A STUDY ON THE EFFECTS OF INTRAVENOUS DEXMEDETOMIDINE ON THE HAEMODYNAMIC STRESS RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION DURING GENERAL ANAESTHESIA

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CERTIFICATE

This is to certify that this dissertation entitled "**A study on the effects of intravenous dexmedetomidine on the haemodynamic stress response to laryngoscopy and endotracheal intubation during general anaesthesia**" is a bonafide record of the work done by **Dr. Rakhi S.P** under my guidance and supervision in the Department of Anaesthesiology during the period of her postgraduate study for **M.D Anaesthesiology [Branch-X]** from 2012-2015.

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DECLARATION

In the following pages is presented a consolidated report of the study "**A study on the effects of intravenous dexmedetomidine on the haemodynamic stress response to laryngoscopy and endotracheal intubation during general anaesthesia**" a randomized clinical trial, on cases studied and followed up by me at Sree Mookambika Institute of Medical Sciences, Kulasekharam from 2013-2014. This thesis is submitted to the Dr.M.G.R. Medical University, Chennai in partial fulfilment of the rules and regulations for the award of MD Degree examination in Anaesthesiology.

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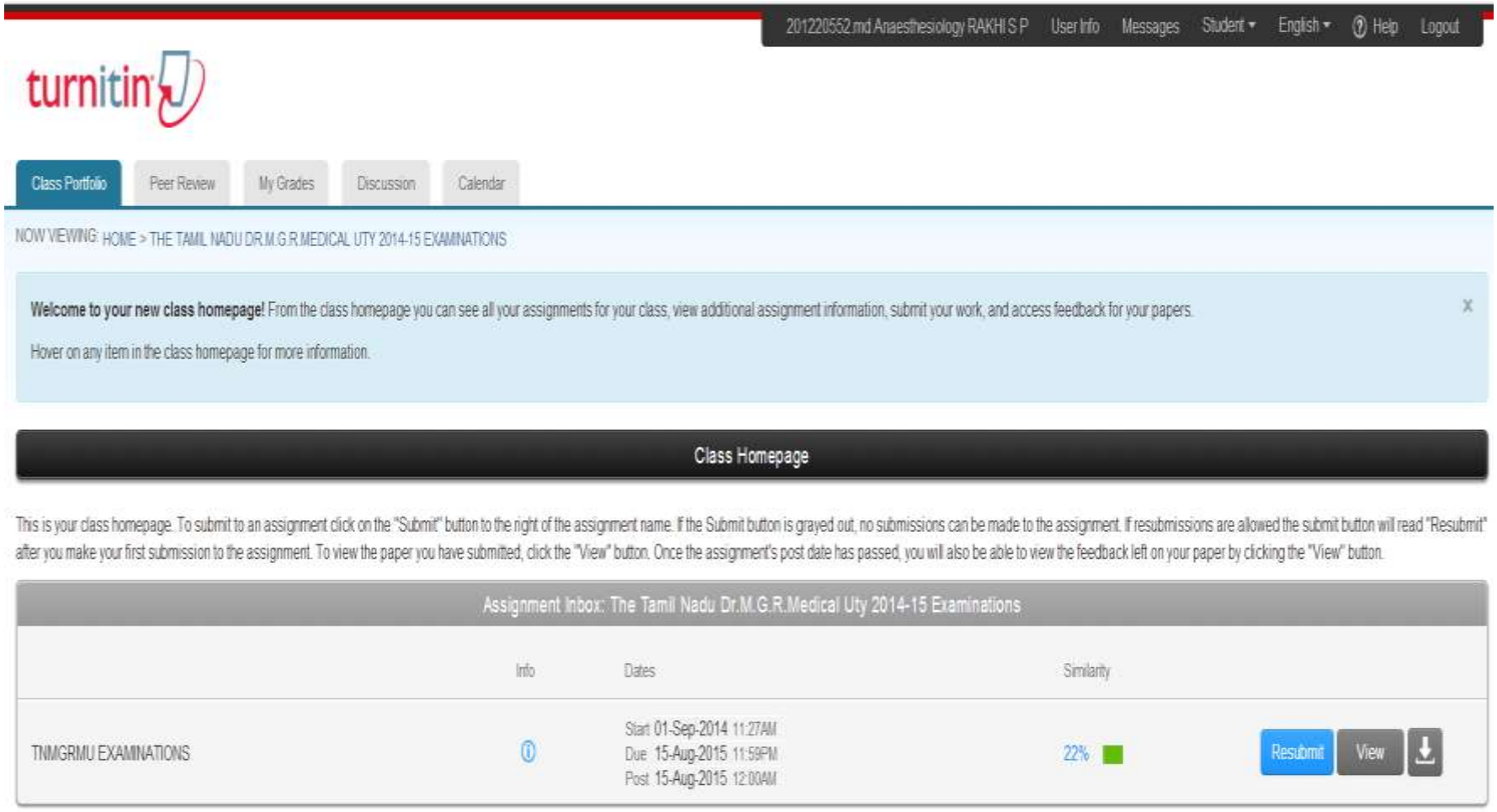
PLAGIARISM SCREENING REPORT



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Dr.Rakhi S.P.

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LIST OF ABBREVIATIONS

ANP	:	Atrial Natriuretic Peptide
ASA	:	American Society of Anaesthesiologists
ATP	:	Adenosine Triphosphate
AVP	:	Arginine Vasopressin
BIS	:	Bispectral Index
CABG	:	Coronary Artery Bypass Grafting
cAMP	:	Cyclic Adenosine Monophosphate
CBF	:	Cerebral Blood Flow
$CMRO_2$	:	Cerebral Metabolic Rate of Oxygen
CNS	:	Central nervous system
CPB	:	Cardio Pulmonary Bypass
CSF	:	Cerebro Spinal Fluid
ECG	:	Electrocardiogram
ERCP	:	Endoscopic Retrograde Cholangio Pancreatography
FDA	:	Food and Drug Administration
GABA	:	Gamma amino butyric acid
ICP	:	Intra Cranial Pressure
ICU	:	Intensive Care Unit
IM	:	Intramuscular
IOP	:	Intra Ocular Pressure
IV	:	Intravenous

LC	:	Locus Coeruleus
MAC	:	Monitored Anaesthesia Care
MAP	:	Mean Arterial Pressure
NS	:	Normal Saline
$PaCO_2$	:	Partial Pressure of Carbon-di-oxide
PACU	:	Post Anaesthesia Care Unit
VAS	:	Visual Analogue Scale

ABSTRACT

Background and Objectives:

During induction of general anaesthesia, hypertension and tachycardia caused by endotracheal intubation may lead to cardiac ischemia and arrhythmias. Dexmedetomidine attenuates the hemodynamic response to endotracheal intubation and reduces anaesthetic requirement. The purpose of this study was to evaluate the effect of intravenous dexmedetomidine 1μg/kg given over 10 minutes before induction of anaesthesia and 0.4mcg/kg/hour as maintenance during the surgery, on haemodynamic stress response resulting from laryngoscopy and endotracheal intubation and the haemodynamic stability during surgery.

Materials and Methods:

Seventy patients scheduled for elective surgery were randomized into two groups each having thirty five patients-dexmedetomidine group (Group 1) and control group (Group 2). Heart rate, systolic blood pressure, and diastolic blood pressure were recorded at just before intubation, immediately after intubation, 1, 2, 3, 4, 5 minutes after intubation followed by every 5 minutes till the first 45 minutes of surgery. Anaesthesia was induced with inj.Propofol 2mg/kg IV followed by succinyl choline 2mg/kg for endotracheal intubation. Anaesthesia was maintained with oxygen, nitrous oxide, isoflurane, atracurium. Any further need for analgesia was supplemented by IV fentanyl.

Statistical Analysis:

The data was analysed by SPSS 16.0 with independent t-test.

Results:

Pretreatment with dexmedetomidine 1 ug/kg attenuated the cardiovascular and catecholamine responses to tracheal intubation after induction of anaesthesia. In our present study, the rise in heart rate, systolic blood pressure and diastolic blood pressure after intubation, 1, 2, 3, 4, 5 and 10 minutes after intubation was significantly less in the dexmedetomidine group. The patients in dexmedetomidine group also had better haemodynamic stability during surgery. The requirement of opioids and isoflurane were significantly less in the dexmedetomidine group.

Conclusions:

Intravenous dexmedetomidine significantly attenuates sympathoadrenal response to laryngoscopy and endotracheal intubation and also cause reduction in intra operative anaesthetic requirement, without affecting intraoperative cardiovascular stability

Keywords:

Dexmedetomidine, endotracheal intubation, premedication, sedation, α2 adrenergic

INTRODUCTION

Balanced anaesthesia protocols include combination of drugs of different classes used with specific purpose so as to create unconsciousness, muscle relaxation, analgesia and amnesia. As the drugs are used in low to moderate doses, the adverse effects are reduced. So anaesthesia induction, maintenance and emergence are safer, smoother and comfortable. Maintenance of heart rate, blood pressure and depth of anaesthesia are important in the intra-operative period. Laryngoscopy and intubation can lead to hemodynamic stress response which can be controlled by suitable agents. Various drugs like lignocaine, nifedipine, Beta blockers, nitro glycerine etc. are used to reduce hemodynamic stress response to laryngoscopy and intubation.

Dexmedetomidine is a high selective centrally acting, potent alpha2 adrenergic agonist with less duration of action. Alpha 2 to alpha 1 selectivity for dexmedetomidine is 1620:1 compared to 220:1 for clonidine. Dexmedetomidine has sedative, anxiolytic, analgesic and sympatholytic properties.

Various studies have been done using intravenous dexmedetomidine for analgesia, anxiolysis and sedation during surgery. In our study we are analysing the effect of intravenous dexmedetomidine1microgm/kg given over 10 minutes before induction of anaesthesia and then as continuous infusion at 0.4microgm/kg/hr during the maintenance of anaesthesia.

AIMS AND OBJECTIVES

1. To study if dexmedetomidine can reduce hemodynamic stress response to laryngoscopy and tracheal intubation.
2. Assess hemodynamic stability during the surgery when dexmedetomidine is used.
3. To study the complications when dexmedetomidine is used.

HYPOTHESIS AND JUSTIFICATIONS OF THE STUDY

Hypothesis

Intravenous Dexmedetomidine decreases haemodynamic stress response during laryngoscopy and endotracheal intubation.

Scientific Justification of the Study

It is very important to maintain stable haemodynamics throughout the surgery. Laryngoscopy and endotracheal intubation leads to haemodynamic instability. This leads to increase in cardiac workload and myocardial oxygen consumption. This is deleterious in patients with pre-existing cardiovascular disease. So it is important to find a suitable drug for reducing the haemodynamic stress response during laryngoscopy. Various drugs like lignocaine, nifedipine, beta blockers, nitro glycerine etc. are used to reduce haemodynamic stress response to laryngoscopy and intubation. Dexmedetomidine has additional analgesic, anxiolytic, sedative and sympatholytic properties which are useful in general anaesthesia. So the dose of other drugs and their adverse effects can be reduced along with reduction of hospital expenditure and maintenance of stable haemodynamics.

REVIEW OF LITERATURE

Two predictors of perioperative cardiac morbidity are increase in heart rate and blood pressure. Increase in heart rate and acute hypertension deleteriously affect myocardial oxygen supply and demand. Different techniques are being tried to prevent or attenuate the hemodynamic effects following laryngoscopy and tracheal intubation, like deepening of anaesthesia, avoiding anticholinergic drugs prior to surgery, pre-treatment with lignocaine, vasodilators like nitroglycerin, beta blockers, calcium channel blockers and opioids.

Reid and Brace, first explained the hemodynamic effects to direct laryngoscopy and endotracheal intubation[6].These hemodynamic changes were noticed after the emergence of muscle relaxants such as tubocurarine and succinylcholine for facilitating endotracheal intubation during anaesthesia induction. King et al[7] studied the hemodynamic changes to laryngoscopy in the year 1951. They proposed that the cardiac dysrhythmias, tachycardia and hypertension related to laryngoscopy and tracheal intubation were the result of reduced vagal tone or a rise in sympatho-adrenal activity. They noted that laryngoscopy alone can cause an elevated blood pressure. Intubation amplified this effect and was capable of causing arrhythmias. Wycoff[8] compared laryngoscopy and endotracheal intubation under general anaesthesia with the same under cricothyroid block. The block produced smaller changes in blood pressure and heart rate. Dingle[9]

observed a rise in systolic blood pressure of more than 100mm Hg following endotracheal intubation.

Bedford described the relation of CNS to the cardiovascular response[10]. During laryngoscopy and endotracheal intubation, hemodynamic instability ensues as larynx, trachea and carina are having sympathetic nervous system reflexes which respond to substances or objects which they come in contact with. Other elements such as a lighter plane of anaesthesia are also contributory to this stress response.

C Prys Roberts et al[10] demonstrated the electrocardiographic and hemodynamic responses to induction of anaesthesia followed by laryngoscopy and endotracheal intubation. Takashima K et al[11] conducted a study to find out the real cause for cardiovascular response to rapid anaesthesia induction and endotracheal intubation and showed that the cardiovascular response during endotracheal intubation was mainly the result of insertion of the laryngoscope blade. The variations in ECG found during intubation results from stimulation of vagus nerve by laryngoscopy. The reason for these cardiovascular fluctuations was studied and concluded that pressure exerted by the laryngoscope blade on the soft tissues adjacent to the epiglottis probably contributed to the electrocardiographic findings.

Cardiovascular response to laryngoscopy and endotracheal intubation is mediated by autonomic nervous system. The parasympathetic response which is sinus bradycardia is more common

in infants and small children, but infrequently seen in adults also. As this reflex is mediated by an increase in vagal tone at sino-atrial node, it is considered as a monosynaptic response to a painful stimulus.

Sinus tachycardia is the sympathetic response to laryngoscopy and intubation. Derbyshire et al[12,13] suggested that tracheal intubation is accompanied by both increased sympathetic activity and an increased adreno-medullary catecholamine activity. The common cardiovascular responses to tracheal intubation are produced by these sympathetic efferents. These pathways are polysynaptic and traverse from the vagal and glossopharyngeal afferents to the sympathetic systems through the brain and spinal cord causing a diffuse autonomic response, including an increased firing of the cardio-accelerator fibres and the release of norepinephrine from adrenergic nerve endings in many vascular beds, and release of adrenaline from the adrenal medulla. As renin released from the juxtaglomerular apparatus of kidney has β adrenergic activity, renin angiotensin system activation also plays a role in the hypertensive change to intubation.

In studying the cardiovascular responses to laryngoscopy and endotracheal intubation, the effect of laryngoscopy has been studied separately from intubation. To avoid the stimulus of rigid laryngoscopy and succinylcholine, Ovassapian et al[14] used awake fiberoptic nasotracheal intubation and reported that the highest rise in blood pressure happened during the introduction of endotracheal tube through the passage. The maximum rise in heart rate occurred when

the endotracheal tube was placed in the trachea. Shribman et al[15] also studied the cardiovascular changes to laryngoscopy with or without intubation. They demonstrated significant and similar rise of blood pressure and circulating catecholamine concentrations with or without intubation. Intubation causes a higher increase in heart rate, which was not seen with laryngoscopy only. Finfer et al[16] compared direct laryngoscopy with fiberoptic intubation and found out that both laryngoscopic and bronchoscopic intubation resulted in significant increase in blood pressure and heart rate without any difference between the groups. It seems that maximum increase in blood pressure occurs with laryngoscopy and the maximum rise in heart rate occurs with endotracheal intubation.

Elderly patients constitute a high percentage of both inpatient and outpatient hospital population and have an greater incidence of coronary artery disease, cerebrovascular disease and a higher baseline blood pressure which makes them particularly susceptible to fluctuations in blood pressure and heart rate during laryngoscopy and endotracheal intubation leading to increased risk of cerebro vascular accident, myocardial infarction, congestive cardiac failure or sudden death.[17,18]

The prevalence of cardiovascular diseases significantly affects both cardiac and non-cardiac surgeries. As more patients are undergoing non-cardiac surgery, the impact of cardiovascular disease on such patients is higher than in the cardiac surgery group. The

number of non-cardiac surgical patients at risk of cardiac morbidity is found to be 7 to 8 million patients per annum.[19]

Mangano stated that it is difficult to assess the incidence of perioperative cardiac morbidity. In the elderly group the range is 2-15%.[20]

Rose and Tinker[21] stated that final outcome (i.e. perioperative myocardial infarction, patient alive or dead), should be differentiated from process outcome (i.e. myocardial ischemia, hypertension, tachycardia during surgery). When process outcome is considered, reduction of these different physiologic disturbances during anaesthesia and surgery will be better for the patient. It is not yet proved that reducing such physiological changes actually improves final outcome, as a very large population study is needed to show relatively small but significant differences.

Goldman and Caldera[22] concluded that hypertension and the history of cardiac dysrhythmias were important risk factors in the issue of whether preoperative ischemia can be a predictor of negative outcome. Raby et al[23] stated that preoperative ischemia was a more important risk factor, which was in contrast to Mongano et al [24] whose study concluded that postoperative ischemia was more important.

The time during which intubation is done is principally a high risk interval[24,25]. Known or suspected cardiac disease is one among the commonest indications for modifications of

haemodynamic effect. Patients requiring stable haemodynamics include patients with a symptomatic aortic aneurysm, ischemic heart disease, recent myocardial infarction, intracranial hypertension and cerebral aneurysm. Slogoff and Keats [26] stated that most of the ischemic episodes during anaesthesia were related to intubation and surgical stimulation, particularly if tachycardia occurs. Similarly Kleinman et al[25] stated that increase in heart rate and an increase in afterload due to laryngoscopy and endotracheal intubation can be related with myocardial ischemia occurring secondary to coronary artery vasoconstriction.

The study by Goldman and Caldera and editorial by Prys Roberts[27] give rationale for delaying surgery in patients whose blood pressure control is not optimal. Moreover, Steen et al[28], concluded that almost double the reinfarction rate is seen perioperatively in patients who had hypertension preoperatively. Stone et al[29] stated that substantial risk of developing myocardial ischemia is more in hypertensive patients untreated before induction and that the ischemia occurring during the stress of induction and intubation was always associated with rise in heart rate.

Two academic interpretors of perioperative cardiac morbidity are rise in heart rate and rise in blood pressure[30,31]. The haemodynamic changes due to intubation resulting from sympathetic nervous stimulation which predispose patients to ischemia comprise of increase in heart rate, blood pressure,

pulmonary capillary wedge pressure and reduced ejection fraction. An increase in heart rate deleteriously affect myocardial oxygen supply (reduced diastolic filling time) and demand (increased cardiac work load). Blood pressure has direct relation with cardiac output and systemic vascular resistance. Acute increase in blood pressure affects both myocardial oxygen supply and oxygen demand. During systemic hypertension, peak systolic ventricular wall tension occurs, which increases myocardial oxygen consumption.

Cardiac output and systemic vascular resistance are related to each other with variations in one resulting in a compensatory response in the other. Both heart rate and blood pressure are primary determinants of balance between myocardial oxygen supply and oxygen demand. Heart rate is there on both oxygen supply and oxygen demand sides of the myocardial equation. Myocardial oxygen supply can increase by a reduction in heart rate and rise in diastolic blood pressure, both within physiological limits. They act by allowing a prolonged diastolic filling time and a greater coronary perfusion pressure respectively. Myocardial oxygen demand increases according to rise in heart rate, resulting in a less diastolic filling time and myocardial perfusion time.

It has been recognized that there are six determinants of myocardial work i.e. myocardial oxygen consumption. They are:

Minor factors (which are more or less fixed):

1. Metabolism (20%)
2. External work (17%)
3. Activation energy (3%)

Major factors (can be altered by pharmacological or physical methods):

1. Systolic wall tension (30-40%)
2. Contractility (10-15%)
3. Heart rate

Systolic wall tension is the most significant determinant of left ventricular work, accounting for 30-40% of the energy needs of the beating heart. It is directly proportional to the product of arterial blood pressure (afterload) and left ventricular filling pressure (preload). Therefore an increase in either of these beyond their normal range will cause an increased myocardial work by increasing systolic wall tension. This also has a linear relation with the myocardial oxygen consumption. The concept of rate pressure product (heart rate x systemic blood pressure), introduced by Georta et al (1957) has been found to effectively reflect changes in myocardial oxygen consumption.

Myocardial contractility accounts for 10-15% of myocardial oxygen consumption and cardiac work. Increase in heart rate is

associated with a rise in myocardial contractility. Therefore rise in heart rate means rise in myocardial work load i.e. increase in oxygen demand.

On the other side of the scale is the myocardial oxygen supply. Supply is regulated by adjusting coronary blood flow, which is dependent on coronary vascular resistance. As myocardial blood flow occurs in diastole, diastolic blood pressure gives an estimate of the perfusion pressure. A diastolic blood pressure of 60mm Hg is generally accepted as a lower limit, below which the perfusion is likely to be compromised. Duration of diastole is another important factor affecting myocardial oxygen supply. At a normal heart rate of 75/minute, diastole occupies more than 60 percentage of the cardiac cycle. When the heart rate increases, systolic intervals change little while diastolic intervals decreases significantly. At a maximum heart rate of 180/minute, diastole occupies only 40 percentage of the cardiac cycle. Here, an increase in rate impairs the myocardial supply and can lead to ischemia or infarction when the balance between oxygen supply and demand is already compromised. These facts show the importance of attenuating the stress response.

Various techniques are available for haemodynamic modification and the selection of one may be difficult. Thomson[32] stated that the method for obtaining desired haemodynamic result depends on the

clinical scenario and anaesthesiologist's preference. Methods may be less significant compared to final result.

During general anaesthesia, it is difficult to detect periods of inadequate myocardial oxygenation because angina pectoris, the most reliable indicator of myocardial ischemia cannot be identified. Hence other indices have to be used to assess the adequacy of myocardial oxygenation. The rate pressure product reflects the myocardial oxygen demand and is obtained by multiplying systolic blood pressure and heart rate. Rate pressure product has a constant association with the onset of angina pain. Patients whose rate pressure product were over 12000 showed ischemic changes in V5 lead during the pre-bypass period of coronary artery surgery (Kaplan 1975). Thus it is better to monitor the rate pressure product in all patients with coronary artery disease and maintain it less than 12000 during surgery, particularly during periods of stress such as intubation.

Some regimens reduce the resulting hypertension, but fewer reduce resulting tachycardia. Each of those methods has their own advantages, disadvantages and risks. It is difficult to compare most of the studies as methodological differences exist in size and type of patient populations, use of preoperative and concomitant drugs, induction agents, dosage and timing of study, duration of laryngoscopy, maintenance drugs, frequency and methods of blood pressure monitoring.

Duration of laryngoscopy has been shown to exert an important effect on the severity of cardiovascular response. Attempts to reduce stress changes to laryngoscopy and endotracheal intubation could seem to be the most suitable when intubation is likely to take greater than 30 seconds. This is particularly significant in coronary artery disease or intracranial hypertension. Prolonging laryngoscopy greater than 60 seconds produces more rise in pulse rate and blood pressure (Stoelting, 1977).

Different methods have been described in literature to supress the cardiovascular responses to laryngoscopy and endotracheal intubation. Some of them are:

1. Prophylactic use of Beta blockers prior to laryngoscopy and endotracheal intubation (acebutolol[33], propranolol[34], atenolol[35], metoprolol[36], labetolol[37,38] and esmolol[39]. Side effects of beta blockers include bronchospasm, bradycardia, hypotension, cardiac dysrhythmias and heart failure.

2. Thoracic epidural anaesthesia (Watwill et al[40])

3. Inducing deeper plane of anaesthesia using volatile anaesthetic agents. (King et al[7])

4. Use of calcium channel blockers[41-43] (intravenous verapamil, 10mg nifedipine sublingually). They may not be able to prevent tachycardia.

5. Magnesium sulfate i.v[44-46] inhibits catecholamine release.

6. Vasodilators such as sodium nitroprusside 1-2mcg/kg i.v 15seconds prior to laryngoscopy[47], hydralazine, phentolamine, nitroglycerine[48-50].

7. 2ml nitroglycerine solution 60mg, 1 minute prior to induction. (Fassoulaki and Kaniaris[50]).

