENDICECTOMY	84	86	83	78	136	140	128	124	78	80	74	70	88	100	92	88	3	3	3