8. Nitroglycerine ointment 2% applied to skin 12 minutes before laryngoscopy (Elkayam U, Aronow WS)

9. Buprenorphine i.v[51]

10. Fentanyl 1-2mcg/kg 2-4 minutes before laryngoscopy[52]

11. Alfentanil 15-30mcg/kg (Black et al[53]

12. Sufentanil 0.5-1mcg/kg (Kay et al[54])

13. ATP[55,56] iv 0.05 and 0.1mg/kg given simultaneously with start of laryngoscopy (Mikawa et al[57])

14. IV Esmolol infusion of 500mcg/kg started 3 minutes prior to laryngoscopy and intubation, followed by a continuous infusion of either 100mck/kg/min, 200mcg/kg/min or

300mcg/kg/min found that all three doses significantly reduced the stress response. (Menkhaus et al[58])

15. IV Lidocaine 1.5mg/kg 3 minutes before intubation minimizes blood pressure fluctuations after endotracheal intubation. (Lev & Rosen[59])

16. Lidocaine gargles prior to laryngoscopy and intubation. (Stoelting[60])

17. Lignocaine 4% spray into larynx and trachea before intubation. (Delinker et al[61])

18. Fentanyl 6mcg/kg completely abolished haemodynamic stress response compared to attenuation by 2mcg/kg. (Kautto U.M et al[62])

The most recent studies which aim in control or attenuation of haemodynamic stress effects to laryngoscopy and intubation focused on the effect of remifentanyl at various dosing regimens. Remifentanil in a dose of 1mcg/kg bolus over 30 seconds followed by an infusion of 0.5mcg/kg/min was found to efficiently attenuate the stress response to intubation in a study by Thompson et al[63].

The use of alpha-2-adrenoreceptor agonists as anaesthetics is not new. Veterinarians used to employ xylazine and medetomidine for analgesia and sedation in animals and much of our knowledge was gained from this application. It is evident now that complete

anaesthesia is possible by use of new, more potent alpha-2-adrenoreceptor agonists, like medetomidine and its stereoisomer, Dexmedetomidine. The initial movement for the use of α-2-adrenoreceptor agonists in anaesthesia was a result of observation made in patients who were received clonidine therapy[64] during anaesthesia. Kaukinen S et al[65] demonstrated the preoperative and postoperative use of clonidine with neurolept anaesthesia. This was soon followed by description of Minimum Alveolar Concentration requirement of halothane by clonidine by Bloor BC et al[66].

Dexmedetomidine is a far more selective α-2-adrenoreceptor agonist, with a 1600 fold greater selectivity for the alpha 2 than alpha 1 receptor[67]. Dexmedetomidine possesses sedative, anxiolytic, sympatholytic, analgesic and hypnotic properties without causing significant respiratory depression[68-71]. The sympatholytic effect reduces mean arterial pressure and heart rate by reduction in noradrenaline secretion[72,73]. Moreover, Dexmedetomidine has the ability to decrease both the anaesthetic and opioid analgesic requirements in the perioperative period[74,75]. It was introduced in clinical practice in the United States in 1999 and was approved by the FDA only for use as short term (<24hrs) sedative for adult ICU patients who are under mechanical ventilation. Since Dexmedetomidine shows an opioid-sparing effect without any respiratory depression, it is increasingly used “off label” during different types of surgeries.

Off-label use of dexmedetomidine outside the ICU include sedation and adjunct analgesia in the operating room, sedation for diagnostic and procedure units, and for other uses such as withdrawal detoxification/amelioration in adult and paediatric patients[76,77].

Dexmedetomidine is an imidazole compound. It is the pharmacologically active dextroisomer of medetomidine which has specific and selective alpha-2-adrenoreceptor agonism. It has a unique mechanism of action and it differs from those other currently used sedatives including clonidine. Activation of receptors in brain and spinal cord inhibits neuronal firing resulting in hypotension, bradycardia, analgesia and sedation. The responses to activation of receptors in other areas include reduction in salivation, bowel motility and secretion in the gastrointestinal tract; contraction of vascular and other smooth muscles; inhibition of renin release, rise in glomerular filtration and rise in secretion of sodium and water in the kidney, reduction in intraocular pressure and reduction in insulin release from pancreas. In general, presynaptic activation of alpha-2-adrenoreceptor inhibits the secretion of noradrenaline, terminating the transmission of pain signals. Postsynaptic activation of alpha-2-adrenoreceptors in CNS causes inhibition of sympathetic activity resulting in reduction in blood pressure and heart rate. These effects when combined can produce analgesia, sedation and anxiolysis.

Dexmedetomidine exhibits all these effects, which helps in avoidance of some of the adverse effects of multiagent therapy.

One of the highest densities of alpha-2-adrenoreceptors has been found in locus coeruleus, main noradrenergic nucleus in brain and a key modulator of vigilance. Sedative and hypnotic effects of alpha-2-adrenoreceptor activation is attributed to this site of origin for the descending medullo-spinal noradrenergic pathway, which is known to be a significant modulator of nociceptive neurotransmission. In LC, alpha-2-adrenergic and opioidergic systems are having common effector mechanisms, demonstrating that dexmedetomidine has supraspinal site of action.

It can be concluded from these findings that the major antinociceptive and sedative effects of dexmedetomidine can be attributed to stimulation of alpha-2-adrenoreceptors in locus coerulus. Moreover, studies in transgenic mice have demonstrated that the alpha-2-adrenoreceptors subtype is liable for relaying the analgesic and sedative properties of dexmedetomidine.

Bloor BC et al[78,79] studied the effect of dexmedetomidine in humans and concluded that lower doses (0.25mcg/kg and 0.5mcg/kg) resulted in monophasic reduction in mean arterial blood pressure response. The transient pressor phase is unimportant in anaesthesia and should probably be avoided by slow infusion rate, particularly in patients with impaired cardiac

function. The second phase of the biphasic response is longer lasting reduction of mean arterial blood pressure and concomitant decrease in heart rate. They proved that dexmedetomidine is well tolerated by all subjects. In another study they concluded that i.v dexmedetomidine caused marked sedation, mild hypercapnia and hypoventilation, and an early transient rise in oxygen consumption. The minimal effect of dexmedetomidine in ventilation indicates that alpha-2-adrenoreceptor agonists may be useful in providing analgesia and sedation without ventilatory depression.

The effects of dexmedetomidine for perioperative control of haemodynamics were investigated by many. Villela NR et al[80] concluded that dexmedetomidine use as premedication, infusion during anaesthesia or in the postoperative period improves haemodynamic stability. Anaesthetic consumption is reduced during anaesthesia. Patients sedated with dexmedetomidine may awaken when requested and become cooperative. Even high doses of dexmedetomidine do not cause respiratory depression. Bradycardia is a frequent side effect which may be minimized by slow drug infusion. Therefore, dexmedetomidine is an important additional resource to anaesthetic practice that may be used in different patients and surgical procedures. Kallio A et al[81] in their study concluded that the administration of single i.v dose of dexmedetomidine results in almost complete inhibition of noradrenaline release from the sympathetic nerves. This decrease of

sympathetic tone was associated with reduction in heart rate and blood pressure, without any compensatory changes found in the monitored endocrine systems, release of AVP and ANP or plasma renin activity.

As an intravenous premedicant, dexmedetomidine reduces thiopental requirements (by ± 30%) for short procedures, reduces the requirements of the volatile anaesthetics (by ± 25%), and more effectively attenuates the haemodynamic stress response to endotracheal intubation compared with 2mcg/kg of fentanyl. Yildiz et al[82] conducted study to see the effectiveness of dexmedetomidine on reducing haemodynamic stress changes to laryngoscopy and tracheal intubation. They concluded that a single dose of dexmedetomidine administered preoperatively results in blunting of haemodynamic stress response during laryngoscopy, causes progressive increases in sedation and decreases requirement of opioids and anaesthetics. Moreover, dexmedetomidine reduced not only blood pressure and heart rate but also recovery time after the surgery.

Scheinin et al[83] showed that dexmedetomidine reduces sympathoadrenal responses to endotracheal intubation and decreases the requirement of thiopentone and perioperative fentanyl. This was studied in a randomised, placebo controlled, double blind trial in 24 American Society of Anaesthesiology 1 patients. Dexmedetomidine 0.6mcg/kg or saline was administered

intravenously 10minutes prior to induction of anaesthesia. The dose of thiopentone sodium required was significantly less in the dexmedetomidine group than in control group and the drug reduced the haemodynamic responses to laryngoscopy and endotracheal intubation. Concentration of noradrenaline in the mixed venous plasma was lesser in the dexmedetomidine group throughout the phases of induction.

In the study conducted by Hulya et al[84], a single dose of 0.5mcg/kg of dexmedetomidine administered preoperatively 10minutes before induction caused significant sedation, reduction in dose of thiopentone and blunted haemodynamic response to intubation without any change in recovery characteristics. Jaakola et al[85], demonstrated that dexmedetomidine reduced the increase in heart rate and blood pressure during intubation. Varshali et al[86] showed that dexmedetomidine causes attenuation of sympathoadrenal response to endotracheal intubation and decreases the amount of perioperative anaesthetics required. Sixty patients, scheduled for elective surgery of more than three hours duration is randomly selected. Control group received isoflurane-opioid-dexmedetomidine anaesthesia. The need for thiopentone and isoflurane reduced by 30% and 32% respectively in dexmedetomidine group compared to control group. After the endotracheal intubation, maximal average increase was 8% in systolic BP and 11% in diastolic BP in dexmedetomidine group compared to 40% and 25% respectively in the control group.

Similarly, average increase in heart rate was 7% and 21% in dexmedetomidine group and control group respectively. Lawrence et al[87]` found that a single dose of dexmedetomidine prior to induction of anaesthesia reduced the haemodynamic stress response to both intubation and extubation.

Bajwa et al[88] showed that the pressor response to laryngoscopy, intubation, surgery and extubation were efficiently decreased by dexmedetomidine. One hundred patients posted for elective general surgery were divided into two groups. Group D were given 1mcg/kg of dexmedetomidine and fentanyl while Group F received 2mcg/kg of fentanyl preoperatively. Anaesthesia was induced using thiopental and was maintained with oxygen-nitrous oxide and Isoflurane. The mean dose of fentanyl and isoflurane were also reduced significantly (50%). The mean recovery time was also shorter in the dexmedetomidine group.

Turan et al[89] demonstrated that without interfering with the recovery time, dexmedetomidine 0.5mcg/kg given 5minutes before the end of surgery causes stabilization of haemodynamics, allows easy extubation, provides a smoother recovery and allows early neurological assessment after intracranial surgeries.

Alex Bekker et al[90] conducted a study to see outcome of dexmedetomidine on perioperative haemodynamics in patients undergoing craniotomy. They demonstrated that a continuous infusion of dexmedetomidine provided the haemodynamic stability

in patients undergoing intracranial surgery without causing any increase in the incidence of hypotensive episodes and bradycardia.

Similarly Zerrin Ozkose et al[91] concluded that combination of preoperative loading and intraoperative intravenous infusion of dexmedetomidine caused blunting of pressor response to tracheal intubation and surgery, reduced requirement of desflurane shortened the recovery time, improved haemodynamic stability and reduced postoperative pain levels in patients who underwent lumbar discectomy under desflurane anaesthesia. In a prospective, randomized, double blind trial, dexmedetomidine infusion (1mcg/kg or saline placebo) before induction was used to reduce the haemodynamic stress change to intubation along with low dose fentanyl and etomidate in 30 patients who underwent myocardial revascularization receiving beta blocker treatment. After induction the drop in heart rate was higher in the dexmedetomidine group as compared with placebo group. One minute after intubation heart rate significantly raised in placebo group while it reduced in dexmedetomidine group. Incidence of hypertension which required treatment was significantly higher in the placebo group[92].

Pekka Talke et.al[93] conducted a study to find out the haemodynamic and adrenergic effects of administration of perioperative dexmedetomidine infusion for vascular surgery. They concluded that dexmedetomidine (plasma concentration in the

range of 0.18 to 0.35ng/ml) attenuates increase in heart rate and plasma noradrenaline concentration seen during emergence from anaesthesia. Tulfanigullari B et al[94] studied on the effect of dexmedetomidine infusion on recovery outcome variables during laparoscopic bariatric surgery. They found that, use of intraoperative dexmedetomidine infusion (0.2-0.8mcg/kg/hr) reduced fentanyl use, antiemetic therapy and the total duration of stay in PACU. Likewise Hassan S[95] also concluded in his study that Infusion of dexmedetomidine intraoperatively reduced the total amount of propofol and fentanyl necessary to maintain anaesthesia, offered a better control on the intraoperative and postoperative haemodynamics, reduced postoperative pain levels, reduced the total amount of morphine used and showed a better recovery profile compared to placebo.

Jeongmin Kim et al[181] (2014), conducted a study on agitation during emergence following desflurane anaesthesia in paediatrics. They found out that infusion of low dose dexmedetomidine intraoperatively along with fentanyl decreases emergence agitation occurring after desflurane anaesthesia in paediatric patients undergoing strabismus surgeries.

Dhara A. Vyas, et al,[182] in 2013 compared dexmedetomidine with midazolam for sedation and cardiovascular changes occurring during tympanoplasty and modified radical mastoidectomy. They selected 50 patients of age group 15 to 50 years of American Society of

Anaesthesiology grade 1 and 2. They divided them in to two groups: First group received Inj. Dexmedetomidine 1µg/kg over 15min, which was followed by 0.5µg/kg/hr infusion and the other group received Inj. Midazolam 0.05 mg/kg slow i.v, followed by an infusion of 0.01mg/kg/hr. Their arterial heart rate, blood pressure and sedation level were monitored. They concluded that Dexmedetomidine could be a better alternative over Midazolam for MAC in ENT surgeries done under local anaesthesia.

Tanuja, Shobha Purohit, Amit Kulshreshtha, 2014,[183] conducted a study on effects of dexmedetomidine on intraocular pressure and haemodynamic changes in response to laryngoscopy and tracheal intubation. Fifty American Society of Anaesthesiology -1 / 2 patients of 20-50 years, undergoing elective intracranial tumour surgery were selected and were divided into two groups, Group D (Dexmedetomidine group) and Group C (Control group). Dexmedetomidine 0.8 mcg/kg i.v. (in 20-ml saline) or placebo (normal saline 20 ml IV) were given slowly over 10 minutes in groups D and group C, respectively. Haemodynamic parameters and IOP were measured 1 minute after induction of anaesthesia, after intubation and then at 1, 3, 5 and 10 minutes of intubation. They concluded that the preinduction administration of single dose dexmedetomidine in the dose of 0.8 mcg/kg decreases the magnitude of stress-induced sympathoadrenal effect on intra ocular pressure and on haemodynamic parameters during laryngoscopy and intubation and it also decreases the requirement of dose of propofol for induction of general anaesthesia.

Dalia Abdelhamid Nasr, et al,[184] in 2013, conducted study on the effectiveness of dexmedetomidine administered caudaly on the stress response and postoperative pain in cardiac surgery in children. Forty patients, (American Society of Anaesthesiology 2,3), 1-3-years of age were randomly divided into 2 groups; group I received caudal bupivacaine 0.25%, 2.5 mg/kg and dexmedetomidine 0.5 µg/kg and group II received bupivacaine 2.5 mg/kg and fentanyl 1 µg/kg. They concluded that caudal dexmedetomidine is a useful adjuvant in anaesthesia for children undergoing cardiac surgeries, it reduces the cardiovascular and neuroendocrine stress responses caused by trauma and CPB, and it also provides adequate postoperative analgesia and short time to extubation.

Kwon-Hui Seo1, et al,[185] in 2014 conducted a study on effective dose of dexmedetomidine for reducing haemodynamic response during emergence in patients who underwent laparoscopic total hysterectomy. Patients undergoing laparoscopic total hysterectomy were randomly divided to receive 0.9% normal saline (control group) or dexmedetomidine (0.5 µg/kg, 0.75 µg/kg or 1.0 µg/kg 30 min) before extubation. Heart rate, systolic blood pressure and diastolic blood pressure and extubation time were measured before drug administration, immediately after administering drug. 10 min after administering the drug, immediately after extubation and 5 min after extubation. They concluded that Intravenous infusion of 0.5 µg/kg dexmedetomidine 30 minutes prior to the end of surgery attenuated the haemodynamic responses during emergence without prolonging the

extubation time. Dexmedetomidine doses of more than 0.5 µg/kg did not exert any surplus positive effects on cardiovascular responses, but did significantly prolong the extubation time.

Ashraf M. Eskandr, et al, [186] in 2014, conducted a study to evaluate the effects of adding dexmedetomidine to local anaesthetics on the sensory and motor block of the subtenon block in patients undergoing phacoemulsification cataract surgery. 60 patients of American Society of Anaesthesiology grade 1-3, aged between 18 and 70 years, posted for phacoemulsification cataract surgery were randomly assigned to 2 equal groups. In control group, patients were given 2 ml mixture containing 2% lignocaine and 0.5% bupivacaine and Dexmedetomidine group were given 2 ml of a mixture containing 2% lignocaine and 0.5% bupivacaine plus dexmedetomidine(0.5 µg/kg). Onset and duration of sensory and motor block was recorded. Pain while administering anaesthesia and during surgery was graded and recorded. Intraocular pressure, hemodynamic, and sedation parameters were recorded before and after surgery. The study demonstrated that adding dexmedetomidine(0.5 µg/kg) in a mixture of 2% lignocaine and 0.5% bupivacaine in subtenon block for patients undergoing cataract phacoemulsification surgery, resulted in rapid onset and prolongation of analgesia and akinesia with decreased intra ocular pressure and stable hemodynamic changes.

Fuhai Ji, MD,[187] in 2013, conducted a study to know if perioperative dexmedetomidine use can cause reduction in incidence of

complications and mortality following cardiac surgery. The study was done on 1134 patients who had coronary artery bypass surgery and CABG plus valvular surgery or other procedures. Among these patients 568 received dexmedetomidine infusion intravenously while 566 did not. Mortality and postoperative major cardiocerebral adverse events like stroke, coma, perioperative myocardial infarction, heart block, or cardiac arrest were the primary out comes measured. Secondary outcomes were kidney failure, septicemia, delirium, ventilation hours needed postoperatively, length of stay in hospital and readmission within 30-days. The study demonstrated that cardiac surgical patients who received intravenous dexmedetomidine infusion after cardiopulmonary bypass had a better in-hospital, 30-day, and 1-year survival rate. The use of dexmedetomidine perioperatively also caused significant reduction in incidence of postoperative complications including delirium. There were no evidences of adverse hemodynamic effects of dexmedetomidine in patients who underwent cardiac surgery.

Rasha S Bondok, et al[188], in 2014, conducted a study for investigating the effect of intraoperative equisedative doses of dexmedetomidine and propofol on supraclavicular nerve block in patients having ischemic heart disease. Patients having ischemic heart disease, scheduled for upper-limb orthopaedic surgery after an effective ultrasound-guided supraclavicular nerve block were selected. Patients were randomly divided for receiving either dexmedetomidine0.5 μg/kg or propofol 0.5 mg/kg as an initial loading dose for 10 minutes which was followed by a maintenance dose

adjusted intraoperatively to a bispectral index of 70-80. In the PACU, the sedation score was assessed every 10 minutes until discharge. The degree of pain was assessed hourly for the first 12 hours and at 18 and 24 hours postoperatively. Duration of analgesia and need of rescue analgesia were calculated. This study concluded that intravenous sedative doses of dexmedetomidine can prolong the analgesic effect of supraclavicular brachial plexus nerve block and maintain a constant cardiorespiratory status. These properties make it an ideal adjuvant especially in patients with ischemic heart disease.

Kanchan Gupta, et al [(189)], in 2014, conducted a randomised double-blind study for comparing the effect of dexmedetomidine and tramadol in peri-operative shivering in surgeries done under sub arachnoid block. The study was conducted in 50 American Society of Anaesthesiology Grade 1 and 2 patients of either gender of age between 18 and 65 years, posted for various surgical procedures under spinal anaesthesia. The patients were randomised in to 2 groups of 25 patients, each to receive either dexmedetomidine0.5 µg/kg or tramadol 0.5 mg/kg as slow intravenous bolus. The grade of shivering, onset of shivering, time for cessation of shivering, recurrence, response rate and adverse effects were observed at scheduled intervals. The study concluded that both dexmedetomidine(0.5 µg/kg) and tramadol (0.5 mg/kg) were effective in treating patients with post-spinal anaesthesia shivering. But the time taken for complete cessation of shivering was shorter with dexmedetomidine as compared to tramadol. Moreover, dexmedetomidine causes fewer adverse effects like nausea and

vomiting. Sedation caused by dexmedetomidine offers additional comfort to the patient.

Mohamed Essam Abdel-Meguid, [190] in 2013, did a research to determine the efficiency of dexmedetomidine to achieve fast tracking and improvement of postoperative pain management in patients undergoing off-pump coronary artery bypass surgery. 30 patients posted for off-pump CABG were divided into 2 groups: Group I were given dexmedetomidine 0.5 ug/kg/hour infusion just after the anaesthesia induction followed by 0.3 ug/kg/hour on shifting to the ICU which was continued up to 12 hours after extubation. Group II patients were given normal saline at a similar volume and infusion rate visual analog scale of 10-100 was informed well to all the patients at the time of pre-anaesthesia check-up. Management of Postoperative pain was done using morphine. Extubation time and visual analog scale was noted every two hourly for 12 hours after extubation. In conclusion, dexmedetomidine as an adjunct to anaesthetic management of off-pump CABG provides a better quality of postoperative analgesia with opioid-sparing effect, while at achieving the ultimate goal in management of off-pump coronary artery bypass which is fast tracking of patients.

Rayner SG, et al [191], in 2012, did a retrospective study of 20 patients in intensive care unit treated with dexmedetomidine for alcohol withdrawal refractory to benzodiazepine. The alcohol withdrawal severity scores and medication doses for 24 hours before

dexmedetomidine therapy were compared with values during the initial hours of dexmedetomidine administration. Dexmedetomidine is an attractive adjunct drug for treating of severe alcohol withdrawal as it is capable of providing sedation and reducing autonomic hyperactivity with potentially decreased incidence of respiratory distress and delirium than found while using benzodiazepine. It is particularly useful when the symptoms are refractory to even high doses of benzodiazepines, as it acts through pathway independent of GABA. Here, adjunct therapy using dexmedetomidine in patients with severe alcohol withdrawal who were poorly controlled on, or were experiencing significant side effects with traditional treatment led to a decrease in alcohol withdrawal scoring, reductions in benzodiazepine dosing, and decreases in heart rate and blood pressure.

Shailesh Bhadla, et al (192), in 2013, conducted a study on comparing dexmedetomidine and midazolam as premedication in paediatric patients who underwent ophthalmic day-care surgeries. 60 patients were allocated to group I and group II and given Inj Dexmedetomidine 0.4 μg/kg diluted in 10 ml slowly i.v. and Inj Midazolam 0.05mg/kg i.v. accordingly. Level of sedation, parent separation, response to induction, heart rate, blood pressure, peripheral oxygen saturation, post operative agitation and shivering was noted. The study concluded that dexmedetomidine is superior than Midazolam as premedication in paediatric patients with more intense sedation, favourable induction conditions, excellent parent separation, lower

incidence of postoperative agitation and shivering along with hemodynamic stability and no respiratory depression.

SS Harsoor, et al (1993), in 2013, conducted a research to assess the effects of intra venous dexmedetomidine on sensory, motor, haemodynamic parameters and sedation during subarachnoid block procedures. A total of 50 patients undergoing infraumbilical and lower limb surgeries under subarachnoid block were selected. Group I received intra venous dexmedetomidine 0.5 mcg/kg bolus over 10 min before subarachnoid block, followed by 0.5 mcg/kg/h infusion throughout the surgery. Group II received similar volume of normal saline infusion. Time for onset of sensory and motor blockade, cephalad level of analgesia and duration of analgesia were noted. Sedation scores using Ramsay Sedation Score and haemodynamic parameters were assessed. The study concluded that intravenous supplementation of loading dose of dexmedetomidine 0.5 mcg/kg followed by infusion at 0.5 mcg/kg/h hastens the onset of sensory block and prolongs the duration of sensory block, analgesia and motor block with lesser incidence of bradycardia. Moreover, intravenous dexmedetomidine supplementation during subarachnoid block produces adequate arousable sedation without causing respiratory depression.

Anbarasu Annamalai, et al (194), in 2013, conducted a study for evaluating the effectiveness of intravenous dexmedetomidine on prolongation of spinal anaesthesia, level of sedation, post-operative analgesic requirement. Ninety adult patients classified as ASA 1 or 2

posted for elective surgical procedures below umbilicus under spinal anaesthesia were double blind divided to one of the three groups. All patients received 0.5% hyperbaric bupivacaine 2.5 ml spinal anaesthesia. Group I Patient receiving intravenous normal saline 10 ml over 10 minutes, 10 minutes before spinal anaesthesia with 0.5% hyperbaric bupivacaine 2.5 ml and normal saline 10 ml over 10 minutes after 30 minutes of spinal anaesthesia. Group II Patients were given dexmedetomidine 1 µg/kg i.v. over 10 minutes, 10 minutes before spinal anaesthesia. Group III patients were given dexmedetomidine 1 µg/kg i.v. over 10 minutes after 30 minutes of spinal anaesthesia. The study concluded that Intravenous dexmedetomidine prolonged spinal bupivacaine sensory blockade in both the groups and also provided sedation and additional analgesia.

Tarek Shams, et al [195], in 2013, conducted a comparative study of dexmedetomidine versus esmolol on induced hypotension for functional endoscopic sinus surgery. Forty patients scheduled for functional endoscopic sinus surgery were randomly divided for receiving either dexmedetomidine 1 µg/kg over 10 minute prior to induction of anaesthesia followed by an infusion of 0.4-0.8 µg/Kg/h during maintenance in Group I, or esmolol. A loading dose of 1mg/kg was infused over one minute followed by an infusion of 0.4-0.8 mg/kg/h during maintenance in group II. So that mean arterial blood pressure between 55-65 mmHg. Maintenance of general anaesthesia was done using sevoflurane 2%-4%. Assessment of surgical field was done to calculate average blood loss. Hemodynamic variables,

intraoperative fentanyl consumption, arterial blood gas analysis, plasma cortisol level, time for emergence and total recovery from anaesthesia were recorded. Sedation score was assessed at 15, 30 and 60 minutes after extubation and time to complain pain was recorded. The study demonstrated that dexmedetomidine or esmolol with sevoflurane are safe agents for controlled hypotension and both are useful in providing ideal surgical field during functional endoscopic sinus surgery. Compared with esmolol, dexmedetomidine offers the benefit of inherent analgesic, sedative and anaesthetic sparing effect.

Hazra R, et al [196], in 2014, conducted a study to compare the effects of intravenously administered dexmedetomidine with clonidine on hemodynamic responses during laparoscopic cholecystectomy. 60 patients of age between 18 to 50 years, of both the sex posted for elective laparoscopic cholecystectomy were randomly divided into 3 groups in a double-blind fashion. They were given either clonidine 1µg/kg in normal saline, dexmedetomidine 1µg/kg in NS or NS intravenous respectively. Total volume of the study drug was adjusted to 50 ml and given over a period of 15 minutes before induction. Administration of clonidine or dexmedetomidine prior to commencement of pneumoperitoneum was found effective in attenuating hemodynamic response to pneumoperitoneum. However, the study concluded that dexmedetomidine blunts the hemodynamic response to pneumoperitoneum more efficiently with a greater chance of developing hypotension and bradycardia.

Usta B, et al [197], in 2011, conducted a study for evaluating the effect of dexmedetomidine administration on shivering during spinal anaesthesia. Sixty patients posted for elective minor surgeries under subarachnoid block with hyperbaric bupivacaine, were selected. They were given either saline or dexmedetomidine. Motor block was assessed. The occurrence of shivering was evaluated by a blinded observer after the completion of injection of drug in the subarachnoid space. They found that infusion of dexmedetomidine postoperatively causes significant reduction of shivering associated with subarachnoid block during minor surgeries without causing any major side effect. So, the study concluded that dexmedetomidine infusion is effective for prevention of shivering and for providing sedation for patients during subarachnoid block.

Kim YS, et al, [198] in 2013, conducted a study to find out the optimum dose of dexmedetomidine for prevention of postanaesthetic shivering. 132 patients posted for elective laparoscopic total hysterectomy were selected for this randomized, placebo-controlled study. Patients were randomly divided to receive dexmedetomidine in 4 groups: group I received 0.9% NS, 2nd group received dexmedetomidine 0.5 µg/kg, group III received dexmedetomidine 0.75 µg/kg and group IV received dexmedetomidine 1.0 µg/kg. Time to extubation and the tympanic temperature during and after operation were measured. Shivering was graded at the time of arrival to the post anaesthesia care unit and every ten minutes thereafter up to forty minutes. Sedation and first rescue analgesic time at the post

anaesthesia care unit were evaluated. They concluded that dexmedetomidine 0.75 or 1.0µg/kg i.v. can provide effective prophylaxis for against postoperative shivering as well as an analgesic effect. Although potential for intraoperative requirement for atropine, sedation in the immediate recovery period and delayed extubation time with dexmedetomidine was observed, there were no major clinical impacts on the overall recovery from anaesthesia.

Suvadeep Sen, et al,[199] in 2013, conducted a study for evaluation of the effect of dexmedetomidine on propofol requirement for induction and maintenance of desired depth of anaesthesia on the basis of targeted bispectral index value in spine surgery on prone patients under general anaesthesia. 70 adult patients of age 20-60 years undergoing elective spinal surgeries under general anaesthesia were selected for this study. They were divided into 2 groups. 1st group received loading dose of dexmedetomidine at 1 mcg/kg over the period of 10 minutes, followed by maintenance of dexmedetomidine at a rate of 0.2 mcg/kg/h. Heart rate, saturation of peripheral oxygen, systolic blood pressure, diastolic blood pressure, MAP, electrocardiogram and consciousness level were closely monitored in the patients. Propofol was started initially at 5 mg/kg/h and then adjusted to maintain a bispectral index value in range of 40-60 and its requirement was observed and recorded in each patient. The study concluded that infusion of dexmedetomidine in the perioperative period provided significant reduction in requirement of propofol for the induction and

maintenance of adequate depth of anaesthesia with stable haemodynamics.

S S Harsoor, et al, [200] in 2014, conducted a study for evaluating the effect of intravenous dexmedetomidine infusion during general anaesthesia for abdominal surgeries on blood glucose levels and on Sevoflurane requirements during anaesthesia. 40 patients posted for abdominal surgery under general anaesthesia were divided into Dexmedetomidine group and Placebo group of 20 each. Dexmedetomidine group were given loading dose of Inj. Dexmedetomidine at 1 µg/kg/10 minutes diluted to 20 ml, followed by maintenance with 0.5 µg/kg/h., till the end of surgery. Placebo group received similar volume of IV normal saline. Anaesthesia was maintained using nitrous oxide, oxygen and sevoflurane keeping entropy between 40 and 60. The study concluded that Dexmedetomidine as a preanaesthetic medication and intraoperative infusion was effective in attenuating metabolic stress response to major surgeries as indicated by stable blood glucose levels. It also reduced intraoperative anaesthetic requirement and had significant anaesthetic sparing property during entropy guided general anaesthesia. Moreover, continuous intraoperative administration of Dexmedetomidine does not affect intraoperative cardiovascular stability.

Alka Shah, et al,[207] in 2013, studied to evaluate the intraoperative haemodynamics and postoperative analgesia of intrathecal administration of dexmedetomidine added to ropivacaine.

50 patients posted for lower abdominal and lower limb surgery were included. Each patient was given 4 ml of 0.75% isobaric ropivacaine + 5 microgram dexmedetomidine. Pulse rate and blood pressure were recorded at intervals of 1, 2, 5, 10, 20, 30 minutes and 1, 2 and 3 hours. Postoperative pain scores were assessed using VAS. The patients had excellent hemodynamic stability and good postoperative analgesia to the combination of ropivacaine and dexmedetomidine.

Priyam Saikia, et al,[208] in 2014 found the use of dexmedetomidine, in the postoperative management of a transoral odontoidectomy patient and required mechanical ventilation. Dexmedetomidine at 0.5-0.7 μg/kg/h was used for postoperative management and continued until extubation of trachea and provided sedation level of Richmond Agitation-Sedation Scale −1 to −2. He was easily arousable and co-operative during neurological evaluations. Dexmedetomidine was stopped 22 h after completion of surgery. Within 15 min his Richmond Agitation-Sedation Scale rose to a score of 0, and trachea was extubated smoothly. They concluded that dexmedetomidine, by its opioid sparing effect and preserved attentive behavior, is a useful adjunct to multimodal analgesic regimen in postoperative patients who needs sedoanalgesia for mechanical ventilation.

Mahima Gupta, et al,[209] in 2014 conducted a study to evaluate and compare the characteristics of subarachnoid blockade, hemodynamic stability and adverse effects of intrathecal

dexmedetomidine and intrathecal buprenorphine as an adjuvant to 0.5% hyperbaric bupivacaine for lower abdominal surgeries. Sixty patients aged 18-60 years posted for elective lower abdominal surgeries. The patients were randomly allotted to 2 groups for receiving intrathecal 3ml of 0.5% bupivacine with 60µg of buprenorphine in group I or 3ml of 0.5% bupivacaine with 5µg of dexmedetomidine in group II. The onset time to peak sensory level, motor block, duration of motor block, sedation, haemodynamic variables, analgesia and any adverse effects were noted. The duration of motor and sensory block in dexmedetomidine group was 413 minutes and 451 minutes which was considerably different from 205 minutes and 226 minutes of buprenorphine group. Also duration of analgesia was 493 minutes in dexmedetomidine group compared to 289 minutes of buprenorphine group. They concluded that intrathecal dexmedetomidine 5µg when compared to intrathecal buprenorphine 60µg causes longer duration of sensory and motor block. The requirement for additional sedation and rescue analgesia was less in dexmedetomidine group and the haemodynamics were comparable in both the groups without causing any significant side effects.

MS Saravana Babu, et al,[(210)] in 2013, conducted a study for evaluating the efficacy of epidural route of administration and for comparing the efficacy and clinical characteristics of dexmedetomidine and clonidine as adjuvants to ropivacaine, in epidural analgesia with particular importance on the quality of analgesia and the ability for providing a smooth post-operative course. 60 patients, aged between 18

and 65 years who underwent surgeries of spine were divided into 2 groups. 1st group patients were given 20 ml of 0.2% ropivacaine and 1 µg/kg of dexmedetomidine while 2nd group were given 20 ml of 0.2% ropivacaine and 2 µg/kg of clonidine via the epidural catheter. Onset of analgesic action, time of peak action, duration of analgesia, cardiorespiratory parameters, requirement of rescue I.V analgesics and side-effects were noted. They concluded that the epidural route provided adequate analgesia in spine surgeries in terms of visual analogue scale score and overall patient satisfaction and it eluded the requirement of intravenous analgesics in both groups. Dexmedetomidine was found to be a better neuraxial adjuvant to ropivacaine as compared to clonidine for provision of early onset and long lasting post-operative analgesia and stable haemodynamic parameters.

Dalia Abdelhamid Nasr, et al,[211] in 2013, conducted study to evaluate the efficacy of caudal dexmedetomidine on lesser response and postoperative pain in children undergoing cardiac surgery. Forty patients, 1-3-years old were divided into two groups; group I patients were given caudal bupivacaine 0.25%, 2.5 mg/kg and dexmedetomidine 0.5 µg/kg and group II patients were given bupivacaine 2.5 mg/kg and fentanyl 1 µg/kg. They found that Serum cortisol level and blood glucose level were increased in both groups but increases were considerably less in dexmedetomidine group. They found out that caudal dexmedetomidine proves to be a useful adjuvant in paediatric cardiac anaesthesia, by attenuating the cardio vascular and

neuroendocrinal stress response to surgical trauma and cardio pulmonary bypass and in providing adequate postoperative analgesia and short time to extubation.

Lili Jiang, et al,[212] in 2014, conducted a study to investigate whether dexmedetomidine is capable of attenuating rat pulmonary damage induced by ischemia-reperfusion injury, which is a type of acute sterile lung injury. From the study, they suggested a potential clinical application of dexmedetomidine for reducing lung ischemia-reperfusion injury in an experimental model.

Friesen RH, et al,[213] in 2013, conducted a study for quantifying the effects of initial loading doses of dexmedetomidine on mean pulmonary artery pressure in paediatric patients with and without pulmonary arterial hypertension. Paediatric patients undergoing cardiac catheterization either for routine surveillance after cardiac transplantation or for pulmonary arterial hypertension studies were included. After anaesthetic induction using sevoflurane and endotracheal intubation, sevoflurane was discontinued and anaesthesia maintenance was done using midazolam 0.1 mg/kg IV and remifentanil infusion 0.5 to 0.8 µg/kg/min i.v. Patients were mechanically ventilated to maintain PCO2 of 35 to 40 mm Hg. When the end-tidal concentration of sevoflurane was 0% and fraction of inspired oxygen was 0.21, baseline heart rate, MAP, pulmonary arterial pressure, right atrial pressure, right ventricular end-diastolic pressure, pulmonary artery occlusion pressure, cardiac output, and arterial blood gases were

measured, index pulmonary vascular resistance and index systemic vascular resistance and cardiac index were calculated. Each patient was then given a 10 minute infusion of dexmedetomidine of 1µg/kg, 0.75µg/kg or 0.5µg/kg. The same measurements and calculations were done again at the end of the infusion. Initial loading doses of dexmedetomidine were associated with considerable systemic vasoconstriction and hypertension, but analogous response was not seen in the pulmonary vasculature, even in paediatric patients with pulmonary arterial hypertension. They concluded that dexmedetomidine do not seem to be contraindicated in paediatric patients having pulmonary hypertension.

Siddareddigari Velayudha Reddy, et al,[214] in 2014, conducted a study to compare the clinical effects of dexmedetomidine and esmolol in attenuating the presser response during laryngoscopy. 90 adult scheduled for non-cardiac surgery requiring intubation were selected. The patients were allocated into 3 groups. 1st group received placebo, 2nd group received 2.0 mg/kg of esmolol and 3rd group received 1.0 µg/kg of dexmedetomidine, intravenously over 10 min and 3 min before induction of general anaesthesia. All patients were uniformly pre-medicated, induced and intubated using thiopentone and succinylcholine as per the standard protocol. Heart rate and systemic blood pressures were recorded at baseline, after study drug infusion, after induction, immediately and 3, 5, 7, 10 minutes after intubation. Evaluation of baseline and immediately after intubation values, revealed a greater percentage variation in mean arterial pressure in the

esmolol and control groups as compared to that in dexmedetomidine group. They stated that administration of a single dose of dexmedetomidine prior to general anaesthesia induction was an effective method for attenuating the hemodynamic response to tracheal intubation.

Yu Zhang, et al,[215] in 2014, performed a study to evaluate the hypothesis that adding dexmedetomidine to ropivacaine prolongs axillary brachial plexus block. Forty-five patients of aged 25-60 years who were posted for forearm and hand surgery were randomly allocated into 3 equal groups and received 40 ml of 0.33% ropivacaine + 1 ml dexmedetomidine (50 μg) (group 1), 40 ml of 0.33% ropivacaine + 1 ml dexmedetomidine (100 μg) (group 2) or 40 ml of 0.33% ropivacaine + 1 ml saline (group 3) in a double-blind fashion. The onset and duration of sensory and motor blocks and adverse effects were noted. Sensory and motor block onset times were same in the three groups. Sensory and motor blockade durations were found to be prolonged in 2nd group compared to group 3. No significant variations in the sensory blockade duration were found between group 1 and group 3. Bradycardia, hypertension and hypotension were not observed in group 3 and occurred more often in group 2 than in group 1. They concluded that dexmedetomidine added to ropivacaine for an axillary brachial plexus block prolongs the duration of block. Dexmedetomidine can cause adverse effects like bradycardia, hypertension, and hypotension.

Pant D, et al,[216] in 2014 conducted a study to compare the effects of sublingual midazolam and dexmedetomidine used for premedicating children. The study enrolled hundred children of age 1 to 12 years posted for orchidopexy, inguinal hernia repair or circumcision under general anaesthesia. The selected children were divided into two groups of 50 each. Patients in group I were given sublingual midazolam 0.25 mg/kg as premedication, while those in group II received sublingual dexmedetomidine 1.5µg/kg as premedication. Sedation was assessed. They concluded that sublingual dexmedetomidine offers a better preoperative sedation compared to sublingual midazolam in all the age groups and also provides a smoother induction of anaesthesia and emergence particularly in the preschool children.

Na Young Kim, et al,[217] in 2014, conducted a study for assessing the effect of dexmedetomidine infusion on the requirement of sevoflurane, recovery profiles, and emergence agitation in paediatric patients undergoing ambulatory surgery. Forty paediatric patients undergoing ambulatory hernioplasty or orchiopexy were divided into 2 groups. Patients in dexmedetomidine group received dexmedetomidine 1 µg/kg, followed by 0.1 µg/kg/h i.v. till the end of surgery, while the saline group was given same volume of normal saline. Induction and maintenance of anaesthesia was done by sevoflurane and caudal block was performed in all the patients. End-tidal concentration of sevoflurane, the incidence of agitation on emergence, pain scores, and sedation scores were noted. Hemodynamic variations and other side

effects were evaluated in the perioperative period. End-tidal sevoflurane concentration of dexmedetomidine group was significantly reduced in 23.8-67% compared to saline group during surgery. Incidence of emergence agitation found lower in dexmedetomidine group than in saline group. Postoperative pain was similar and discharge time did not vary between the groups. MAP and heart rate were considerably lower in dexmedetomidine group during surgery. They concluded that infusion of dexmedetomidine intraoperatively reduced sevoflurane requirements and reduced agitation during emergence without any delay in discharging the paediatric patients who undergo ambulatory surgery. Anaesthesiologists should be cautious about bradycardia and hypotension.

Shan-Shan Wang, et al,[218] in 2013, conducted a study on sedative effects and attenuation of haemodynamic and arousal responses during induction of anaesthesia and intubation in paediatric patients by comparing two different doses of preoperative dexmedetomidine. Forty paediatric patients of age from 3 to 6 years, posted for adenotonsillectomy were administered either dexmedetomidine 1 $\mu g \cdot kg^{-1}$ (group 1) or 2 $\mu g \cdot kg^{-1}$ (group 2) 30 minutes before anaesthesia induction. Anaesthesia induction was done using sevoflurane in oxygen flow. Heart Rate and Mean arterial pressure were measured and bispectral index was used as an index of arousal response and were recorded every 5 minutes after giving dexmedetomidine and measured every 1 minute for 5 minutes post intubation. Assessment of behaviour scores, sedation status and mask

induction scores were done. Dexmedetomidine 2 $\mu g \cdot kg^{-1}$ i.v. given 30 minutes before induction of anaesthesia provided significant attenuation of increase in mean arterial pressure caused by intubation response. Variations in heart rate and bi-spectral index also show that dexmedetomidine premedication causes effective attenuation of response to intubation. Preoperative dexmedetomidine 2 $\mu g \cdot kg^{-1}$ also provides optimal-sedation and smoother anaesthesia induction. Premedication of dexmedetomidine is effective in reducing cardiovascular and arousal responses to tracheal intubation.

Gaurav Jain, et al,[219] in 2012, conducted a study to analyze the effect of perioperative administration of dexmedetomidine on the incidence of chronic pain in patients who undergo surgery for breast cancer. 86 patients were divided to 2 groups and were given either dexmedetomidine (2 μg/ml) in group I or saline in group II, in a loading dose of 0.5 ml/kg, i.v, 30 minutes before induction, followed by 0.25 ml/kg/h i.v. as continuous infusion till the end of surgery and then the dose was reduced to 0.1 ml/kg/h for up to 24 hours. The requirement of isoflurane and fentanyl intra-operatively and paracetamol postoperatively was considerably lower in Group I. They concluded that infusion of dexmedetomidine perioperatively has a crucial role in reducing the severity and incidence of chronic pain and providing better quality of life in patients who undergo breast cancer surgery.

Sukhminder Jit Singh Bajwa, et al, [220] in 2011, conducted a study for comparing the efficiency and clinical characteristics of dexmedetomidine and clonidine, in epidural anaesthesia with special attention on their sedative properties and an ability for providing smooth intra-operative and post-operative pain relief. The study was done in 50 adult females of age 44 to 65 years posted for vaginal hysterectomy. The patients were divided into 2 groups of 25 patients each. Group I was given 17 ml of 0.75% epidural ropivacaine and 1.5 µg/kg of dexmedetomidine, whereas group II were given a mixture of 17 ml of 0.75% ropivacaine and 2 µg/kg of clonidine. Onset and duration of analgesia, sensory and motor block levels, sedation and adverse effects were noted. They concluded that dexmedetomidine is a better adjuvant for neuraxial anaesthesia when compared with clonidine for obtaining early onset of analgesia, optimal sedation and prolonged post-operative analgesia.

Eike Martin, et al,[221] in 2003, conducted a study on the role of Dexmedetomidine in sedation of postoperative patients in the ICU. In this study, dexmedetomidine was assessed for sedation of 401 postsurgical patients. Either dexmedetomidine or saline was started when the patients arrive in the ICU(1.0 mcg/kg for 10 minutes), then titrated at 0.2 to 0.7 mcg/kg/h to effect. Patients were given propofol when needed. Morphine was given for relief of pain. 60% of the dexmedetomidine patients did not require any other sedative, 21% required < 50 mg propofol. 76% of the control group patients required propofol, 59% received ≥ 50 mg. Dexmedetomidine patients needed

considerably less morphine for analgesia. Continuous administration of dexmedetomidine throughout the ICU stay did not affect oxygen saturation, respiratory rate, weaning duration, or times to extubation. Most of the patients who received dexmedetomidine could maintain blood pressures in the normal range, without any rebound. Hypertension, rigors and atelectasis occurred more often in the control group, whereas hypotension and bradycardia were seen more often in the dexmedetomidine group.

All these studies led to conclusion that dexmedetomidine a highly specific alpha$_2$ agonist drug possesses sedative, anxiolytic, sympatholytic, analgesic and hypnotic properties and provides perioperative haemodynamic stability.

Pharmacology

Dexmedetomidine

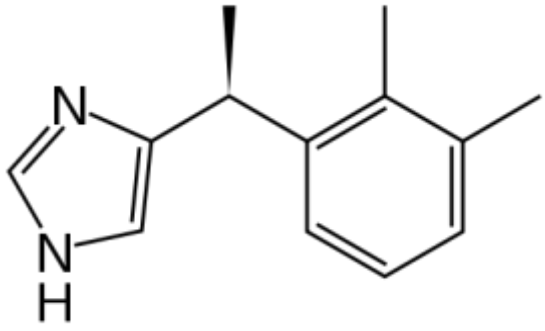


Fig -1: Chemical structure of dexmedetomidine

Physicochemical Characteristics

Dexmedetomidine is the d-enantiomer of medetomidine, a substance that has been used for sedation and analgesia in veterinary medicine for many years. It is highly specific for the α_2 receptor ($\alpha_{2/}\alpha_1$ 200:1), making it a complete alpha$_2$ agonist. Dexmedetomidine is included in imidazole subclass of alpha$_2$ receptor agonists like clonidine, and its structure is illustrated in Fig 1. It is freely soluble in water.

Preparation of Solution

Dexmedetomidine is available as 100mcg/ml. It must be diluted in normal saline to achieve the required concentration before administration. Preparation of solution is the same, for both loading dose and maintenance infusion.

Co-administration with other Fluids

Dexmedetomidine hydrochloride infusion is not to be administered via the same intravenous catheter along with blood or plasma as the physical compatibility is not yet established.

Dexmedetomidine is shown to be incompatible while given with amphotericin B and diazepam.

Dexmedetomidine is shown to be compatible while given with the following i.v fluids:

- Normal Saline

- 5% dextrose in water
- 20% mannitol
- Ringer's Lactate solution
- 100mg/ml magnesium sulfate solution
- 0.3% potassium chloride solution

Compatibility with Natural Rubber

It is shown that dexmedetomidine has the potential for absorption to some types of natural rubber. So it is advisable to use the administration components made of synthetic, or coated natural rubber gaskets.

Availability

100mcg/ml in glass vials and ampoules

Fig 2: Dexmedetomidine Vial and Ampoule

Storage and Handling

- Dexmedetomidine 100mcg/ml is available in 2ml clear glass vials and 1ml ampoules. Vials are intended for single use only.

- Dexmedetomidine should be stored in room temperature, 25^0C (77^0F) and variations allowed are 15^0C - 30^0C (59^0F-86^0F).

Clinical Pharmacology

Mechanism of Action

Dexmedetomidine is an imidazole compound, d-enantiomer of medetomidine with a highly selective alpha$_2$ selective receptor agonism. Alpha$_2$ adrenoreceptors are membrane-spanning G proteins. Intracellular pathways include adenylate cyclase inhibition and ion channel modulation. Three subtypes of α_2 receptors are described in humans: α_{2A}, α_{2B}, α_{2C} (Fig. 3)[111]. The α_{2A} adrenoceptors are mainly distributed in the periphery, while α_{2B} and α_{2C} are in the brain and spinal cord. Postsynaptic alpha$_2$ adrenoreceptors in peripheral blood vessels produce vasoconstriction, while presynaptic alpha$_2$ adrenoreceptors inhibit the release of noradrenaline, potentially attenuating the vasoconstriction. The overall response to alpha$_2$ adrenoreceptor agonists is associated with stimulation of alpha$_2$ receptors located in CNS.

These receptors are involved in the sympatholysis, sedation and antinociceptive effects of alpha$_2$ adrenoreceptors[70].

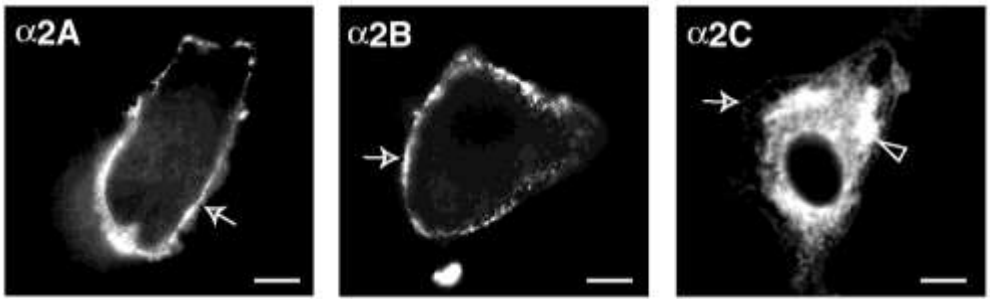


Fig -3: The different α_2 adrenoreceptors

Dexmedetomidine with selective alpha$_2$ agonism has a primary action on locus coeruleus[112]. Neuronal hyperpolarisation is a major component in mechanism of action of alpha$_2$ adrenergic receptor agonist. Presynaptic activation of the alpha$_2$ receptor inhibit secretion of noradrenaline and postsynaptic activation of alpha$_2$ receptor decreases sympathetic activation of CNS.

The mechanisms of analgesic effects of alpha$_2$ receptor agonists is not completely understood. It is modulated by transmission of nociceptive signals in the central nervous system at different sites including both spinal and supraspinal sites. Dexmedetomidine has been shown to stimulate alpha$_2$ receptor presynaptically and postsynaptically and directly in the spinal cord, hence causing inhibition of firing of nociceptive neurons[113]. Even peripheral alpha$_2$ adrenoreceptor may mediate antinociceptive action. Agonists can act at these sites and decrease transmission of nociceptive signals causing pain relief. G1-protein-gated potassium channels are activated and result in membrane hyperpolarisation,

reducing rate of firing of excitable cells in central nervous system. This becomes important in the inhibitory neuronal actions of alpha$_2$ adrenoreceptor agonists. An additional important physiologic action attributed to alpha$_2$ adrenoreceptor 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 G_0 proteins. The above two mechanisms illustrates two different means of effective pain relief. In the first one, prevention of nerve from over firing occurs while in the next one, the propagation of signal to its neighbour is affected. The receptors in substantia gelatinosa of dorsal horn of spinal cord while stimulated inhibits nociceptive neuronal firing which are stimulated by the peripheral A, B and C fibres and also cause inhibition of secretion of nociceptive neurotransmitter- substance P. The above mechanism is the reason for using clonidine for epidural administration in spite of its primary use as an intravenous drug.

Pharmacokinetics

Following IV administration, dexmedetomidine shows the following pharmacokinetic characteristics- a rapid distribution phase with distribution half-life of about 6mins; context sensitive half time ranges from 4mins following 10min infusion to 250min following 8hr infusion; a terminal elimination half-life of about

2hrs; and steady-state volume of distribution (V_{SS}) of about 118litres. Clearance is found to be about 39L/hr. The mean body weight related to the estimated clearance was 72kg[114].

Dexmedetomidine shows linear pharmacokinetics in dose ranging from 0.2-0.7mcg/kg/hour while given by i.v. infusion upto 24hrs[114].

Distribution

Dexmedetomidine has a steady-state volume of distribution (V_{SS}) of about 118 litres. Protein binding of dexmedetomidine was estimated in plasma of healthy adults. The average protein binding was found to be 94% was same in the various plasma concentrations evaluated. Protein binding was comparable in both gender. Fraction of protein bound dexmedetomidine hydrochloride was considerably reduced in subjects having liver dysfunction compared with healthy subjects[115].

The ability for displacement of protein binding of Dexmedetomidine by ketorolac, fentanyl, theophylline, digoxin and lignocaine was studied in vitro, and insignificant variations in protein binding displacement of warfarin, ibuprofen, phenytoin, propranolol, theophylline and digoxin by Dexmedetomidine was studied in-vitro and these drugs did not seemed to be considerably displaced by Dexmedetomidine[116].

Metabolism

Dexmedetomidine transforms almost completely and a very small amount of dexmedetomidine is eliminated without any change in urine and feces. Direct glucuronidation and cytochrome P450 facilitated metabolism takes place. The main pathways of dexmedetomidine metabolism include direct N-glucuronidation into inactive metabolites, aliphatic hydroxylation (facilitated mainly by CYP2A6) of dexmedetomidine to form 3-hydroxy-dexmedetomidine, the glucuronide of 3-hydroxy-dexmedetomidine and 3-carboxy dexmedetomidine; and N methylation of dexmedetomidine to form 3-hydroxy N-methyl-dexmedetomidine, 3-carboxy N-methyl-dexmedetomidine, and dexmedetomidine-N-methyl O-glucuronidation[117].

Elimination

Terminal elimination half-life of dexmedetomidine is found to be about 2 hours and clearance is about 39 L/hour. Dyck and co-workers [118] found that its pharmacokinetics in volunteers is best described by a three-compartment model. These pharmacokinetic parameters apparently are unchanged by age or weight or renal failure but clearance is a function of height [119, 120].

Properties

Sedation

Dexmedetomidine is approved by the FDA for short term (<24 hours) sedation of mechanically ventilated patients in the ICU setting.

The alpha$_2$ agonists produce their sedative-hypnotic effect by acting on alpha$_2$ receptors in the locus caeruleus and an analgesic action at alpha$_2$ receptors within the locus caeruleus and within the spinal cord. [121]The quality of sedation produced by dexmedetomidine seems different compared with that produced by other sedatives acting through the GABA systems. In this setting, it appears to offer some clinical advantages because it produces a unique type of sedation-analgesia with less respiratory depression than the commonly used sedative-hypnotic and opioid analgesic drugs. Patients receiving dexmedetomidine infusion as part of their sedation regimen in the postoperative ICU setting have been described as being very easy to wake up and having the ability to follow commands and cooperate while being endotracheally intubated. Undisturbed patients were noted to fall asleep right away. [122] Despite good levels of sedation with dexmedetomidine, there is limited respiratory depression, offering wide safety margins. [123] This property allows for “daily wake up” tests to be done in a safe manner. This critical test- when ventilated ICU patients are taken off all sedatives to assess their mental status and titrate sedation- shortens their ventilated and ICU length of stay[124].

The alpha$_2$ agonists act via the endogenous sleep-promoting pathways to employ their sedative effect. Dexmedetomidine produces a decrease in activity of the projections of the locus caeruleus to the ventrolateral preoptic nucleus. This increases the GABAergic and galanin release in the tuberomamillary nucleus, causing a decrease in histamine release in cortical and subcortical projections. [125] The

alpha$_2$ agonists seem to inhibit ion conductance through L-type or P-type cacium channels and facilitate conductance through voltage gated calcium-activated potassium channels.[126]The similarity between natural sleep (non-rapid eye movement) and dexmedetomidine –induced hypnosis has been speculated to maintain the cognitive and immunologic function in the sleep-deprived states (as in the ICU)[126]. Dexmedetomidine can produce profound sedation and it has been used as a total IV anaesthetic when given at 10 times the normal sedation concentration range.

Dexmedetomidine has been shown to induce a non-rapid eye movement sleeping pattern (NREM). The stimulation of the locus caeruleus (LC) by dexmedetomidine releases the inhibition the LC has over the ventrolateral preoptic nucleus (VLPO). The VLPO subsequently releases GABA onto the tuberomammillary nucleus (TMN). This inhibits the secretion of the arousal-promoting histamine on cortex and forebrain, inducing unconsciousness.

Dexmedetomidine binds with alpha$_2$ receptors from the locus ceruleus inhibiting noradrenaline release in the ventrolateral prepotic nucleus. The disinhibited ventro-lateral preoptic nucleus decreases arousal by means of GABA-mediated and galanin-mediated inhibition of hypothalamic, midbrain and pontine arousal nuclei.

The alpha$_2$ agonists have the advantage that their effects are readily reversible by alpha$_2$-adrenergic antagonists (e.g, atipamezole). [128]Atipamezole is not currently approved for human use. Similar to

other adrenergic receptors, the α_2 agonists also show tolerance after prolonged administration. [129] Because dexmedetomidine is approved by the FDA only for short-term sedation (24hours), tolerance, dependence, or addiction does not seem to be a problem. Dexmedetomidine can be employed for addiction treatment. Dexmedetomidine has been described for use in rapid opioid detoxification, cocaine withdrawal, and iatrogenic induced opioid and benzodiazepine tolerance after prolonged sedation. [130] In animals, dexmedetomidine, in contrast to opioids, does not result in hyperalgesia or allodynia after its withdrawal. [131] Rats rendered tolerant to morphine also showed a decrease in efficacy of hypnotic and analgesic effects of dexmedetomidine. As tolerance to opioids recovers, there is a more rapid recovery of the hypnotic effect of dexmedetomidine than its analgesic efficacy.[132]The data would tend to indicate a possible cross-tolerance between receptors.

Analgesia

The analgesic action of dexmedetomidine is complex. $Alpha_2$ agonists also exert an analgesic effect when injected intrathecally or epidurally. [133]Clonidine injected into the neural axis helps with short term pain cancer pain and neuropathic pain. [134, 135] Intrathecally injected dexmedetomidine in sleep reduces blood pressure in 1 minute. When dexmedetomidine is injected into the epidural space, it rapidly diffuses into the CSF (in one study [136] 22% of the injected dose was identified in the CSF). The effects on blood pressure are slower in

onset with an epidural injection than with an intrathecal administration. Epidural effects are seen in 5 to 20 minutes. The primary site of analgesic action appears to be in the spinal cord. [136] Systemic use of dexmedetomidine shows reduction in narcotic requirement. In the postoperative ICU setting, narcotic requirements were decreased by 50% in patients receiving a dexmedetomidine drip compared with placebo[122].

Some of the systemic analgesic effects have been attributed to the confounding sedative effects. [137] In human pain studies, the results of systemic administration of dexmedetomidine are not consistent. Modest decreases in pain were observed in cold pressor tests when patients were receiving dexmedetomidine. [138] More recently, in a model of heat and electrical pain in human volunteers, dexmedetomidine was not capable of attenuating the pain response in the clinical dose range when subjects were conscious. [127]The analgesic effect of dexmedetomidine has been compared with that of remifentanil. In a noxious heat versus pain intensity graph attained in a group of adults, dexmedetomidine was less efficient in decreasing pain (less of a right shift of the curve) than remifentanil. The slope obtained was different, which suggests a difference in the mechanism of action and an effect of sedation. [139].In the clinical setting, when pain is likely to occur and if dexmedetomidine need to be used, it is warranted to add a narcotic.

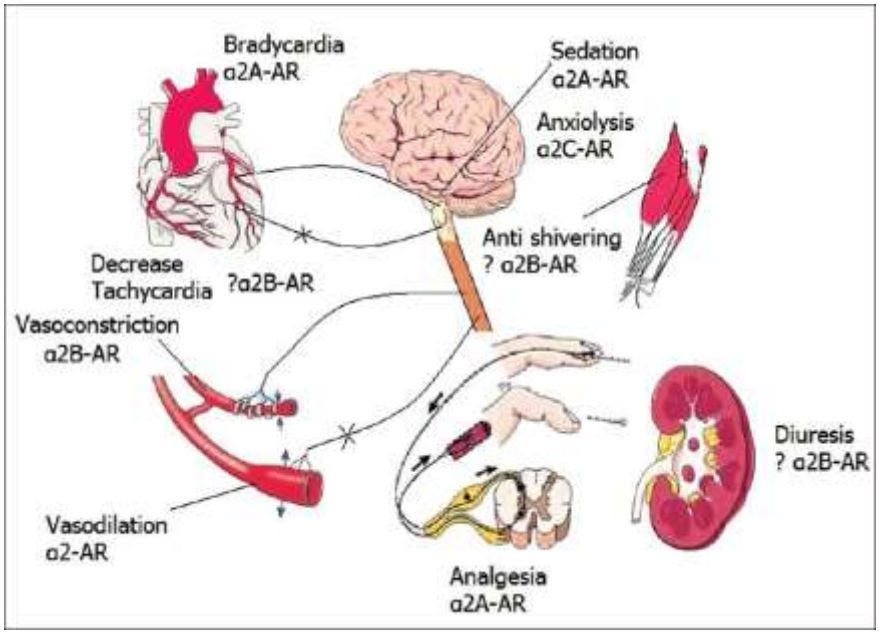


Fig. 4: Physiology of dexmedetomidine

Central Nervous System Protection and other Central Nervous System Effects

The central nervous system protective effects are not well defined. In animal models of incomplete cerebral ischemia and reperfusion, dexmedetomidine decreases cerebral necrosis and improves the neurologic outcome. In a model of focal ischemia in rabbits, dexmedetomidine administered at doses that reduced the MAC of halothane by 50%, resulted in less cortical neuronal damage than when halothane was administered alone at equieffective MAC concentrations[116]. In a rat model of unilateral carotid ligation accompanied by systemic hypotension, the administration of dexmedetomidine provided lower plasma catecholamines with less

neurologic and histopathologic damage. [140]The prevalent idea was that dexmedetomidine reduced the intracerebral catecholamine outflow during injury and resulted in a less neural tissue damage with better neurologic outcome. [141]Others have found no reduction in cerebral catecholamines after receiving dexmedetomidine during injury. [142]The neuroprotection may be attributed to modulation of proapoptotic and antiapoptotic proteins. Also, decrease in the excitatory neurotransmitter glutamate during injury may explain some of the protective effects. [143]

The neuroprotective properties of dexmedetomidine in humans have not been investigated. Little is known of the effects of dexmedetomidine alone on ICP and CBF. In patients after pituitary surgery, a target concentration of 600ng/mL of dexmedetomidine resulted in no increase in lumbar CSF pressure. [144]In dogs, in the presence of volatile anaesthetic agents and dexmedetomidine, CBF was decreased, and oxygen consumption was maintained. [145, 146] CBF velocity, as measured by transcranial Doppler, decreased with increasing concentrations of dexmedetomidine in parallel with decreasing MAP and increasing $Paco_2$. [147] These reductions in CBF are not accompanied by a reduction in $CRM0_2$. Despite the significant reduction in CBF with dexmedetomidine, there was no evidence of cerebral ischemia in a dog model. In a preliminary research in patients who underwent cerebrovascular surgery using dexmedetomidine, there was no evidence of a detrimental effect on local brain tissue oxygenation. [148] More recently, in a study in six

normal volunteers, administration of dexmedetomidine to achieve serum levels of 0.6ng/mL and 1.2ng/mL (with and without hyperventilation) produced the predicted reduction of CBF with a concomitant reduction in $CRM0_2$. [149]This finding suggests the maintenance of the cerebral oxygen supply-to-demand relationship, however, further work in injured brains needs to be done.

In a rat seizure model, dexmedetomidine showed significant proconvulsant action, which is consistent with formal findings that inhibition of central noradrenergic transmission causes facilitation of seizure expression. [150]) This finding is in contrast to an anticonvulsant effect shown in rats after kainic acid induced seizures. [151]As yet there have been no reports of seizures in humans. Dexmedetomidine has been used in neurosurgical procedures involving neurophysiologic monitoring. Cortical evoked potentials amplitudes and latencies were minimally affected when using dexmedetomidine intraoperatively in patients who underwent craniotomies. [148]Dexmedetomidine is also shown to decrease muscle rigidity after administration of high-dose opioids. [152]In resting volunteers, dexmedetomidine increased growth hormone secretion in a dose-dependent manner, but had no effect on other pituitary hormones. [153, 154]Dexmedetomidine ablates memory in a dose-dependent manner. In concentrations used for clinical sedation (i.e., 0.7 ng/mL), recall of picture cards is preserved. Increasing the concentration of dexmedetomidine to 2ng/mL largely ablates recall and recognition of a picture card. [155]

Effects on the Respiratory System

In volunteers, dexmedetomidine at concentrations causing significant sedation decreases minute ventilation, but retains the slope of the ventilatory response to increasing carbon dioxide. [156]The changes in ventilation were similar to those observed during natural sleep. Ebert and colleagues, [157] infusing dexmedetomidine to concentrations of 15ng/mL in spontaneously breathing adults, did not show any variation in arterial oxygenation or pH. At the maximum concentration, $Paco_2$ raised by 20%. Respiratory rate rose with rising concentration from 14 breaths per minute to 25 breaths per minute. [155]When dexmedetomidine and propofol were titrated to get equal sedative end points (BIS of 85), both did not cause any change in respiratory rate. [157] In a research comparing the effects of remifentanil and dexmedetomidine on respiratory profiles in normal adults,[158] the hypercapnic ventilatory response was not affected even at doses which caused unresponsiveness to vigorous stimulation. $PaCo_2$ showed mild increase with dexmedetomidine, but it reached a plateau following the first increment. Dexmedetomidine also exhibited a hypercarbic arousal phenomenon, which has been described during normal sleep and is a safety feature. Intravenous or inhaled dexmedetomidine has been shown to block histamine- induced bronchoconstriction in dogs. [159]

Effects on the Cardiovascular System

The basic effects of alpha$_2$ agonists on the cardiovascular system was reduced heart rate, reduced systemic vascular resistance, and indirectly reduced myocardial contractility, systemic blood pressure and cardiac output. By developing highly selective agonists, it is hoped to reduce some of these adverse cardiovascular effects and to maximize the desirable hypnotic-analgesic properties. The hemodynamic effects of a bolus dose of dexmedetomidine in humans show a biphasic response. An acute intravenous injection of 2 µg/kg resulted in an initial rise in blood pressure (22%) and reduction in heart rate (27%) from baseline that happened at 5 minutes after the administration. This initial rise in blood pressure is possibly caused by vasoconstrictive effects of dexmedetomidine by stimulation of peripheral alpha$_2$ receptors. Heart rate returned to baseline in 15 minutes, and blood pressure gradually reduced to approximately 15% below baseline in 1 hour. After an IM injection of the same dose, the initial rise in blood pressure was not seen; and heart rate and blood pressure remained within 10% of baseline. [118]

Ebert and colleagues [155] performed an elegant study in healthy subjects using a target-controlled infusion system so as to provide rising concentrations (0.7 to l5 ng/mL) of dexmedetomidine. The lowest two concentrations caused a reduction in MAP (13%) followed by an increase (12%). Rising concentrations of dexmedetomidine also produce progressive reduction in heart rate and cardiac output (35%).

[136] Infusion of dexmedetomidine in healthy subjects also resulted in compensated decrease in systemic sympathetic tone without causing change in baroreflex sensitivity. It also blunts the heart rate and systemic sympathetic activation owing to sweating but is less efficient in reducing cardiac sympathetic response to shivering. [160]The incidence of hypotension and bradycardia can be related to administration of a loading dose. Avoiding the loading dose or not giving more than 0.4 mcg/kg decreases the incidence of hypotension, or makes it less pronounced. Giving loading dose over 20 minutes also reduces the transient hypertension. [161]) In several studies after IM and IV administration, dexmedetomidine caused, in a small percentage of patients, profound bradycardia (<40 beats/min) and occasionally sinus arrest/pause. These episodes resolved spontaneously or were readily treated without adverse outcome by anticholinergics. It would be expected from its profile that dexmedetomidine would be beneficial to the ischemic myocardium. In animal models dexmedetomidine showed some beneficial effects on the ischemic myocardium through decreased oxygen consumption and redistribution of coronary flow from nonischemic zones to ischemic zones after acute brief occlusion. [162]Dexmedetomidine also decreases serum lactate in a dog model of coronary ischemia with an associated reduction in heart rate and measured catecholamines. It also produced a rise in the endocardial/epicardial blood flow ratio by 35%. [163]

The perioperative use of alpha$_2$ agonists reduces the incidence of perioperative myocardial ischemia. [69] More recently, Wallace and

associates showed that administration of clonidine in the preoperative period reduces the incidence of perioperative cardiac ischemia from 31% to 14%, and reduces the mortality for 2 years from 20% to 15% compared with placebo. The only data on potential benefits in perioperative ischemia prevention with dexmedetomidine are provided in an underpowered study in vascular surgery patients who received the drug in the perioperative period. Blood pressure and heart rate were lower in the dexmedetomidine group. No reductions of ischemic events were noted. No rebound effects were found when discontinuing Dexmedetomidine drip, even when it is given for more than 24 hours. (166)

Indication

Labelled:

- Dexmedetomidine is indicated for sedation of intubated and mechanically ventilated patients during treatment in the ICU setting.
- Sedation of non-intubated patients before and / or during surgical or other procedures.

Off Labelled

1. Premedication:

Dexmedetomidine possesses anxiolytic, analgesic, sedative, antisialogogue and sympatholytic properties, which render it suitable

as a premedication agent. Dexmedetomidine potentiates the anaesthetic effects of all intra-operative anaesthetic agents.

Grant and colleagues [167] described the use of dexmedetomidine while securing the airway with a fiberoptic intubation in three patients undergoing cervical spine surgery. The procedure was well tolerated without any hemodynamic compromise or respiratory depression.

2. Intra-operative uses:

Use of dexmedetomidine as adjunct to general anaesthesia: The use of intra-operative dexmedetomidine may increase haemodynamic stability due to attenuation of the stress-induced sympathoadrenal responses to tracheal intubation, during surgery and during emergence from anaesthesia.

In patients given an infusion regimen to achieve a plasma concentration of slightly less than 1 ng/mL, combined with 70% nitrous oxide, dexmedetomidine decreased isoflurane requirements by 90% compared with a control group.[168] One retrospective study and two prospective, randomized controlled trials in bariatric surgical patients have found that a balanced anaesthesia with desflurane or propofol plus dexmedetomidine (0.5 - 0.8 µg/kg bolus plus 0.4 µg/kg/hr infusion) reduces postoperative pain scores and morphine consumption, and improves hemodynamics compared to desflurane-fentanyl or propofol-fentanyl anaesthetics. [169, 170, 171]

Dexmedetomidine reduces vasoconstriction threshold and increases shivering threshold leading to a lower incidence of shivering.

It is also being used for conscious sedation/ Monitored Anaesthesia care. Because this drug provides good sedation with only minimal respiratory depression, it has been used in patients undergoing awake craniotomies with functional testing, and electrocorticograph [172] or awake carotid endarterectomies with fewer fluctuations from the desired sedation level and a more stable hemodynamics. [1173]

- Use of dexmedetomidine for regional anaesthesia

The use of dexmedetomidine as an adjuvant in regional anaesthesia is still not validated. Maarouf [177] explored the effect of epidural dexmedetomidine on the incidence of postoperative shivering in 60 patients undergoing orthopedic surgery. He found out that patients who received dexmedetomidine at a dose of 100 µg added to 20 ml 0.5% bupivacaine showed lower incidence in postoperative shivering, compared to patients who received epidural bupivacaine alone (10% vs. 36%). Memis [178] noted that addition of 0.5 µ.g/kg dexmedetomidine to lignocaine for intravenous regional anaesthesia improves the quality of anaesthesia and perioperative analgesia without causing adverse effects.

Kanazi et al [179] investigated the effect of adding a small dose of 3 µg of intrathecal dexmedetomidine to 12 mg bupivacaine. They found a significant prolongation of sensory and motor block, compared to bupivacaine alone. In this study, the effect of 3µg intrathecal dexmedetomidine was similar to that produced by the addition of 30 µg of intrathecal clonidine.

3. Postoperative period:

In 1999, FDA approved dexmedetomidine as a sedative and supplement to sedation in ICU for patients who require mechanical ventilation of less than 24 hours duration. Availability of an antagonistic agent Atipamezole, [201],[202] makes it an ideal drug for intravenous titration both as a sole agent and for continuous infusion in the intensive care units, operating room, and other areas. Its unique sedative action mimics normal sleep, which has an advantage during weaning from mechanical ventilation. Dexmedetomidine need not be discontinued and the ongoing sedation can be maintained following tracheal extubation, so as to prevent emergence delirium and agitation. [203],[204]

It's special properties favour its use in the recovery room. In addition to its sympatholytic effects, analgesic effects, reduced rate of shivering and the preservation of respiratory function allows continuation of dexmedetomidine infusion in the exubated spontaneous breathing patient. The possibility of ongoing sedation and sympathetic block can be useful in decreasing the high rates of early postoperative ischemic events in high risk patient undergoing noncardiac surgery.

4. Perioperative administration of dexmedetomidine could be beneficial in chronic opioid users and alcoholics, in high- risk patients and also in cardiac patients with good to moderately reduced left ventricular function.

5. *Cocaine poisoning*

Andrew C. Kontak, et al[(205)] conducted a research in 15 nontreatment-seeking cocaine-addicted patients and 12 cocaine-naive healthy adults to find the dose of intravenous dexmedetomidine that lower mean arterial pressure and heart rate in the absence of acute-cocaine challenge. They also conducted a placebo-controlled study in 26 cocaine-addicted subjects to find out if dexmedetomidine reverses mean arterial pressure and heart rate increases after cocaine (3 mg/kg). They found out that in a low nonsedating dose, dexmedetomidine can be used as a new treatment for cocaine-induced acute hypertension. But they found that higher sedating doses can cause an unpredictable increase in blood pressure during acute-cocaine challenge and should be avoided.

6. *Use in paediatric patients*

Byung Ju Ko et al [(206)] in 2012 conducted a study on Procedural sedation using dexmedetomidine for paediatric ERCP guided stone retraction. As a sedative, dexmedetomidine can maintain spontaneous breathing and preserve oxygenation and ventilation even during deeper level of sedation. Here, the total time taken for the procedure and infusion were short and the child completely recovered from sedation within 30 minutes without any adverse events. They came to the conclusion that, when patients are given adequate analgesia, use of dexmedetomidine for sedation for paediatric ERCP would be safe and is accompanied by better outcomes than sedation with other drugs.

Side Effects

Hypotension, Bradycardia, and Sinus Arrest

Episodes of bradycardia and sinus arrest which are clinically significant have been reported when dexmedetomidine is administered in young, healthy adults with high vagal tone or with various routes of administration which includes rapid i.v. or bolus administration.

Reports of bradycardia and hypotension have been seen with dexmedetomidine infusion. If medical intervention is needed, management includes reducing or stopping the infusion of dexmedetomidine, increasing the rate of intravenous fluid administration, lower limb elevation and the use of vasopressors. As dexmedetomidine can augment the bradycardia induced by stimulation of vagus, clinicians should be prepared for intervention. Administration of intravenous anticholinergic agents like glycopyrrolate or atropine ought to be considered to modify vagal tone. In clinical studies, glycopyrrolate and atropine were found to be effective in treating of most episodes of dexmedetomidine hydrochloride-induced bradycardia. Nevertheless, in some patients with considerable cardiovascular dysfunction, more advanced resuscitative methods were needed. [174]

Caution must be exercised while administering dexmedetomidine to patients having advanced heart block and severe ventricular dysfunction. As dexmedetomidine reduces sympathetic nervous system activity, hypotension and bradycardia are expected to be more marked

in patients with hypovolemia, chronic hypertension or diabetes mellitus and in geriatric patients.

In studies where other vasodilators or negative chronotropic drugs were given along with dexmedetomidine, an additive pharmacodynamic effect was not seen. However, caution should be executed when such drugs are used along with dexmedetomidine. [175]

Transient Hypertension

Transient hypertension is seen mainly during the loading dose associated with the initial peripheral vasoconstrictive effects of dexmedetomidine. Treatment of this transient hypertension is usually not necessary, though decreasing the loading infusion rate may be desirable. [155]

Arousability

Some patients receiving dexmedetomidine were found to be arousable and alert when stimulated. This alone should not be taken in to account as an evidence for lack of efficacy, in the absence of other clinical signs and symptoms. [161]

Withdrawal

While administered up to 7 days regardless of dose, 12 (5%) dexmedetomidine subjects experienced at least 1 event in relation to withdrawal within the first 24 hours folowing discontinuation of the drug and 7 (3%) dexmedetomidine subjects experienced at least 1 event

24 to 48 hours following the end of drug. The commonest events were nausea, vomiting, and agitation. Tachycardia and hypertension that required intervention in the 48 hours after discontinuation of dexmedetomidine occurred at a frequency of < 5%. If tachycardia or hypertension occurs after stoppage of dexmedetomidine, supportive treatment is indicated. [160]

Withdrawal symptoms were not reported following discontinuation of short term infusions of dexmedetomidine (< 6 hours).

Tolerance and Tachyphylaxis

Use of dexmedetomidine for more than 24 hours is seen to be associated with tolerance and tachyphylaxis, and a dose related rise in adverse reactions.

Hepatic Impairment

Since dexmedetomidine clearance reduces with severity of liver dysfunction, dose reduction must be considered in patients with liver dysfunction. [161]

Others

- Dry mouth
- Limited amnestic effect
- Excessive sedation
- Animal studies show reduction in CBF/$CMR0_2$ ratio

Drug Interaction

Anaesthetics, Sedatives, Hypnotics, Opioids

Administration of dexmedetomidine along with anaesthetics, sedatives, opioids and hypnotics can cause potentiation of their effects. Specific studies have established these effects with isoflurane, sevoflurane, alfentanil, propofol, and midazolam. No pharmacokinetic interactions have been demonstrated between dexmedetomidine and isoflurane, propofol, alfentanil and midazolam. Though, due to possible pharmacodynamic interactions, when administered along with dexmedetomidine, a decrease in dosage of dexmedetomidine or the concomitant anaesthetic, sedative, hypnotic, or opioid may be needed.

Neuromuscular Blockers

A study of 10 healthy volunteers showed that dexmedetomidine administration for 45 minutes at a plasma concentration of 1µg/mL did not result in clinically significant increase in level of neuromuscular blockade associated with administration of rocuronium. Dexmedetomidine may displace extensively protein bound drugs, but this is usually not significant.

Antagonist

Atipamazole, dose - 50 microgm/kg[176]

MATERIALS AND METHODS

Source of Data:

The study was conducted in the Department of Anaesthesiology at Sree Mookambika Institute of Medical Sciences, Kulashekharam, Kanyakumari district after getting permission from the Institutional ethical committee. The study was conducted over a period of 14months from June 2013 to July 2014.

Study Design

Double Blind Randomized clinical trial.

METHOD OF COLLECTION OF DATA

Inclusion Criteria:

1. Patients giving valid consent.
2. Patients under American Society of Anaesthesiology physical status 1 and 2.
3. Patients undergoing elective surgeries under general anaesthesia.
4. Patients aged between 18 to 55 years.

Exclusion Criteria:

1. Refusal by the patient.
2. Patients with American Society of Anaesthesiology physical status 3 or more.
3. Patients posted for emergency surgeries.

4. Patients with history of alcohol or drug abuse.
5. Patients who are allergic to any of the test drugs.
6. Contraindication to general anaesthesia.

Sample Size:

Sample size of each group: 35

Total sample size of the study: 70

Scientific basis of sample size used in the study:

Non-randomised purposive sampling technique.

Procedures in Detail:

The study was conducted on 70 patients between 18 and 55 years of age belonging to American Society of Anaesthesiology physical status 1 and 2 of either sex undergoing a variety of elective surgeries under general anaesthesia in Sree Mookambika Institute of Medical Sciences, Kulasekharam.

Pre-operative Check-up

A thorough pre-anaesthetic check-up was carried out. Detailed history was taken and systems were examined. Pulse, blood pressure and respiratory rate were noted. Height and weight were recorded. Routine investigations like haemogram, bleeding time, clotting time, chest X-ray, ECG were obtained before taking up for surgery. After applying the exclusion criteria, 70 patients about to undergo general anaesthesia with endotracheal intubations were selected.

Pre-operative Preparation

All the selected patients were visited on the day prior to surgery, explained in detail about the anaesthetic procedure and informed written consent was obtained. All patients were kept NPO 6 hours prior to surgery. They received Tablet Ranitidine 150mg and Tablet metoclopramide 10mg on the previous night and on the morning of surgery and injection glycopyrrolate 0.2mg iv and injection midazolam 2mg iv 30 minutes before surgery as premedication.

Intra-operative monitoring included- Pulse oximetry, non-invasive blood pressure, ECG, Capnography.

Preparation of drug for infusion

Dexmedetomidine 1ml containing 100mcg is added to 50ml normal saline to make a solution containing dexmedetomidine 2mcg/ml and taken in a 50ml syringe to be administered using a syringe pump.

Patients were divided randomly into 2 groups.

Group I:Dexmedetomidine Group; patients received dexmedetomidine1µg/kg over 10minutes before the induction of anaesthesia and thereafter 0.4µg/kg as continuous infusion till the end of surgery.

Group II:Control Group; patients received normal saline intravenously administered in the same manner.

In operation theatre all monitors were attached and baseline values recorded. Patients were pre-oxygenated with 100% oxygen for 3 minutes followed by inj.Fentanyl 1.5mcg/kg IV. Anaesthesia was induced with inj.Propofol 2mg/kg IV. This was followed by succinyl choline 2mg/kg and endotracheal intubation was done with appropriate size endotracheal tube. Patients requiring more than 20 seconds to achieve successful tracheal intubation were excluded from the study. Maintenance of anaesthesia was done with nitrous oxide: oxygen 2:1 and atracurium for muscle relaxation after intubation. Heart rate, systolic and diastolic blood pressures were recorded just before intubation, immediately after intubation, 1, 2, 3, 4, 5 minutes after intubation followed by every 5 minutes till the first 45 minutes of surgery. Any further need for analgesia was supplemented by IV fentanyl. At the end of surgery neuro-muscular blockade was reversed using inj.neostigmine 0.05mg/kg and inj.glycopyrrolate 0.008mg/kg and the patients were observed in the post anaesthesia care room for 2 hours. Side effects if any were noted.

Observations

Pulse rate and blood pressure were recorded as per the proforma.

Main arterial Pressure was calculated by the formula

MAP = DBP + 1/3 (SBP-DBP)

Where DBP – diastolic blood pressure, SBP – systolic blood pressure.

Change in pulse rate 20% of base line value was considered bradycardia or tachycardia. Patients whose heart rate fell below 50 were given inj.atropine 0.6mg IV.

Statistical methods of analysis:

All parameters to be entered in Microsoft excel spread sheet and statistically analysed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Statistical analysis of demographic data, heart rate changes, blood pressure changes were done by unpaired 't' test. Student's t test was used for comparing means of two populations.

A p value of >0.05 is not significant

<0.05 is significant

<0.001 is highly significant.

STATISTICAL ANALYSIS

The data is expressed in mean and standard error of mean. The data was analysed by SPSS (16.0) version. Significant between group-I and group-II was analysed by independent t test. P values less than 0.05 ($P<0.05$) are considered significant at 95% confidence interval.

Comparison of Demographic Data

Table-1: Distribution of Sample according to Age

Age (years)	Group-I (Study)		Group-II (Control)	
	Number	Percentage (%)	Number	Percentage (%)
18-30	11	31.43	13	37.14
31-40	5	14.29	8	22.88
41-50	8	22.86	7	20.00
>50	11	31.43	7	20.00

In the study group, 31.43% patients each were of the age groups 18-30 and 51-55, 22.86% patients were of the age group 41-50 and 14.29% patients were of the age group 31-40 years. In the control group, 37.14% patients were of the age group 18-30, 22.88% patients were of the age group 31-40, 20% patients each were of age group 41-50 and 51-55 years. (This is shown in the below graph).

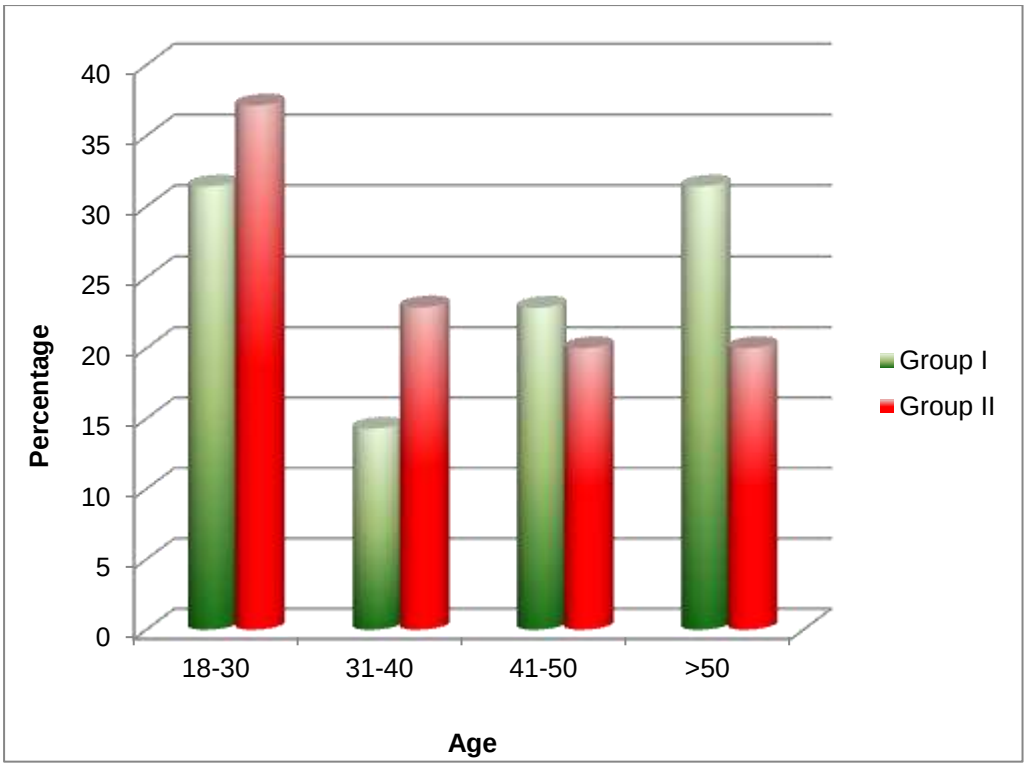


Fig-5: Distribution of Sample according to Age of patients

Table-2: Distribution of sample according to gender of patients

Gender	Group-I (Study)		Group-II (Control)	
	Number	Percentage (%)	Number	Percentage (%)
Male	19	54.28	14	40
Female	16	45.72	21	60

In the study group, 54.28% patients were males and 45.72% patients were females. In the control group 60% patients were females and 40% patients were males. (This is shown in the below graph).

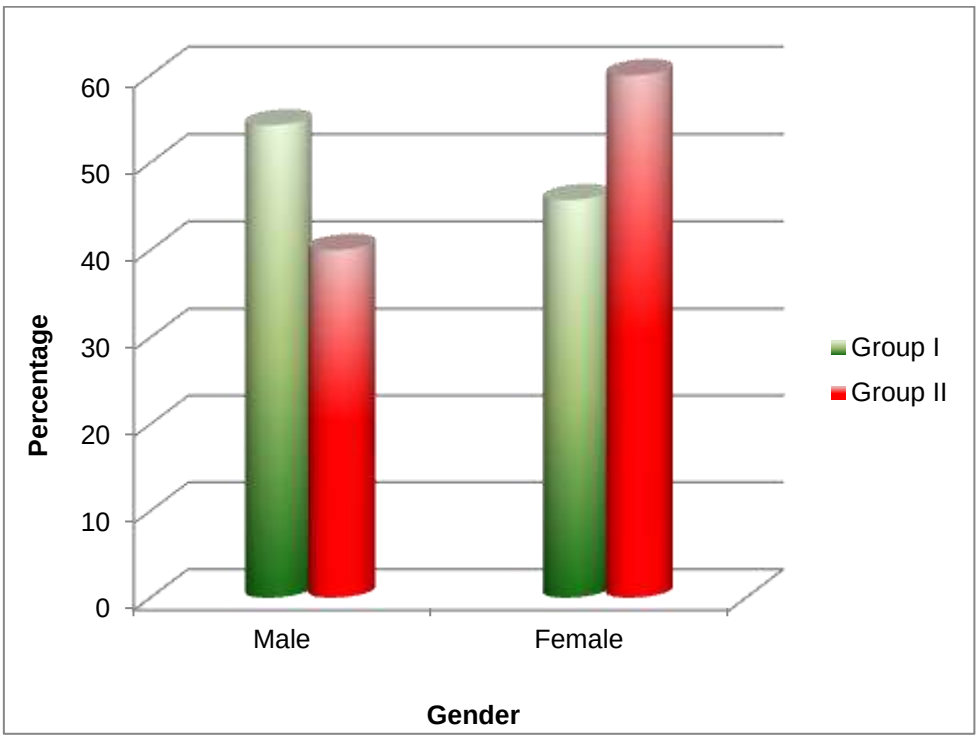


Fig-6: Distribution of sample according to gender of patients

Table-3: Comparison of mean body weight between controls and study group

Groups	Body weight (Kg) (MEAN±SEM)
Group-I	62.57±1.14
Group-II	60.57±6.59

The mean body weight of group I patients were 62.57±1.14 and the mean body weight of group II patients were 60.57±6.59.

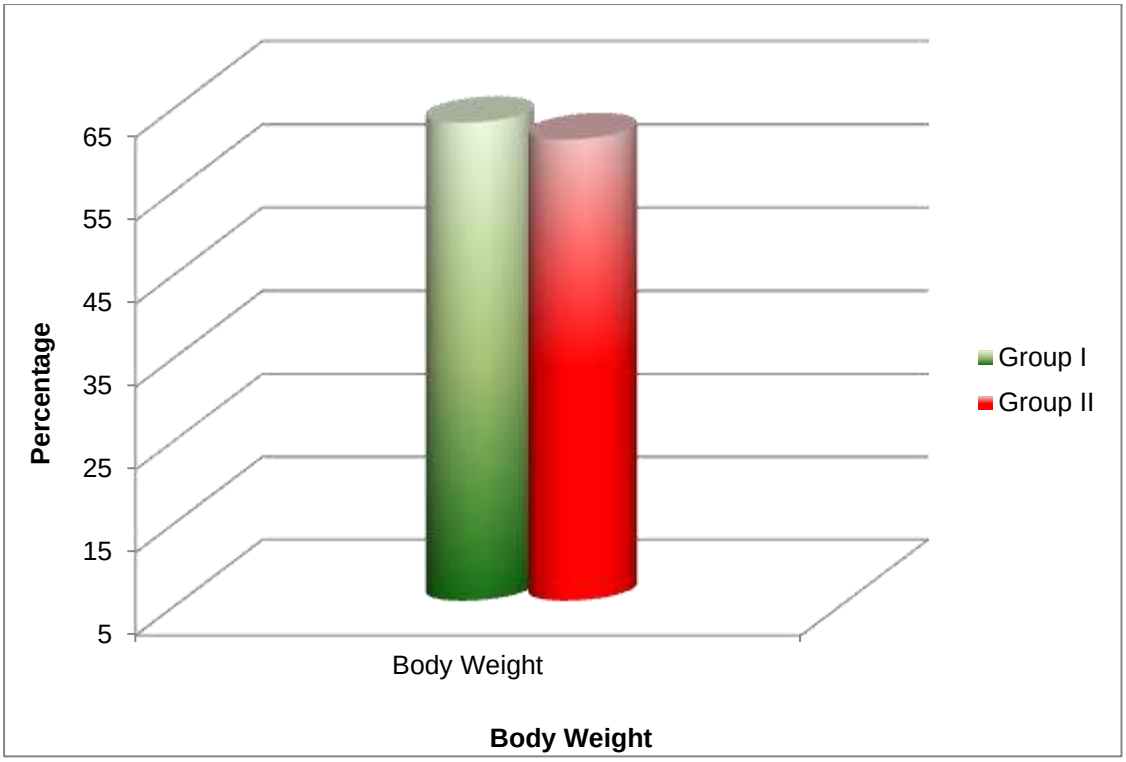


Fig-7: Comparison of mean body weight between controls and study group

Table-4: Comparion of American Society of Anaesthesiologists score between controls and study group

ASA physical status	Group-I (Study)	Group-II (Control)
ASA 1	25	27
ASA 2	10	8

In the study group 25 patients were ASA 1 and 10 patients were ASA 2. In the control group 27 patients were ASA 1 and 8 patients were ASA 2. This is shown in the below graph.

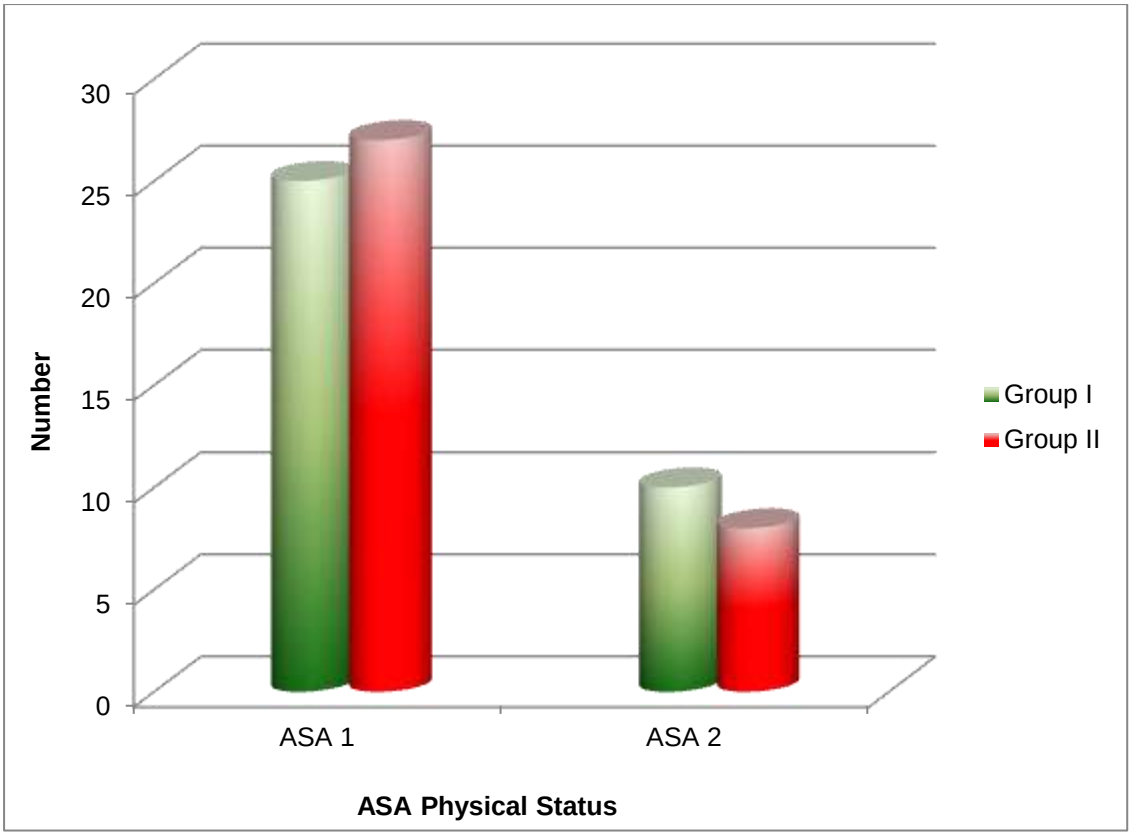


Fig-8: Comparion of American Society of Anaesthesiologists score between control and study group

Table-5: Comparison of number of patients who underwent different types of surgery in group-I and group-II

Type of surgery	Group-I (Study)	Group-II (Control)
Urology	02	02
Head & Neck Surgery	09	11
Laparoscopic Surgery	06	08
Orthopaedic Surgery	09	09
Lower Abdominal Surgery	04	02
Laparotomy	03	01
Breast Surgery	02	02
Total	35	35

The above table shows the number of patients who underwent different types of surgery in group-I and group-II. In the dexmedetomidine group 9 patients each underwent head and neck surgery and orthopaedic surgery, 6 patients underwent laparoscopic surgery, 4 patients underwent lower abdominal surgery, 3 patients underwent laparotomy and 2 patients each underwent urologic and breast surgeries. In the control group, 11 patients underwent head and neck surgery, 9 patients underwent orthopaedic surgery, 8 patients underwent laparoscopic surgery, 2 patients each underwent urologic, lower abdominal and breast surgeries and 1 patient underwent laparotomy.

Heart Rate Changes

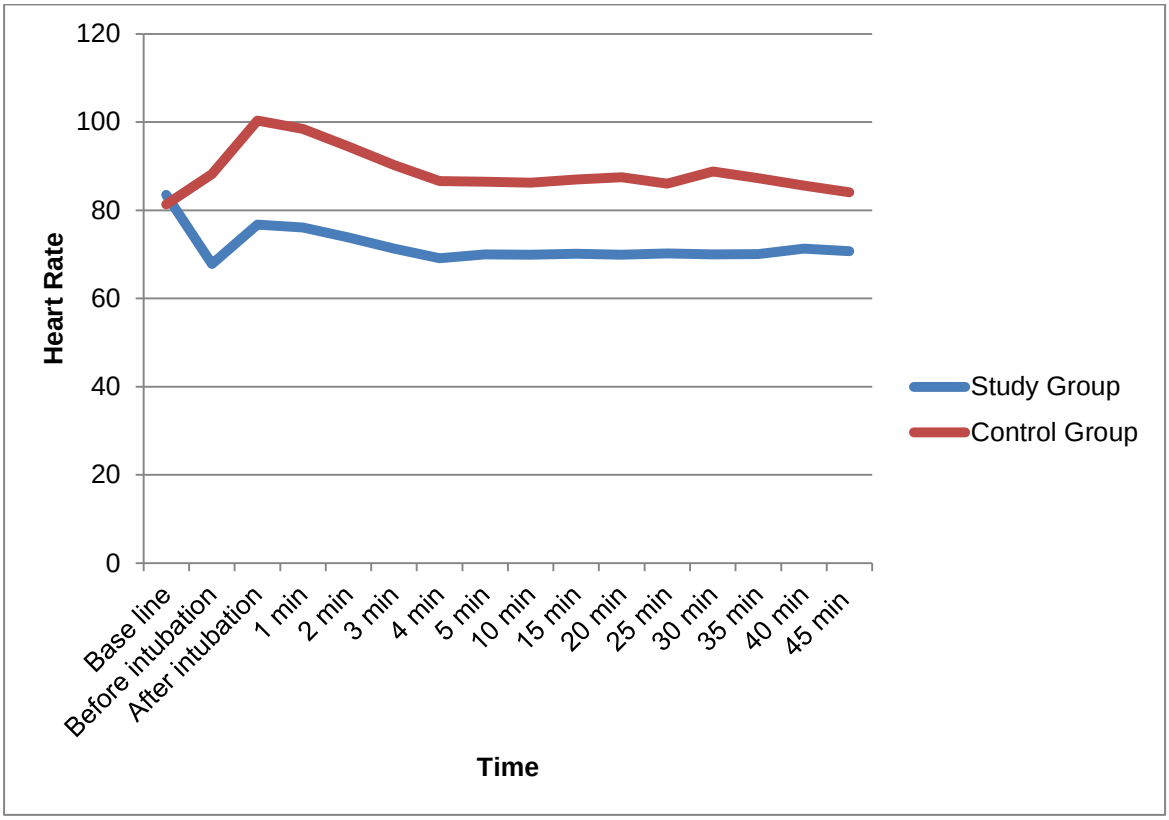
Table-6: Comparison of heart rate changes between groups at various time intervals

Time (min)	Heart rate (MEAN±SEM)		P value
	Group-I (Study)	Group-II (Control)	
Base line	83.54±1.03	81.34±1.26	0.279
Before intubation	67.80±7.71*	88.20±1.14	0.042
After intubation	76.77±7.63*	100.37±1.31	0.002
1 min	76.11±8.13*	98.46±1.29	0.030
2 min	73.82±7.07*	94.48±1.18	0.005
3 min	71.03±7.09*	90.26±1.18	0.005
4 min	69.14±6.62*	86.60±1.22	0.000
5 min	70.00±5.98*	86.51±1.10	0.001
10 min	69.91±6.12*	86.29±1.08	0.001
15 min	70.14±6.05*	87.00±1.05	0.003
20 min	69.94±6.21	87.48±9.66	0.050
25 min	70.20±5.95	86.06±16.23	0.031
30 min	70.03±6.21	88.79±9.09	0.047
35 min	70.08±6.14	87.31±1.00	0.046
40 min	71.28±6.47	85.63±9.39	0.226
45 min	70.71±5.94	84.11±9.49	0.114

(*P<0.05 which represents significant reduction in heart rate at different time intervals between group-I and II)

Above table shows that there was no significant difference in the baseline heart rate values. Statistically significant reduction in heart rate occurred in dexmedetomidine group patients before intubation, after intubation, 1 min, 2 min, 3 min, 4 min, 5 min, 10 min and 15 min. After 15 min there was no significant difference in heart rates between the two groups. (The same is represented in the following graph).

Fig-9: Time depend changes in heart rate of group-I and group II patients



Systolic Blood Pressure Changes

Table-7: Comparison of mean systolic blood pressure changes between groups at various time intervals

Time (min)	Systolic blood pressure (MEAN±SEM)		P value
	Group-I (Study)	Group-II (Control)	
Base line	128.17±1.73	127.66±1.53	0.825
Before intubation	105.54±1.59*	123.23±1.42	0.000
After intubation	112.80±1.43*	147.31±1.66	0.000
1 min	113.54±1.47*	143.94±2.03	0.000
2 min	113.69±1.45*	140.40±1.89	0.000
3 min	113.33±1.56*	137.09±1.74	0.000
4 min	112.57±1.52*	137.14±1.79	0.000
5 min	112.57±1.49*	135.43±1.64	0.000
10 min	111.71 ±1.38*	131.77±1.67	0.000
15 min	110.17 ±1.37*	127.71±1.30	0.000
20 min	107.14 ±3.28*	125.66±1.20	0.000
25 min	109.40±1.70*	125.94±1.22	0.000
30 min	108.69 ±1.71*	128.69±1.25	0.000
35 min	108.74 ±1.60*	130.63±1.07	0.000
40 min	109.26 ±1.44*	130.57±1.14	0.000
45 min	110.29 ±1.38*	129.77±1.24	0.000

(*P<0.05 represents significant reduction in mean systolic blood pressure at different time intervals between group-I and II)

The above table shows that there was no significant difference in the baseline systolic blood pressure. Statistically highly significant reduction in systolic blood pressure occurred in dexmedetomidine group patients for all other readings from before intubation till 45 minutes. (The same is represented in the following graph).

Fig-10: Time dependent changes in systolic blood pressure in group-I and II patients

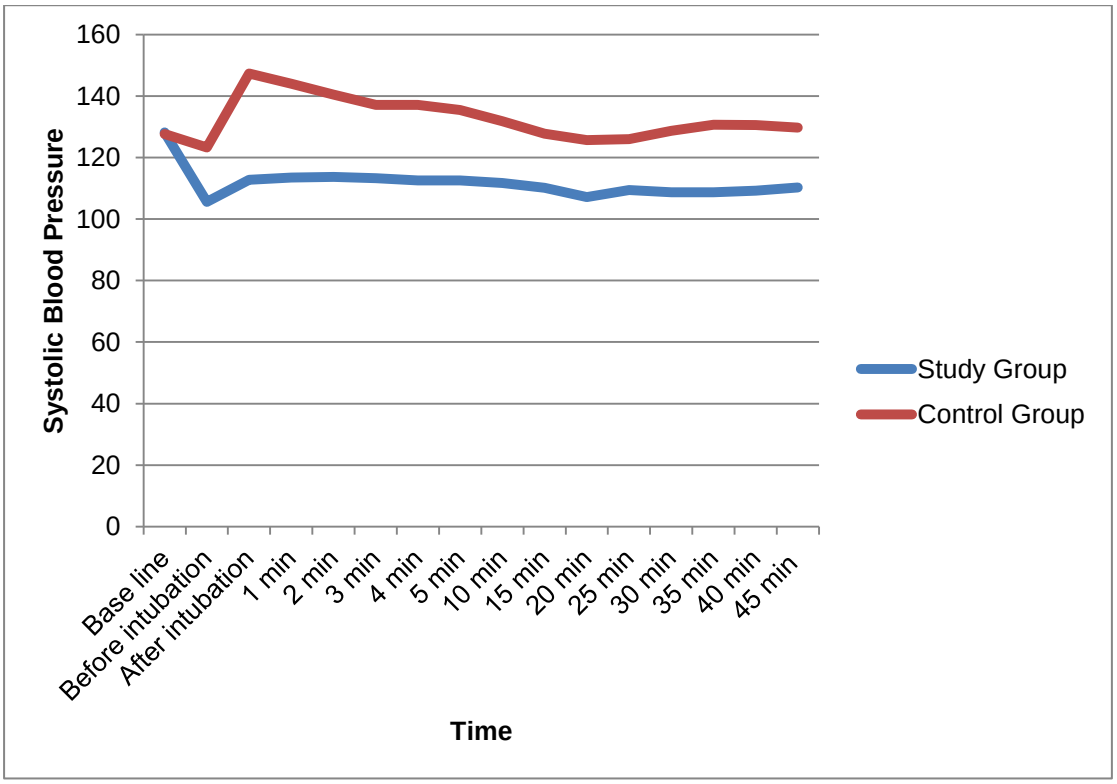


Table-8: Comparison of mean diastolic blood pressure changes between groups at various time intervals

Time (min)	Diastolic blood pressure (MEAN±SEM)		P value
	Group-I	Group-II	
Base line	82.62±1`.08	82.31±1.01	0.768
Before intubation	68.17±0.70*	79.33±0.88	0.000
After intubation	74.85±0.73*	90.05±0.89	0.000
1 min	74.80±0.72*	86.85±0.98	0.000
2 min	74.40±0.68*	85.94±1.10	0.000
3 min	74.97±0.78*	84.62±1.07	0.000
4 min	74.51±0.84*	83.65±1.05	0.000
5 min	73.88±0.79*	83.08±0.99	0.000
10 min	76.05±0.78*	82.74±0.87	0.000
15 min	72.68±0.84*	82.05±0.85	0.000
20 min	73.94±0.89*	82.28±1.06	0.000
25 min	72.68±0.79*	82.74±1.11	0.000
30 min	71.42±0.76*	84.57±1.18	0.000
35 min	71.37±0.75*	84.05±1.01	0.000
40 min	72.00±0.76*	82.68±0.85	0.000
45 min	72.62±0.79*	82.51±0.77	0.000

(*P<0.05 significant compared mean diastolic blood pressure at different time intervals between group-I and II)

The above table shows that there was no significant difference in the baseline diastolic blood pressure. Statistically highly significant reduction in diastolic blood pressure occurred in dexmedetomidine group patients for all other readings from before intubation till 45 minutes. (The same is represented in the following graph).

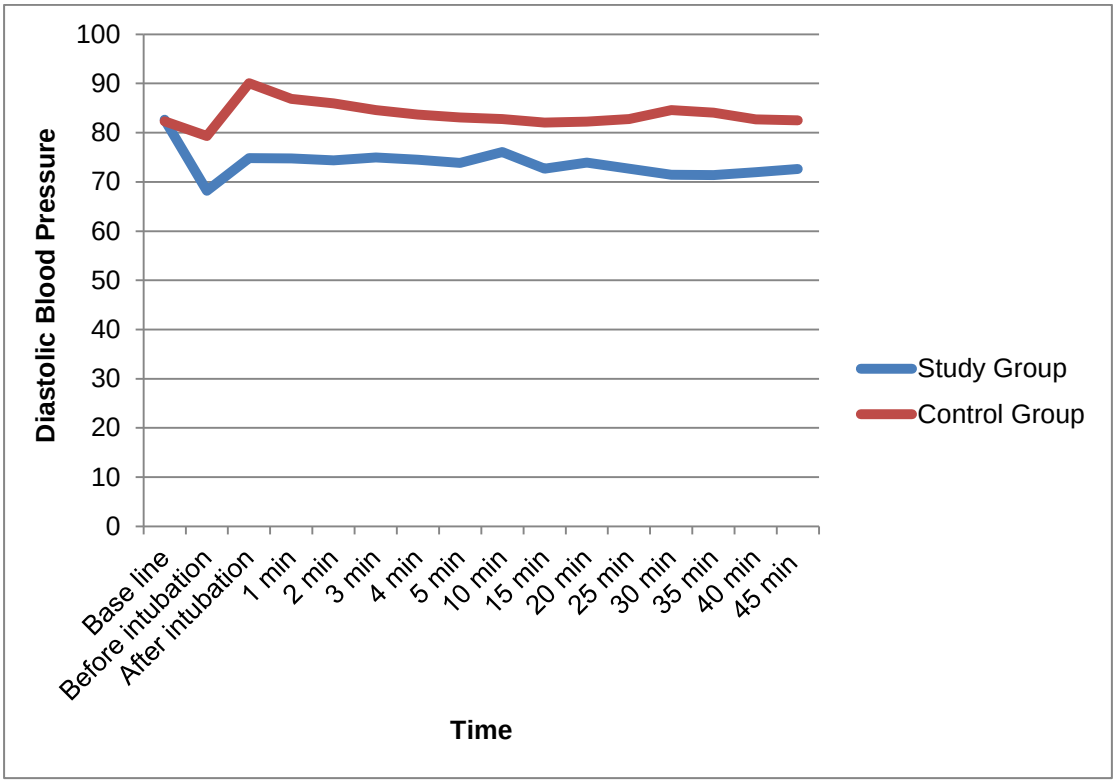


Fig-11: Time dependent changes in diastolic blood pressure in group-I and II patients

Table-9: Comparison of mean arterial pressure changes between groups at various time intervals

Time (min)	Mean arterial pressure (MEAN±SEM)		P value
	Group-I	Group-II	
Base line	97.80±1.15	97.46±7.03	0.834
Before intubation	80.62±0.75*	93.56±5.63	0.000
After intubation	87.50±0.75*	108.85±5.68	0.000
1 min	87.71±0.82*	105.86±6.63	0.000
2 min	87.49±0.75*	103.28±1.84	0.000
3 min	87.75±0.86*	101.60±7.44	0.000
4 min	87.20±0.87*	99.47±7.45	0.000
5 min	86.78±0.792*	100.78±7.24	0.000
10 min	87.94±0.87#	98.51±5.71	0.001
15 min	85.18±0.816#	97.27±4.79	0.001
20 min	85.00±1.40*	96.80±5.30	0.000
25 min	84.92±0.89*	96.79±5.70	0.000
30 min	83.84±0.89*	99.22±6.20	0.000
35 min	83.8±0.89*	99.34±5.14	0.000
40 min	84.41±.844*	97.90±3.70	0.000
45 min	84.41±0.76*	98.27±4.56	0.000

(*P<0.05 significant compared mean arterial pressure at different time intervals between group-I and II)

The above table shows that there was no significant difference in the baseline mean arterial pressure. Statistically highly significant reduction in mean arterial pressure occurred in dexmedetomidine group patients for all other readings from before intubation till 45 minutes. (The same is represented in the following graph).

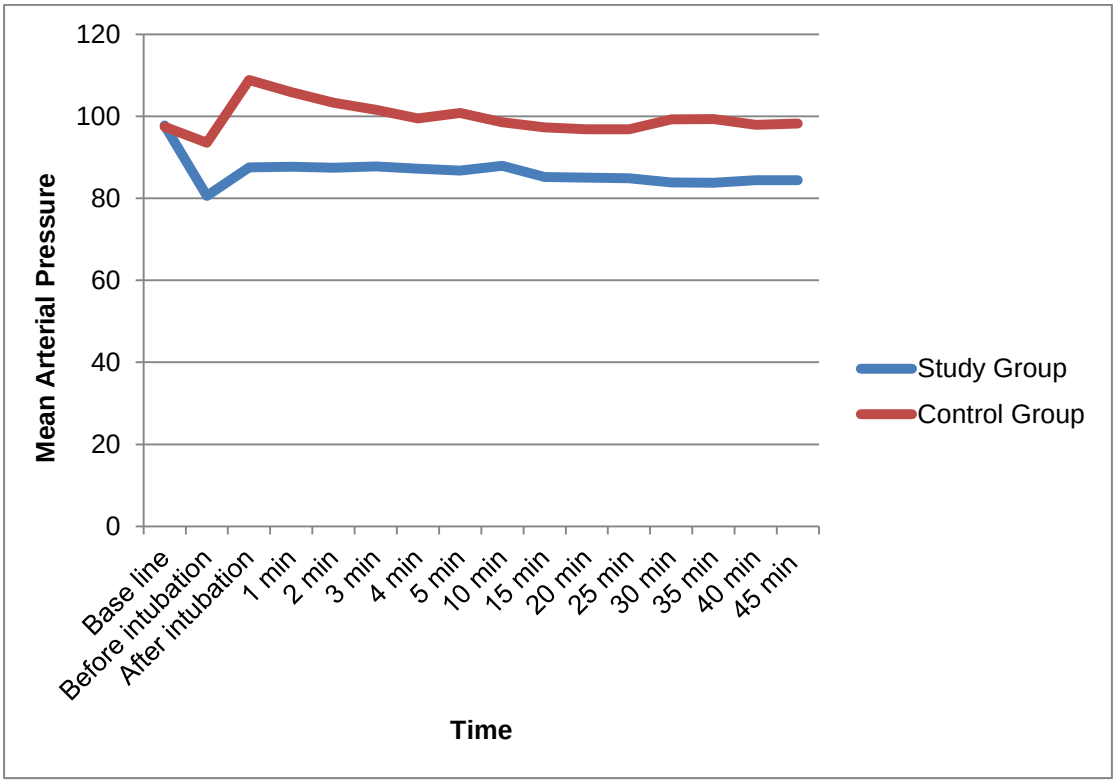


Fig-12: Comparison of mean arterial pressure changes between groups at various time intervals

Table No-10 : Comparison of Isoflurane concentration used in Study and Control Groups

Concentration of Isoflurane	Group-I (Study)		Group-II (Control)	
	Number	Percentage (%)	Number	Percentage (%)
0.0.5%	29	82.85	2	5.71
0.6-1%	6	17.14	15	42.85
>1%	0	0	18	57.43

Supplemental opioid requirement in the intraoperative period

Table No-11: No. of patients receiving supplemental Opioid in intraoperative period

Study Group		Control Group	
N	**%**	**N**	**%**
5	14.28	35	100

All patients in the control group required supplemental opioids, while 5 out of 35 patients in the study group required supplemental opioids.

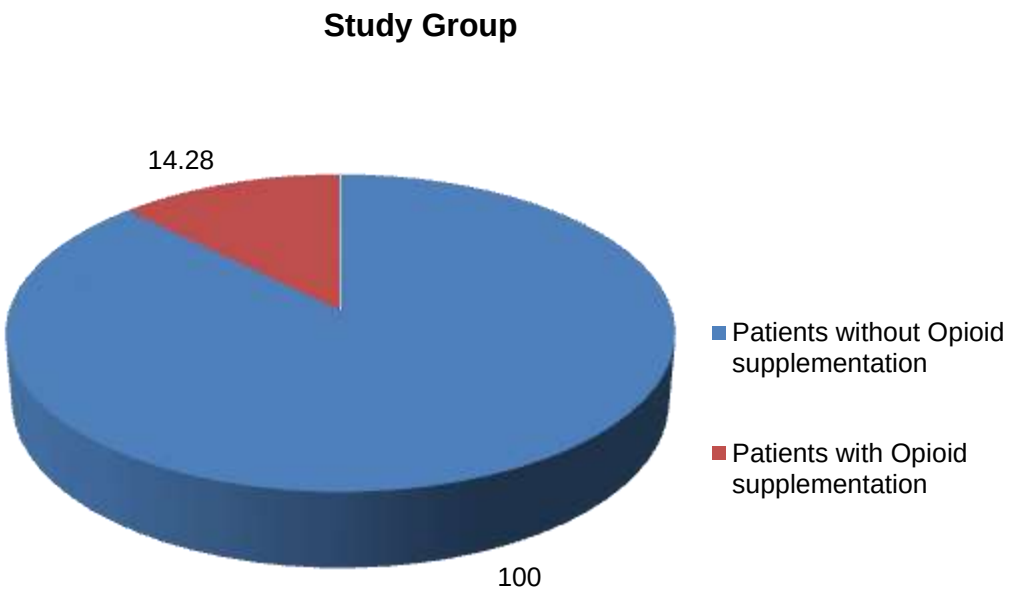


Fig-13: No. of patients receiving supplemental Opioid in intraoperative period

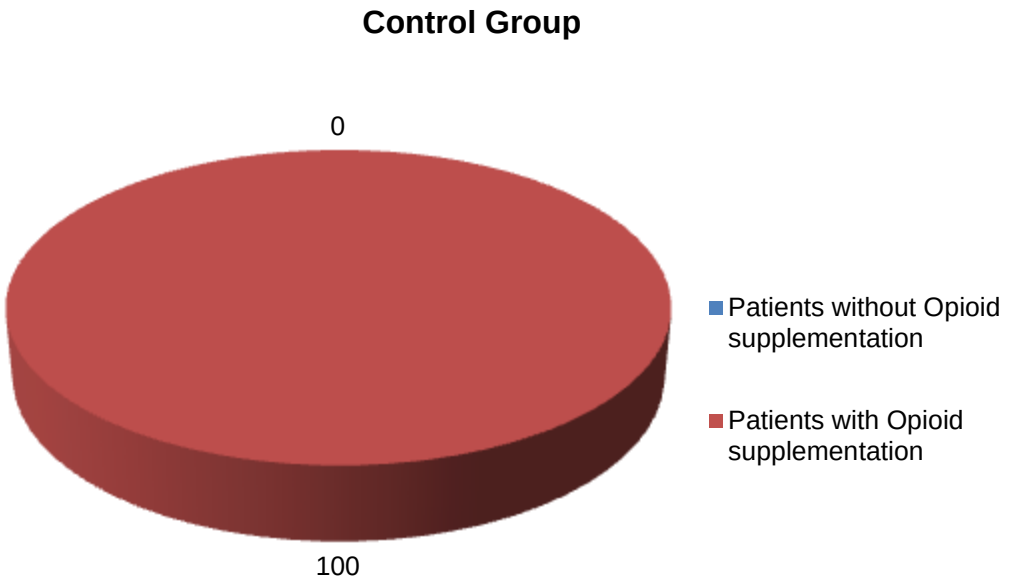


Fig-14: No. of patients receiving supplemental Opioid in intraoperative period

Side Effects

Two patients developed bradycardia in the study group but it settled without intervention.

None of the patients developed hypotension, hypertension or respiratory depression.

DISCUSSION

Laryngoscopy and tracheal intubation are considered as the most critical events during general anaesthesia, as they provoke a transient but significant, sympathetic and sympathoadrenal response. Various antihypertensive drugs are available for treating perioperative hypertension. Beta blockers like esmolol and metoprolol is commonly used to treat hypertensive episode, its use is complicated by bradycardia and conduction delays. Calcium channel blockers cause dose dependent cerebral vasodilatation, inhibition of auto regulation and higher incidence of hypotension. The final common pathway which leads to perioperative hypertension appears to be sympathetic nervous system activation. Alpha$_2$–adrenergic drugs like clonidine or dexmedetomidine reduce these potentially harmful cardiovascular responses during anaesthesia induction.

This prospective, randomized, double blind placebo controlled study was conducted to know whether dexmedetomidine, a newer alfa $_2$ -agonist, with additional properties such as sedation, anxiolysis and sympatholysis is effective for attenuating the hemodynamic response to laryngoscopy and endotracheal intubation. The study demonstrated that a loading dose of 1 mcg/kg of intravenous dexmedetomidine followed by continuous infusion of 0.4mcg/kg dexmedetomidine caused significant attenuation of heart rate and blood pressure response to laryngoscopy and intubation and also reduced intraoperative isoflurane and opioid requirement compared to control group receiving placebo.

Dexmedetomidine exhibits a unique pharmacological profile with sedation, sympatholysis, analgesia and haemodynamic stability along with the great advantage of avoiding respiratory depression. Dexmedetomidine offers a dose-dependent cooperative sedation which allows interaction with the patient. These above-said aspects of the pharmacological profile of dexmedetomidine render it suitable as an anaesthetic adjuvant and also for intensive care unit sedation.

In our study the two groups were comparable in terms of age, gender and weight. The pre-operative heart rate and blood pressure of the two groups were having no significant difference ($p > 0.05$). After infusion of dexmedetomidine, there was a fall in heart rate and blood pressure in the study group. Patients were sedated but arousable.

Lawrence et al,[87] found that a single dose of 2 mcg/kg of dexmedetomidine before induction of anaesthesia reduced the hemodynamic response to intubation as well as that to extubation. Bradycardia was seen at the 1^{st} and 5^{th} min after administration. This might have been due to relatively higher dose given as bolus administration. A former study evaluated different bolus doses of dexmedetomidine for premedication[110] and as recommended in literature we selected 1 ug/kg bolus dose. Given the property of the drug to cause hypotension or bradycardia when administered to patients, it is important to find out an infusion rate that would maximize the anaesthetic effect and analgesic sparing effect while minimizing the incidence of adverse cardiovascular effects which require therapeutic intervention.

During our study two patients developed bradycardia, which was self-limiting and did not require atropine.

Dexmedetomidine increases the cardiovascular stability by altering the stress-induced sympathoadrenal responses to endotracheal intubation, during surgery and during emergence from anaesthesia.[83] Jaakola *et al.*[85] in a study concluded that dexmedetomidine attenuates the increase in heart rate and blood pressure during endotracheal intubation.

Scheinin et al [83], studied the effect of dexmedetomidine on endotracheal intubation, required dose of induction agent and perioperative analgesic requirements. They concluded that the required dose of thiopentone was considerably lower in the dexmedetomidine group and the drug reduced the hemodynamic effects to endotracheal intubation. The concentration of noradrenaline in mixed venous plasma was lesser in the dexmedetomidine group. Varshali et al [86] showed that dexmedetomidine reduces sympathoadrenal response to endotracheal intubation and decreases perioperative anaesthetic requirements. The need for thiopentone and isoflurane reduced by 30% and 32% respectively in the dexmedetomidine group compared to control group.

Villela NR et al[80]) observed that anaesthetic consumption is reduced in the group given dexmedetomidine. Yildiz M et al [82] found out that preoperative administration of a single dose of dexmedetomidine reduced opioid and anaesthetic requirements. Hassan S[95] also observed in his study that the intra-operative

infusion of dexmedetomidine reduced the total dose of propofol and fentanyl required to maintain anaesthesia, offered a better control of intra-operative and postoperative hemodynamics, reduced postoperative pain level, reduced the total dose of morphine used and showed a better recovery profile compared to placebo.

In our study the concentration of isoflurane required during surgery was significantly lower in the study group compared to the control group. The intraoperative requirement of opioids was also significantly reduced in the study group. Only 5 out of 35 patients in the study group required supplemental opioid while all patients in control group required supplemental opioid.

In a prospective, randomized study by Menda F et al[29], dexmedetomidine was used for attenuation of hemodynamic response to tracheal intubation with low dose fentanyl and etomidate in patients undergoing myocardial revascularization receiving beta blocker treatment. In the dexmedetomidine group systolic, diastolic and mean arterial pressures were lower at all times compared to baseline values. After induction of anaesthesia, the decrease in heart rate was higher in dexmedetomidine group compared to placebo group. One minute after intubation, heart rate considerably increased in placebo group while, it reduced in the dexmedetomidine group. The incidence of hypertension requiring treatment was considerably higher in the placebo group. It is concluded that dexmedetomidine can be safely used to reduce the hemodynamic response to intubation in patients undergoing myocardial revascularization receiving beta blockers.

Sulaiman et al[181] conducted a similar study regarding the efficacy of intravenous dexmedetomidine for attenuation of haemodynamic responses to laryngoscopy and endotracheal intubation in patients having coronary artery disease. Dexmedetomidine at a dose of 0.5 mcg/kg as 10 minutes infusion administered before induction of general anaesthesia reduces the sympathetic response to laryngoscopy and endotracheal intubation in patients undergoing myocardial revascularization. The authors suggest that it can be administered even in patients receiving beta blockers. This confirms the observations in our study though we chose ASA I & II patients.

Similarly, Bajwa et al[88] demonstrated that the pressor response to laryngoscopy, intubation, surgery and extubation were effectively reduced by dexmedetomidine. The mean dose of fentanyl and isoflurane were also decreased significantly (>50%). The mean recovery time was also shorter in the dexmedetomidine group.

In our study the baseline values of heart rate and blood pressure were comparable in both groups. The maximal rise in heart rate and blood pressure occurred immediately after tracheal intubation when compared to the values before intubation in both groups. The dexmedetomidine group had a significantly lower mean heart rate 76.77± 7.63 after intubation compared to control group with mean heart rate of 100.37±1.31 ($p<0.002$). The study group also had lower heart rates at 1, 2, 3, 4, 5, 10 and 15 minutes after intubation compared to control group.

In comparison with the control group, the study group had a

smaller rise in systolic blood pressure after intubation with mean 112.80 ±1.43mm Hg in study group and mean of 147.31±6.6mm Hg in the control group. The values of systolic blood pressure returned to the values before intubation earlier in the study group. The mean systolic blood pressure was also maintained stable during the surgery in the dexmedetomidine group compared to placebo group.

Likewise the diastolic blood pressure and mean arterial pressure of both groups were having comparable baseline values. The values for both these parameters were near the value before intubation at all-time intervals for patients given dexmedetomidine. For the control group there was a significant rise in diastolic blood pressure and mean arterial pressure soon after intubation. Thus in our study pretreatment with dexmedetomidine 1mcg/kg over 10 minutes followed by continuous infusion of 0.4mcg/kg attenuated but not totally obtunded the cardiovascular response to tracheal intubation after induction of anaesthesia. It also maintained the haemodynamic stability during the surgery.

The present study findings corroborate with those of previous studies. No adverse cardiovascular effects from the drug were seen in our study.

CONCLUSION

Intravenous Dexmedetomidine can be used for attenuation of haemodynamic stress response to laryngoscopy and endotracheal intubation. It also causes reduction in intra operative anaesthetic requirement, without affecting intraoperative cardiovascular stability.

SUMMARY

This study was done to evaluate the effectiveness of intravenous dexmedetomidine in attenuating the haemodynamic stress response during laryngoscopy and intubation and haemodynamic stability during the surgery. 70 patients belonging to American Society of Anaesthesiology physical status classification 1 and 2 for either sex, between 18-55 years scheduled for elective surgeries were divided into two groups each consisting of 35 patients. After premedication, group I patients were given dexmedetomidine 1mcg/kg 10 minutes prior to induction followed by continuous infusion of 0.4mcg/kg dexmedetomidine till the end of surgery. All patients were induced with propofol, intubated using succinyl choline and were maintained with atracurium and isoflurane. Analgesic used was fentanyl. Group II patients received intravenous normal saline instead of dexmedetomidine.

Based on the results obtained in the study it can be concluded that dexmedetomidine causes statistically significant attenuation of the haemodynamic stress response to laryngoscopy and intubation and maintains the haemodynamic stability during surgery. Administration of dexmedetomidine also caused a significant reduction in isoflurane requirement during surgery. All patients in the study group were better sedated and cardiostable. The study group also had lesser requirement of intraoperative opioids.

In conclusion, intravenous dexmedetomidine significantly attenuates sympathoadrenal response to laryngoscopy and endotracheal intubation and also cause reduction in intra operative anaesthetic requirement, without affecting intraoperative cardiovascular stability

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APPENDIX I

INSTITUTIONAL HUMAN ETHICS COMMITTEE CLEARANCE

Sree Mookambika Institute of Medical Sciences
Kulasekharam (K.K District, TN) 629161
Phone No: 04651-280866. Fax No. 04651-280740

Institutional Human Ethics Committee

Ref. No. SMIMS/IHEC/2013/A/18 Date: 1st July 2013

Certificate

This is to certify that the Research Protocol Ref. No. **SMIMS/IHEC/2013/A/18,** entitled "A Study on the Effects of Intravenous Dexmedetomidine on the Hemodynamic Stress Response to Laryngoscopy and Endotracheal Intubation During General Anaesthesia" submitted by Dr. Rakhi S. P, Postgraduate of Department of Anaesthesiology, SMIMS has been approved by the Institutional Human Ethics Committee at its meeting held on 30th of May 2013.

[This Institutional Human Ethics Committee is organized and operates according to the requirements of ICH-GCP/GLP guidelines and requirements of the Amended Schedule-Y of Drugs and Cosmetics Act, 1940 and Rules 1945 of Government of India.]

IHEC

Dr. Rema Menon. N
Member Secretary
Institutional Human Ethics Committee
Professor of Pharmacology and HOD
SMIMS, Kulasekharam (K.K District).
Tamil Nadu -629161

APPENDIX II

INFORMED WRITTEN CONSENT FORM

PART 1 OF 2

INFORMATION FOR PARTICIPANTS OF THE STUDY

Dear Volunteers,

We welcome you and thank for your keen interest in participation in this research project. Before you participate in this study, it is important for you to understand why this research is being carried out. This form will provide you all the relevant details of this research. It will explain the nature, the purpose the benefits, the risks, the discomforts, the precautions and the information about how this project will be carried out. It is important that you can read and understand the contents of the form carefully. This form may contain certain scientific terms and hence, if you have any doubts or if you want more information, you are to ask the study personnel or the contact person mentioned below before you give your consent and also at any time during the entire course of the project.

1. **Name of the Principal Investigator**: **Dr.Rakhi S.P.**

   Junior Resident
   Department of Anaesthesiology
   Sree Mookambika Institute of
   Medical Sciences, Kulasekharam.

2. **Name of the Guide:** : **Dr.V.G.Jayaprakash**

   Professor,
   Department of Anaesthesiology,
   Sree Mookambika Institute of
   Medical Sciences, Kulasekharam.

3. Institute : Details with Address

Sree Mookambika Institute of Medical Sciences,
Kulasekharam, Kanyakumari district – 629161
Tamil Nadu.

4. **Title of the study**:

Effects of intravenous Dexmedetomidine on the haemodynamic stress response to Laryngoscopy and Endotracheal intubation during general anaesthesia.

5. **Back ground Information**:-

Laryngoscopy and endotracheal intubation is to be done during general anesthesia. This can lead to an increase in heart rate and blood pressure. Various drugs have been used to reduce this stress response. Dexmedetomidine is an alpha2 adrenergic agonist which has sedative, anxiolytic and analgesic properties.

6. Aims and Objectives:

a. To know if Dexmedetomidine can reduce the haemodynamic stress response to laryngoscopy and intubation during general anesthesia.

b. To assess the haemodynamic stability throughout surgery when Dexmedetomidine is used.

7. Scientific justification of the study:

Maintenance of stable haemodynamics throughout the surgery is very important. The haemodynamic stress response to laryngoscopy and intubation is

dangerous especially in patients with cardiovascular disease. Increase in heart rate and blood pressure will increase the myocardial contractility and myocardial oxygen consumption. This stress response can be reduced using various drugs like lignocaine, Beta blockers, nifedipine etc. Dexmedetomidine is an alpha2 agonist with additional sedative, anxiolytic and analgesic properties which are useful in anaesthesia.

8. Procedure for the study:

General anesthesia has different steps. Premedication will be given with Inj. Midazolam, Inj .Fentanyl, Inj. Glycopyrrolate. Dexmedetomidine 1 microgram/kg iv over 10 minutes will be started before induction of anesthesia and will be continued as a continuous infusion at the rate of 0.4 microgram/kg/hour throughout the surgery. Induction of anesthesia will be done with Inj. Propofol 2mg/kg. Inj. Succinyl choline 1.5-2mg/kg will be used as the muscle relaxant for intubation. Anaesthesia will be maintained with intermittent positive pressure ventilation with 0_2, N_20 and isoflurane. Inj. Atracurium 0.6mg/kg will be given for maintenance of muscle relaxation. The selected patients for the study will be divided in to 2 groups of 35 pts each. Patients of Group I will receive Dexmedetomidine while patients of Group II will receive distilled water as placebo instead of Dexmedetomidine. All other steps of anesthesia are similar in both groups.

9. Expected risks for the participants:

Hypotension and bradycardia may occur.

10. **Expected benefits of research for the participants**:

There may not be any personal benefits, but this study will be beneficial for the betterment of the Health Sector.

11. Maintenance of Confidentiality:

All data collected for the study will be kept confidentially and would reflect on general statistical evaluation only and would not reveal any personal details.

12. **Why have you been chosen to be in the study?**

You are undergoing general anaesthesia and fulfill the criteria of selection.

13. **How many people will be in the study?** :

70

14. A**greement of compensation to the participant**:

Yes.

15. **Anticipated prorated payment, if any, to the participant(s) of the study:**

Nil

16. **Can I withdraw from the study at any time during the study period?** :

Yes

17. **If there is any new findings/information, would I be informed? :**

Yes

18. **Expected duration of Participant's participation in the study:**

Throughout the surgery.

19. Any other pertinent information:

No

20. **Whom do I contact for further information?: Dr. Rakhi S.P**

For any study related queries, you are free to contact

Dr.Rakhi S.P.

Junior Resident

Department of Anaesthesiology

Sree Mookambika Institute of Medical Sciences,

Kulasekharam

Mobile No.9626124177

Email ID - rakhispk@gmail.com

Place:

Date: Signature of Principal Investigator

Signature of the Participant

CONSENT FORM

PART 2 OF 2

PARTICIPANTS CONSENT FORM

The details of the study have been explained to me in writing and the details have been fully explained to me. I am aware that the results of the study may not be directly beneficial to me but will help in the advancement of medical science. I confirm that I have understood the study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason. Without the medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the study titled "Effects of intravenous Dexmeditomidine on the haemodynamic stress response to laryngoscopy and endotracheal intubation during general anesthesia".

Name of the Participant: **Address of the Participant:**

Contact Number of the Participant:

Signature/ Thumb impression of the participant/ Legal guardian

Witnesses:

1.

2.

Date:

Place:

APPENDIX III

PROFORMA FOR THE STUDY

Name of the patient:

Age:

Sex:

IP Number:

Surgical Diagnosis:

Proposed Surgery:

Relevant history:

History of drug allergy, drug reaction, previous surgeries:

GENERAL EXAMINATION

Height: Weight:

Pallor: Icterus: Cyanosis: Clubbing:

Lymphadenopathy:

Edema:

Any other relevant findings:

Pulse rate:

Blood pressure:

Temperature:

SYSTEMIC EXAMINATION

Examination of Cardiovascular system:

Examination of Respiratory system:

Examination of Gastrointestinal system:

Examination of Central Nervous system:

ASSESSMENT OF AIRWAY

Mallampati grade:

Thyro-mental distance:

Mouth opening distance:

Neck – range of motion:

Teeth:

Facial hair:

Morbid obesity:

Short muscular neck:

Micrognathia:

INVESTIGATIONS

Haematological:

Haemoglobin, total count, differential count, ESR

Bleeding time, Clotting time

Blood sugar

Blood urea, Serum creatinine

HIV, HBsAg

Urine examination for sugar, albumin and microscopy

ECG

Chest X-ray- PA view if needed.

ASA physical status

Premedication:

Intra-operative monitoring: pulse rate, blood pressure, peripheral oxygen saturation, end tidal carbondioxide.

APPENDIX IV

CASE RECORD FORM

Name : Age: Sex:

Weight:

I.P No:

Diagnosis :

Procedure:

American Society of Anaesthesiologists Class:

Drugs given:

Tab. Ranitidine 150mg at 10pm & 6am.

Tab. Metoclopramide 10mg at 10pm & 6am.

Inj. Midazolam 2mg iv

Inj. Glycopyrrolate 0.2mg iv

Inj. Fentanyl mcg iv

Inj. Dexmedetomidine mcg (1mcg/kg) iv over 10 minutes started at

Inj. Dexmedetomidine mcg(0.4mcg/kg) as continuous iv infusion started at

Inj. Propofol mg iv

Inj. Succinyl choline mg iv

Inj. Atracurium mg iv at

Oxygen : Nitrous oxide

Isoflurane

Inj. Neostigmine mg iv

Inj. Glycopyrrolate mg iv

Time	Heart Rate (/min)	Blood Pressure	SpO2(%)	EtCO2(mmHg)

APPENDIX V

HEART RATE - DEXMEDETOMIDINE GROUP																
Sl. No	**Baseline**	**Before Intubation.**	**After Intubation.**	**1 min.**	**2 min.**	**3 min.**	**4 min.**	**5 min.**	**10 min.**	**15 min.**	**20 min.**	**25 min.**	**30 min.**	**35 min.**	**40 min.**	**45 min.**
1	94	82	86	84	83	80	76	78	80	82	82	80	78	80	81	82
2	106	82	92	94	86	84	82	80	80	78	78	80	82	78	72	84
3	76	60	78	72	70	66	64	66	68	68	66	64	64	66	64	66
4	86	70	84	82	76	74	72	70	70	72	72	70	70	70	71	72
5	66	52	68	66	64	58	58	60	58	59	60	60	58	59	60	60
6	74	62	70	68	68	66	60	62	62	63	62	64	64	65	66	66
7	68	52	64	62	61	58	54	58	58	60	58	59	60	62	62	60
8	80	66	74	72	70	66	62	62	64	64	61	62	62	60	62	64
9	94	76	86	82	80	74	72	74	72	72	74	72	74	75	75	76
10	80	64	76	74	72	68	66	66	68	66	66	67	67	65	65	66
11	72	62	74	72	70	66	64	66	68	68	66	68	66	68	69	68
12	78	62	68	66	66	64	64	66	66	68	68	68	66	65	67	68
13	72	60	66	64	64	62	62	62	60	60	61	62	62	63	63	64
14	78	64	72	70	68	64	68	68	66	67	67	68	68	66	66	68
15	74	62	70	68	66	64	68	70	68	68	67	67	68	67	68	66
16	90	74	82	84	82	76	74	74	72	72	73	74	75	76	78	77
17	80	66	72	76	72	68	64	66	69	68	67	69	68	66	66	68
18	102	84	92	90	86	84	82	80	80	82	81	82	82	80	82	80
19	80	68	74	72	70	74	70	72	72	72	70	70	68	70	72	71
20	100	78	84	86	83	78	74	76	74	74	75	76	76	78	78	76
21	80	64	76	74	70	66	64	66	66	65	64	64	65	66	66	68
22	92	74	86	84	78	76	70	70	71	71	72	73	72	73	74	74
23	74	62	72	74	71	68	68	70	70	70	68	68	70	70	72	72
24	94	74	82	84	76	74	70	72	72	72	70	70	71	71	72	71
25	80	66	74	72	68	66	64	64	65	65	66	66	65	65	66	66
26	94	74	84	86	84	82	80	80	82	82	80	80	82	82	81	82
27	80	60	66	68	66	64	64	66	64	65	66	66	67	66	67	67
28	90	74	84	86	82	78	72	74	72	72	73	74	74	73	73	72
29	84	66	84	86	80	76	74	74	76	76	75	75	74	76	74	74
30	86	72	80	78	78	75	76	76	75	75	76	77	77	76	75	75
31	98	68	80	78	80	76	74	74	74	76	76	75	75	76	76	74
32	92	75	78	80	82	82	78	80	80	78	78	77	77	78	78	72
33	72	65	67	68	72	70	70	70	68	68	70	70	68	67	78	70
34	70	65	68	70	68	69	68	68	66	66	68	68	66	65	86	64
35	88	68	74	72	72	70	72	70	71	71	72	72	70	70	70	72

HEART RATE - CONTROL GROUP																
Sl. No	**Baseline**	**Before Intubation.**	**After Intubation.**	**1 min.**	**2 min.**	**3 min.**	**4 min.**	**5 min.**	**10 min.**	**15 min.**	**20 min.**	**25 min.**	**30 min.**	**35 min.**	**40 min.**	**45 min.**
1	94	105	114	110	104	104	96	76	94	90	92	98	94	90	86	86
2	72	80	98	96	95	88	83	82	80	82	84	82	80	78	78	76
3	67	80	90	94	88	80	76	76	74	75	72	72	74	76	74	74
4	74	85	106	102	96	84	78	80	82	80	88	88	86	84	84	86
5	112	116	130	128	120	116	112	112	110	110	108	106	100	106	108	110
6	69	78	96	94	88	84	76	78	80	84	80	78	96	76	75	78
7	76	86	95	93	88	84	78	80	82	82	80	88	92	90	84	82
8	78	90	106	108	96	88	88	86	86	86	84	90	88	86	82	82
9	76	84	97	96	88	84	80	78	76	76	80	82	84	82	82	78
10	84	90	113	112	104	96	96	84	82	84	90	98	94	90	86	88
11	86	93	112	98	96	94	92	92	92	98	94	92	88	88	86	86
12	92	100	126	124	106	96	92	90	94	98	98	104	102	98	96	90
13	70	86	98	94	92	90	82	80	80	84	84	82	82	80	82	84
14	88	94	102	98	96	94	92	90	88	86	90	96	94	90	86	86
15	82	98	116	110	104	98	88	90	86	86	90	94	90	88	86	84
16	86	93	106	98	96	92	86	88	88	86	88	88	86	94	84	84
17	64	76	86	84	78	74	72	74	76	78	82	84	86	78	78	76
18	72	80	94	90	86	84	82	82	80	80	84	88	88	84	82	82
19	88	94	110	106	102	94	90	90	94	98	94	92	92	88	88	86
20	102	104	112	110	104	102	104	102	100	98	104	102	106	108	106	104
21	72	75	86	84	80	78	76	76	74	72	76	78	82	84	80	78
22	86	88	96	94	92	90	92	90	90	98	90	92	88	88	86	86
23	78	86	88	82	80	78	70	74	74	76	80	78	76	74	78	82
24	72	78	86	83	80	76	77	80	82	88	86	82	78	78	76	76
25	108	112	126	124	118	104	100	104	104	98	96	10	102	98	96	94
26	64	76	88	84	82	76	70	72	72	74	70	74	78	76	74	72
27	68	72	84	82	76	74	68	88	70	68	66	66	68	72	74	60
28	72	76	82	86	84	82	76	76	78	82	86	82	80	80	78	78
29	78	82	96	94	90	83	80	84	86	88	86	86	82	82	80	78
30	72	82	88	85	82	78	75	76	76	78	88	90	86	84	82	80
31	90	88	94	100	102	102	100	102	98	96	92	90	96	92	88	88
32	84	86	96	99	104	104	102	100	98	96	96	94	94	90	96	90
33	104	108	112	116	118	118	114	112	110	112	108	106	104	112	108	102
34	97	96	106	108	110	110	106	104	102	98	98	96	102	108	102	98
35	70	70	78	80	82	80	82	80	82	80	78	84	88	84	86	80

SYSTOLIC BLOOD PRESSURE - DEXMEDETOMIDINE GROUP																
Sl. No	Baseline	Before Intubation.	After Intubation.	1 min.	2 min.	3 min.	4 min.	5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	35 min.	40 min.	45 min.
1	140	118	122	124	122	120	120	120	120	120	116	116	118	118	114	116
2	130	110	116	118	118	120	118	118	122	118	116	116	114	116	118	118
3	130	106	116	118	118	120	116	118	118	114	116	112	114	112	114	116
4	122	98	104	106	106	106	106	108	110	108	108	106	104	106	108	108
5	140	112	120	122	120	120	120	118	112	116	118	120	128	122	118	116
6	110	92	104	104	104	104	102	100	98	100	102	102	100	98	100	98
7	120	100	110	110	110	108	106	106	106	104	102	102	104	104	106	108
8	118	102	108	110	110	106	104	106	104	102	104	100	100	102	104	106
9	124	104	110	112	112	112	110	110	110	108	106	103	104	106	106	110
10	142	118	126	128	128	128	128	124	122	120	118	122	124	124	126	124
11	128	100	106	108	108	108	108	106	106	110	108	106	104	106	104	106
12	132	104	112	112	112	114	114	112	116	114	114	112	110	110	108	110
13	134	114	120	122	124	124	124	124	124	123	120	118	118	116	118	116
14	138	102	128	126	128	128	124	124	126	123	122	120	118	120	118	120
15	124	98	110	110	110	110	112	112	112	110	10	104	102	102	106	108
16	118	98	104	104	106	106	106	104	104	102	100	100	98	96	96	98
17	112	92	108	108	108	104	106	106	104	100	100	102	98	98	100	102
18	110	100	98	100	100	100	100	100	100	98	96	94	94	94	96	98
19	120	118	108	108	108	110	106	108	106	104	104	102	102	104	108	114
20	142	102	126	128	128	128	130	130	124	124	136	130	126	124	120	124
21	124	96	108	108	108	110	110	108	108	104	104	106	102	104	106	104
22	118	98	102	102	104	100	100	98	98	94	94	96	98	98	100	98
23	120	122	106	106	102	100	104	106	106	106	100	100	98	96	98	102
24	148	130	128	130	130	130	128	126	120	118	128	136	130	126	124	126
25	124	100	110	106	104	104	100	102	102	100	100	98	102	102	104	106
26	132	104	112	112	114	116	110	112	110	114	120	126	120	118	112	112
27	136	106	112	112	114	116	114	116	118	114	114	110	108	108	110	112
28	134	108	116	116	116	116	114	112	112	110	106	104	106	108	112	114
29	126	100	108	108	110	110	108	108	104	102	100	100	102	104	100	102
30	128	100	108	108	108	110	106	104	104	102	100	108	100	100	100	102
31	124	98	108	112	112	102	112	112	112	110	110	108	110	112	118	120
32	118	96	102	104	105	104	102	106	110	110	102	100	96	96	98	98
33	150	126	130	132	128	128	126	128	122	118	118	116	122	122	120	118
34	138	112	120	120	120	122	122	124	120	118	120	116	114	114	114	112
35	132	110	122	120	124	122	124	124	120	118	118	118	116	120	120	118

DIASTOLIC BLOOD PRESSURE - DEXMEDETOMIDINE GROUP																
Sl. No	Baseline	Before Intubation.	After Intubation.	1 min.	2 min.	3 min.	4 min.	5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	35 min.	40 min.	45 min.
1	90	76	86	80	80	80	80	80	82	80	78	78	80	78	80	80
2	86	70	78	78	78	80	80	82	80	78	78	76	74	74	72	74
3	84	72	80	80	80	82	82	82	80	80	78	76	74	72	70	72
4	80	68	76	78	76	78	76	76	74	72	72	70	70	68	68	68
5	86	70	78	78	76	78	76	76	80	78	78	76	74	76	78	78
6	72	62	68	68	68	70	70	70	70	68	66	66	64	64	66	66
7	82	64	68	68	70	70	70	70	70	70	68	70	68	68	70	70
8	82	68	74	74	74	74	74	74	80	76	78	80	80	80	78	80
9	86	70	78	78	78	80	80	80	80	76	78	76	74	74	74	76
10	86	72	80	80	82	80	82	82	80	78	80	78	78	76	78	80
11	72	62	68	70	70	72	70	70	68	66	66	64	64	66	68	70
12	86	72	78	78	78	80	82	80	78	78	80	82	78	76	78	78
13	82	64	70	70	70	70	70	70	78	70	76	74	72	72	74	74
14	86	68	74	74	72	72	72	70	80	68	76	70	70	80	80	80
15	82	66	72	72	72	74	70	70	78	70	74	74	70	70	68	68
16	84	66	70	70	70	70	70	70	76	66	70	70	70	68	68	70
17	82	68	76	70	70	70	70	70	68	66	66	64	62	64	64	68
18	74	64	70	70	70	70	70	68	68	66	66	66	68	70	70	70
19	80	64	72	74	74	74	76	76	76	74	74	72	70	70	72	72
20	86	70	78	78	80	80	84	78	80	80	84	78	78	76	78	80
21	84	70	78	80	80	80	80	78	78	76	76	74	74	72	72	70
22	78	70	78	70	70	72	72	72	74	72	70	70	68	70	70	72
23	70	62	72	72	72	68	68	68	66	66	64	68	70	66	64	62
24	86	64	70	72	68	70	72	70	78	70	76	72	68	72	70	72
25	82	68	78	78	78	78	80	78	78	76	76	74	72	72	72	70
26	78	62	68	70	70	70	70	70	74	74	72	70	68	64	66	66
27	92	70	78	78	76	78	78	76	84	72	82	70	72	72	72	70
28	90	72	78	78	78	70	70	70	78	72	78	76	70	70	78	80
29	86	70	76	74	76	78	78	78	76	76	74	74	70	70	72	72
30	86	72	74	78	78	78	80	80	76	76	74	80	78	78	76	74
31	90	74	78	78	76	76	72	70	76	74	74	74	72	70	70	72
32	70	66	78	72	72	70	64	68	66	62	62	64	64	64	68	68
33	98	78	74	84	76	86	74	74	76	78	76	74	74	74	70	70
34	72	62	70	70	70	72	72	70	78	66	74	70	70	70	72	74
35	82	70	76	76	76	74	74	70	78	74	74	74	72	72	74	76

MEAN ARTERIAL PRESSURE - DEXMEDETOMIDINE GROUP																
Sl. No	Baseline	Before Intubation.	After Intubation.	1 min.	2 min.	3 min.	4 min.	5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	35 min.	40 min.	45 min.
1	106.67	90.00	98.00	94.67	94.00	93.33	93.33	93.33	94.67	93.33	90.67	90.67	92.67	91.33	91.33	92.00
2	100.67	83.33	90.67	91.33	91.33	93.33	92.67	94.00	94.00	91.33	90.67	89.33	87.33	88.00	87.33	88.67
3	99.33	83.33	92.00	92.67	92.67	94.67	93.33	94.00	92.67	91.33	90.67	88.00	87.33	85.33	84.67	86.67
4	94.00	78.00	85.33	87.33	86.00	87.33	86.00	86.67	86.00	84.00	84.00	82.00	81.33	80.67	81.33	81.33
5	104.00	84.00	92.00	92.67	90.67	92.00	90.67	90.00	90.67	90.67	91.33	90.67	92.00	91.33	91.33	90.67
6	84.67	72.00	80.00	80.00	80.00	81.33	80.67	80.00	79.33	78.67	78.00	78.00	76.00	75.33	77.33	76.67
7	94.67	76.00	82.00	82.00	83.33	82.67	82.00	82.00	82.00	81.33	79.33	80.67	80.00	80.00	82.00	82.67
8	94.00	79.33	85.33	86.00	86.00	84.67	84.00	84.67	88.00	84.67	86.67	86.67	86.67	87.33	86.67	88.67
9	98.67	81.33	88.67	89.33	89.33	90.67	90.00	90.00	90.00	86.67	87.33	85.00	84.00	84.67	84.67	87.33
10	104.67	87.33	95.33	96.00	97.33	96.00	97.33	96.00	94.00	92.00	92.67	92.67	93.33	92.00	94.00	94.67
11	90.67	74.67	80.67	82.67	82.67	84.00	82.67	82.00	80.67	80.67	80.00	78.00	77.33	79.33	80.00	82.00
12	101.33	82.67	89.33	89.33	89.33	91.33	92.67	90.67	90.67	90.00	91.33	92.00	88.67	87.33	88.00	88.67
13	99.33	80.67	86.67	87.33	88.00	88.00	88.00	88.00	93.33	87.67	90.67	88.67	87.33	86.67	88.67	88.00
14	103.33	79.33	92.00	91.33	90.67	90.67	89.33	88.00	95.33	86.33	91.33	86.67	86.00	93.33	92.67	93.33
15	96.00	76.67	84.67	84.67	84.67	86.00	84.00	84.00	89.33	83.33	52.67	84.00	80.67	80.67	80.67	81.33
16	95.33	76.67	81.33	81.33	82.00	82.00	82.00	81.33	85.33	78.00	80.00	80.00	79.33	77.33	77.33	79.33
17	92.00	76.00	86.67	82.67	82.67	81.33	82.00	82.00	80.00	77.33	77.33	76.67	74.00	75.33	76.00	79.33
18	86.00	76.00	79.33	80.00	80.00	80.00	80.00	78.67	78.67	76.67	76.00	75.33	76.67	78.00	78.67	79.33
19	93.33	82.00	84.00	85.33	85.33	86.00	86.00	86.67	86.00	84.00	84.00	82.00	80.67	81.33	84.00	86.00
20	104.67	80.67	94.00	94.67	96.00	96.00	99.33	95.33	94.67	94.67	101.33	95.33	94.00	92.00	92.00	94.67
21	97.33	78.67	88.00	89.33	89.33	90.00	90.00	88.00	88.00	85.33	85.33	84.67	83.33	82.67	83.33	81.33
22	91.33	79.33	86.00	80.67	81.33	81.33	81.33	80.67	82.00	79.33	78.00	78.67	78.00	79.33	80.00	80.67
23	86.67	82.00	83.33	83.33	82.00	78.67	80.00	80.67	79.33	79.33	76.00	78.67	79.33	76.00	75.33	75.33
24	106.67	86.00	89.33	91.33	88.67	90.00	90.67	88.67	92.00	86.00	93.33	93.33	88.67	90.00	88.00	90.00
25	96.00	78.67	88.67	87.33	86.67	86.67	86.67	86.00	86.00	84.00	84.00	82.00	82.00	82.00	82.67	82.00
26	96.00	76.00	82.67	84.00	84.67	85.33	83.33	84.00	86.00	87.33	88.00	88.67	85.33	82.00	81.33	81.33
27	106.67	82.00	89.33	89.33	88.67	90.67	90.00	89.33	95.33	86.00	92.67	83.33	84.00	84.00	84.67	84.00
28	104.67	84.00	90.67	90.67	90.67	85.33	84.67	84.00	89.33	84.67	87.33	85.33	82.00	82.67	89.33	91.33
29	99.33	80.00	86.67	85.33	87.33	88.67	88.00	88.00	85.33	84.67	82.67	82.67	80.67	81.33	81.33	82.00
30	100.00	81.33	85.33	88.00	88.00	88.67	88.67	88.00	85.33	84.67	82.67	89.33	85.33	85.33	84.00	83.33
31	101.33	82.00	88.00	89.33	88.00	84.67	85.33	84.00	88.00	86.00	86.00	85.33	84.67	84.00	86.00	88.00
32	86.00	76.00	86.00	82.67	83.00	81.33	76.67	80.67	80.67	78.00	75.33	76.00	74.67	74.67	78.00	78.00
33	115.33	94.00	92.67	100.00	93.33	100.00	91.33	92.00	91.33	91.33	90.00	88.00	90.00	90.00	86.67	86.00
34	94.00	78.67	86.67	86.67	86.67	88.67	88.67	88.00	92.00	83.33	89.33	85.33	84.67	84.67	86.00	86.67
35	98.67	83.33	91.33	90.67	92.00	90.00	90.67	88.00	92.00	88.67	88.67	88.67	86.67	88.00	89.33	90.00

MEAN ARTERIAL PRESSURE - CONTROL GROUP																
Sl. No	Baseline	Before Intubation.	After Intubation.	1 min.	2 min.	3 min.	4 min.	5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	35 min.	40 min.	45 min.
1	102.66	100	117.33	118	83.33	106.66	102.66	106.66	104	101.33	97.33	98.66	104.67	100.67	98	99.33
2	99.33	99.33	112	109.33	80	104.66	100	100.66	96.67	96	100.67	94.66	92.67	95.33	95.33	96
3	101.33	94.66	112	110	76.66	100.66	101.33	100.66	98	100.67	98.67	96.67	98	98.67	96	95.33
4	96	98	109.33	107.33	78.66	102.66	99.33	102.66	102	102	104	98	100.67	102.67	95.67	96
5	101.3	94	115.33	113.33	80.66	102.66	101.33	101.33	98.67	96.67	94	92.67	98.67	102	101.33	100
6	96.6	93.33	106	101.33	72.66	100	96	96.66	93.33	101.33	98.67	96.67	98.67	100	98	96.67
7	100	98	108	103.33	74	99.33	100	98.66	96.67	96	94	94	94.67	96	99.33	98.67
8	98	98.66	112.66	109.33	73.33	102.66	97.33	100	98	95.33	94.67	95.33	94.67	94.66	96.67	99.33
9	100	92	108	105.33	74.66	101.33	100	100.66	96.67	95.33	94	94.67	101.33	103.33	100	98
10	96	94	111.33	101.33	74	99.33	96.66	98.66	96	94.66	93.33	94.67	96.67	96	96.67	98.67
11	102.66	96.33	114.67	110	79.33	106	101.33	102.66	100	98.66	96.67	104.67	108.67	104	102	100.67
12	101.33	96	114.67	108	76	111.33	100	96	98	96	4.6794.6	96	98.67	100	98	98.67
13	91.33	82	106	103	70.68	98.66	93.33	100.66	94.67	93.33	94	98	96	91.33	100	98
14	98.66	94	111.33	106	74.66	102	103.33	98.66	98	96.66	94.67	94.67	96	102.67	100	98
15	96.33	88	103.13	100	72	99.33	94.66	92	96.67	94	93.33	92	96	98.67	98.67	96.67
16	88	86	102.66	98.66	68.66	91.33	88.66	94.66	92.67	90	88.67	89.33	98.67	96.67	93.33	90.67
17	93.33	89.33	102.66	100	69.33	96.66	92.66	96	94.67	98.67	97.33	98.67	100	98.67	99.33	97.67
18	80.66	90.66	107.33	100.66	70	98	92	96.66	96	93.33	94	94	102.67	106.67	100.67	98.67
19	93.33	88	108	105.33	74	95.33	94	94	94	91.33	89.33	92	94.67	95.33	96.67	105.33
20	88.33	87.33	100.66	94.66	68.66	93.33	92.66	89.33	91.33	88.67	87.33	85.33	85.33	87.33	90.67	92.67
21	87.33	86	96	96.33	68	89.33	89.33	92	89.33	92.67	95.33	92	92	93.33	93.33	94.67
22	102	93.33	98	98	69.33	90	89.66	100	94	90	90	89.33	91.33	94	92	89.33
23	106	101.33	106.66	103.33	73.33	100.66	100.66	102.66	97.33	94.67	92	92.67	96	94.66	93.33	98
24	96.66	89.33	117.33	106.66	75.66	101.33	104	98.66	100	100	99.33	100.67	105.33	103.33	100	101.33
25	96	91.33	107.33	102.66	72	98.66	98	96	96.67	95.33	96	97.33	97.33	102.67	99.33	96.67
26	96.33	96	106.66	103.33	72	96.66	94.66	98	96.67	96.67	101.33	96.67	99.33	97.33	98.67	97.33
27	101.33	96	110.66	105.33	74.66	97.33	98	100.66	98	96.67	94.67	97.33	101.33	102	102.67	100
28	96	93.33	110	101.33	73.33	101.33	101.33	92.33	100.67	100	100.67	100.67	104.67	103.33	102	102
29	100	94.66	108	101.33	70	97.33	94.66	99.33	94.67	94.67	95.33	93.67	101.67	94	94	95.33
30	109	98.66	108.66	106	45.33	99.33	98	117.33	99.33	99.33	99.33	97.33	89.67	99	98	96
31	109.33	104	119.33	121.33	12.66	119.33	119.33	116.33	114	111.33	109.33	110	116	112.83	94.44	105.33
32	106.68	101.33	106.66	117.33	119.33	118.66	116.66	105.33	114	108	112.67	109.33	112.33	110	100.67	108
33	89.33	84.66	106	108	108	107.33	106	116.33	100.67	100.66	100	98	101.33	97.33	94	92
34	81.33	83.33	104	106	106	104.66	103.33	105	102.67	101.33	99.33	98.67	99.33	99.33	98	96
35	108.66	102	121.33	123.33	123.33	122.66	120.66	120	114	103.33	103.33	113.33	108	103.33	110	112.67

SYSTOLIC BLOOD PRESSURE - CONTROL GROUP																
Sl. No	Baseline	Before Intubation.	After Intubation.	1 min.	2 min.	3 min.	4 min.	5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	35 min.	40 min.	45 min.
1	140	144	164	166	160	152	150	144	140	132	128	136	134	130	126	134
2	134	130	160	164	156	146	146	138	130	128	126	120	118	126	130	132
3	132	124	156	154	144	134	134	134	130	126	124	122	126	132	128	126
4	124	126	152	154	150	148	148	144	138	130	128	122	134	140	132	128
5	132	126	166	164	156	144	144	140	136	130	126	122	128	134	136	136
6	126	120	142	136	134	136	134	130	124	124	120	122	128	136	134	130
7	132	130	148	138	138	134	136	136	130	124	126	122	120	128	134	132
8	126	124	152	156	144	140	138	136	130	126	128	130	128	124	126	130
9	124	120	138	132	134	132	132	130	122	118	118	124	132	130	128	126
10	124	118	142	132	136	136	134	132	128	124	120	128	134	128	122	120
11	136	126	156	150	146	146	144	140	136	132	130	138	142	140	138	134
12	136	132	160	156	142	138	140	138	130	128	124	124	128	132	134	136
13	110	106	138	130	126	126	116	124	124	120	118	118	116	120	124	126
14	120	126	146	138	134	124	138	134	130	126	124	120	120	128	132	130
15	126	116	138	132	134	138	134	132	130	126	124	120	128	132	136	130
16	116	110	140	136	124	118	118	120	122	118	118	124	128	130	124	120
17	124	120	136	132	128	126	126	124	120	120	124	128	128	124	122	120
18	128	120	142	138	132	130	130	128	124	120	124	126	132	136	130	128
19	132	124	156	152	146	146	144	142	158	130	118	128	132	130	130	140
20	122	118	142	136	132	136	136	134	130	126	124	120	120	122	128	130
21	114	118	132	134	132	128	124	124	120	118	122	116	116	120	120	124
22	118	116	134	130	124	114	122	120	122	118	128	120	126	130	128	124
23	142	136	148	142	144	142	142	140	136	132	122	130	136	140	140	138
24	142	130	156	148	144	144	140	140	136	136	118	126	128	134	132	128
25	118	114	142	136	132	130	130	128	126	126	118	120	120	128	122	118
26	124	120	136	138	132	138	130	128	122	122	128	118	126	130	132	128
27	126	124	148	144	138	130	136	134	130	126	130	120	120	126	132	128
28	128	120	142	132	136	136	134	134	130	128	120	122	126	130	134	130
29	124	120	144	132	130	130	128	128	124	124	124	134	134	130	128	126
30	128	124	138	134	134	132	132	130	126	126	122	124	130	134	130	128
31	148	140	162	164	162	142	160	160	154	150	148	144	140	138	142	144
32	136	128	150	152	154	152	150	150	146	140	138	142	148	150	150	148
33	112	110	138	140	140	138	138	136	130	130	128	126	124	120	118	116
34	122	115	144	146	146	144	146	144	140	136	134	130	138	130	126	128
35	142	138	168	170	170	168	166	164	158	150	146	142	136	130	142	146

DIASTOLIC BLOOD PRESSURE - CONTROL GROUP																
Sl. No	Baseline	Before Intubation.	After Intubation.	1 min.	2 min.	3 min.	4 min.	5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	35 min.	40 min.	45 min.
1	84	78	94	94	90	90	90	88	86	86	82	80	90	86	84	82
2	82	78	88	82	84	84	82	82	80	80	88	82	80	80	78	78
3	86	84	90	88	86	84	86	84	82	88	86	84	84	82	80	80
4	82	80	88	84	86	84	84	82	84	88	92	86	84	84	82	80
5	89	84	90	88	86	84	84	82	80	80	78	78	84	86	84	82
6	82	78	88	84	84	82	82	80	78	90	88	84	84	82	80	80
7	84	80	88	86	84	82	82	80	80	82	78	80	82	80	82	82
8	84	82	92	86	84	84	82	82	82	80	78	78	78	80	82	84
9	88	86	94	92	90	90	86	86	84	84	82	80	86	90	86	84
10	82	78	96	86	86	84	82	82	80	80	80	78	78	80	84	88
11	86	82	94	90	92	88	84	84	82	82	80	88	92	86	84	84
12	84	80	92	84	86	84	84	84	82	80	80	82	84	84	80	80
13	82	78	90	90	86	86	82	82	80	80	82	88	86	86	88	84
14	88	86	94	90	90	86	86	84	82	82	80	82	84	90	84	82
15	80	7874	86	84	82	80	80	82	80	78	78	78	80	82	80	80
16	74	74	84	80	82	78	76	78	78	76	74	72	84	80	78	76
17	78	74	86	84	80	82	80	80	82	88	84	84	86	86	88	86
18	72	74	90	82	78	82	80	80	82	80	80	78	88	92	86	84
19	74	76	84	82	76	76	74	74	92	72	70	84	76	78	80	88
20	72	70	80	74	74	72	74	74	72	70	70	68	68	70	72	74
21	74	72	78	76	72	74	72	72	74	80	84	80	80	80	80	80
22	72	70	80	82	84	80	76	78	80	76	76	74	74	76	74	72
23	82	82	86	84	82	80	80	80	78	76	74	74	76	72	70	78
24	88	84	98	86	86	82	86	84	82	82	84	88	94	88	84	88
25	86	84	90	86	84	86	86	84	82	80	84	86	86	90	88	86
26	82	80	92	86	84	80	80	80	84	84	92	86	86	84	82	82
27	86	84	92	86	86	82	82	80	82	82	80	86	92	90	88	86
28	88	82	94	88	84	86	86	84	86	86	90	90	92	90	86	88
29	82	80	90	86	86	84	84	84	80	80	78	78	76	76	78	80
30	86	82	94	92	94	86	84	82	86	86	88	84	84	82	82	80
31	90	86	98	100	100	98	98	96	94	92	90	98	104	100	92	86
32	92	88	100	100	102	102	100	100	98	92	100	96	94	90	88	88
33	78	72	90	92	92	92	90	90	86	86	86	84	90	86	82	80
34	70	66	84	86	86	88	86	86	84	84	82	80	80	84	84	80
35	92	84	98	100	100	100	98	98	92	80	82	98	94	90	94	96

PATIENTS LIST DEXMEDETOMIDINE GROUP

Sl. No	Name	IP Number	Age in Years	Sex	Weight in Kg	ASA Physical Status	Surgery
1	Valsala	167826	52	F	78	II	Laparotomy
2	Chandran	168654	55	M	65	I	Orthopaedic Surgery
3	Kanija	280059	28	F	57	I	Laparoscopic Surgery
4	Jayasree	152225	28	F	55	I	Head & Neck Surgery
5	Muthurani	169557	54	F	70	II	Head & Neck Surgery
6	Khalil Raz	138941	16	M	50	I	Orthopaedic Surgery
7	Maria Azhagan	174202	53	M	61	I	Head & Neck Surgery
8	Kavitha	170676	27	F	49	I	Laparoscopic Surgery
9	Ramakrishnan	170675	52	M	64	II	Orthopaedic Surgery
10	Sunitha Rani	169870	50	F	58	II	Head & Neck Surgery
11	Jayalekshmi	169544	36	F	57	I	Laparoscopic Surgery
12	Pathrose	167613	38	M	77	I	Urology
13	Mani	174724	50	M	55	I	Lower Abdominal Surgery
14	Rajayyan	18078	54	M	72	II	Breast Surgery
15	Sunitha	170068	35	F	60	I	Head & Neck Surgery
16	Siva Priya	178434	29	F	56	I	Laparoscopic Surgery
17	Sreekumar	177084	48	M	74	I	Orthopaedic Surgery
18	Ratheesh	180557	18	M	53	I	Orthopaedic Surgery
19	Christurajah	181159	45	M	58	I	Orthopaedic Surgery
20	Vishnu	178243	25	M	62	I	Laparotomy
21	Mariya	178597	46	F	75	I	Head & Neck Surgery
22	Vimala Devi	181997	45	F	80	I	Lower Abdominal Surgery
23	Shanthi	178888	48	F	88	II	Lower Abdominal Surgery
24	Murukesan	180743	50	M	61	II	Orthopaedic Surgery
25	Paul Raj	181422	52	M	48	II	Lower Abdominal Surgery
26	Kannan	198418	27	M	80	I	Head & Neck Surgery
27	Haneeshraj	198657	38	M	80	II	Laparotomy
28	Binu kumari	198220	41	F	76	I	Laparoscopic Surgery
29	Rajayyan	187739	47	M	45	I	Orthopaedic Surgery
30	Ayyappan	188101	53	M	65	II	Orthopaedic Surgery
31	Thankamma	201812	40	F	60	I	Breast Surgery
32	Anitha	201543	18	F	56	I	Head & Neck Surgery
33	Shalika	202692	29	F	50	I	Laparoscopic Surgery
34	Shaji	202906	25	M	61	I	Urology
35	Antony	203778	35	M	44	I	Head & Neck Surgery

PATIENT DETAILS - CONTROL GROUP							
Sl. No	**Name**	**IP Number**	**Age in Years**	**Sex**	**Weight in Kg**	**ASA Physical Status**	**Surgery**
1	Radhamani	165231	37	F	62	II	Urology
2	Vinod	167530	30	M	70	I	Head & Neck Surgery
3	Chandran	168063	42	M	49	I	Head & Neck Surgery
4	Satheesh	168945	41	M	60	I	Head & Neck Surgery
5	Simi Jose	169273	26	M	67	I	Head & Neck Surgery
6	Jameela	169359	24	F	52	I	Laparoscopic Surgery
7	Vincent	170584	26	M	64	I	Orthopaedic Surgery
8	Raveendran	176272	30	M	68	I	Orthopaedic Surgery
9	Jayan	170488	55	M	56	I	Head & Neck Surgery
10	Viji	171705	28	F	58	I	Laparoscopic Surgery
11	Moses	173517	55	M	58	II	Lower Abdominal Surgery
12	Unni	173793	47	M	65	I	Orthopaedic Surgery
13	Archana	174114	22	F	60	I	Laparoscopic Surgery
14	Reenamol	174098	26	F	62	I	Laparoscopic Surgery
15	Shobha	174118	33	F	60	I	Head & Neck Surgery
16	Latha	173880	38	F	64	I	Lower Abdominal Surgery
17	Krishnaveni	175083	50	F	72	II	Laparotomy
18	Usha	176124	34	F	65	II	Laparoscopic Surgery
19	Absukhan	176715	33	M	58	I	Head & Neck Surgery
20	Sinthiya	176874	22	F	64	II	Head & Neck Surgery
21	Jessy	177161	42	F	57	I	Breast Surgery
22	Thankabhai	187036	54	F	45	II	Orthopaedic Surgery
23	Prasanna Kumari	170668	49	F	66	II	Urology
24	Esther	18754	55	F	70	I	Orthopaedic Surgery
25	Murugayyan	188222	60	M	65	I	Orthopaedic Surgery
26	Prasad	193008	28	M	60	I	Orthopaedic Surgery
27	Subha	187831	32	F	65	I	Head & Neck Surgery
28	Rekha	186940	24	F	54	I	Laparoscopic Surgery
29	Lally	187575	39	F	71	I	Laparoscopic Surgery
30	Jeba	187740	28	F	56	II	Laparoscopic Surgery
31	Arumugan	187548	43	M	54	I	Head & Neck Surgery
32	Nabisha	190301	40	F	56	I	Breast Surgery
33	Divya	202042	23	F	47	I	Head & Neck Surgery
34	Sreekumari	202145	50	F	60	II	Orthopaedic Surgery
35	Thankarajan	202338	53	M	60	I	Orthopaedic Surgery

MAXIMUM CONCENTRATIONS OF ISOFLURANE USED FOR EACH PATIENT DURING SURGERY

DEXMEDETOMIDINE GROUP			CONTROL GROUP	
Sl. No	**Concentration of Isoflurane**		**Sl. No**	**Concentration of Isoflurane**
1	1%		1	0.80%
2	0.40%		2	1%
3	0.40%		3	1%
4	0%		4	0.80%
5	0%		5	1%
6	0.40%		6	0.60%
7	1%		7	1.20%
8	0%		8	1.60%
9	0%		9	0%
10	0%		10	1.20%
11	0%		11	2%
12	0.80%		12	1.80%
13	0.40%		13	1%
14	0.40%		14	0.80%
15	0.40%		15	0.40%
16	0%		16	1.80%
17	0.60%		17	1.60%
18	0.40%		18	1.20%
19	0%		19	0.80%
20	0%		20	1%
21	0.60%		21	1%
22	0.40%		22	1%
23	0.40%		23	0.80%
24	0%		24	0.60%
25	0%		25	1.80%
26	0%		26	1.20%
27	0.40%		27	2%
28	0.80%		28	1.20%
29	0.40%		29	1.20%
30	0%		30	1.20%
31	0.40%		31	0.80%
32	0.40%		32	1.40%
33	0.40%		33	1.40%
34	0%		34	1.20%
35	0%		35	1.40%