"A COMPARATIVE STUDY OF INTRAVENOUS DEXMEDETOMIDINE AND MIDAZOLAM USED AS A PREMEDICATION FOR LAPAROSCOPIC SURGERIES UNDER GENERAL ANESTHESIA"

Submitted by

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Under the guidance of

DR. VIDYA PATIL M.D.

PROFESSOR

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LIST OF ABBREVIATIONS

SBP	**Systolic Blood Pressure**
DBP	**Diastolic Blood Pressure**
BT	**Bleeding time**
CT	**Clotting time**
Gp	**Group**
Hrs	**Hours**
IV	**Intravenous**
kg	**Kilogram**
mg	**Milligram**
HR	**Heart rate**
SD	**Standard deviation**
ASA	**American Society of Anesthesiologists**
mcg	**Microgram**
CBS	**Cerebral Blood Flow**
ECG	**Electrocardiograph**
CABG	**Coronary Artery Bypass Graft**

ABSTRACT

Introduction:

Laryngoscopy and tracheal intubation in adults are commonly accompanied by an increase in arterial blood pressure and heart rate. The magnitude of haemodynamic changes observed may be dependent on various factors such as depth of anaesthesia, whether any measures are taken prior to airway manipulation, the anaesthetic agent used, the duration of laryngoscopy and intubation. To date, the exact mechanism of haemodynamic responses to laryngoscopy and intubation has not been clarified. The principle mechanism in hypertension and tachycardia is the sympathetic response which may be the result of increase in catecholamine activity.

Alpha-2 agonists have been used for attenuating the sympathetic response and among α-2 agonists both clonidine and dexmedetomidine appear to fulfill all the above criteria. Both Clonidine and dexmedetomidine have actions on both α-1 andα-2 receptors but Dexmedetomidine is highly specific and selective α-2 adrenoceptor agonist with α2: α1 binding selectivity ratio of 1620:1 compared to 220:1 for clonidine.

Aim:

To determine intravenous dexmedetomidine is a better premedicant than midazolam in patients undergoing laparoscopic surgeries under general anaesthesia.

Methodology:

A prospective time bound study was designed in which 50 patients of ASA I & II undergoing elective laparoscopic surgeries under general anaesthesia who are to be intubated were randomly allocated into two groups of 25 each.

Group A, n=25; who received midazolam 0.02 mg/kg iv over 10 minutes.

Group B, n=25; who received dexmedetomidine 0.6mcg/kg iv over 10 minutes .The parameters observed were pulse rate, systolic BP, diastolic BP, MAP , side effects, sedation and dose of propofol required for anesthesia.

Results:

Dexmedetomidine in a dose of 0.6 mcg/kg over 10 minutes suppresses HR, BP and reduces dose of propofol for induction when compared with midazolam in a dose of 0.02mg/kg.

Conclusion:

This study concludes that dexmedetomidine in a dose of 0.6 mcg/kg is a better premedicating agent than midazolam in a dose of 0.02 mg/kg.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF GRAPHS

INTRODUCTION

Laryngoscopy and tracheal intubation in adults are commonly accompanied by an increase in arterial blood pressure and heart rate.[1] The magnitude of haemodynamic changes observed may be dependent on various factors such as depth of anaesthesia, whether any measures are taken prior to airway manipulation, the anaesthetic agent used, the duration of laryngoscopy and intubation. To date, the exact mechanism of haemodynamic responses to laryngoscopy and intubation has not been clarified. The principle mechanism in hypertension and tachycardia is the sympathetic response[2,3] which may be the result of increase in catecholamine activity.[4]

The increase in the pulse rate and blood pressure are usually transitory, variable and unpredictable. Transitory hypertension and tachycardia are probably of no consequence in healthy individuals but either or both may be hazardous to those with hypertension, myocardial insufficiency or cerebrovascular diseases.[4] This laryngoscopic reaction in such individuals may predispose to development of pulmonary edema, myocardial insufficiency and cerebrovascular accident.[5,6]

Pressor response is exaggerated in hypertensive patients even though rendered normotensive pre-operatively by antihypertensive medication.[7] Pressor response may result in intra-operative myocardial infarction,[8] acute left ventricular failure,[8] dysrrhythmias[9] and intracranial bleed[8] in individuals with end organ decompensation.

Intravenous anaesthetic induction agents do not adequately or predictably suppress the circulatory responses evolved by endotracheal intubation.[10] So prior to

initiating laryngoscopy, additional pharmacological measures like use of volatile anaesthetics,[11] topical and intravenous lidocaine,[12,13,14] opioids,[15,16,17] vasodilators – Sodium nitroprusside,[18] Nitroglycerine,[19] Calcium channel blockers[20,21,22] and ββ-blockers[23,24,25] have been tried by various authors.

Besides minimizing the cardiovascular response, anaesthesia induction for patients at risk must also satisfy the following requirements: It must be applicable regardless of patient group, prevent impairment of cerebral blood flow and avoid awareness of the patient; it should neither be time consuming nor affect the duration or modality of the ensuing anaesthesia and also should not have any effect on the recovery characteristics.

None of the drugs mentioned above have been found to be effective to attenuate the sympathetic response to intubation and also not able to meet all the required criteria. Hence there is a need of finding out the drugs which can meet both the requirements.

α-2 agonists have been used for attenuating the sympathetic response[26] and among α-2 agonists both clonidine and dexmedetomidine appear to fulfill all the above criteria. Both Clonidine and dexmedetomidine have actions on both α-1 and α-2 receptors but Dexmedetomidine is highly specific and selective α-2 adrenoceptor agonist with α2: α1 binding selectivity ratio of 1620:1 compared to 220:1 for clonidine.[27]

Various studies have also found that dexmedetomidine can decrease the haemodynamic response to laryngoscopy and intubation.[28,29,30,31,32,33,34,35] Till recently dexmedetomidine was not available in India though it is being used in other countries

since many years. Since it has been recently introduced in India and not many studies have been done in India regarding its usefulness in suppressing intubation response, there is a need to study its effectiveness.

The advantages of intravenous dexmedetomidine as premedicant in anaesthesia setting include sedation, analgesia, anxiolysis and improved haemodynamic stability. Because of these beneficial properties it has been found that the minimum alveolar concentration (MAC) of volatile anaesthetics also decreases significantly up to 90% and hence decreases the requirement of anaesthetics.[30,36]

The present study compares the attenuation of haemodynamic response to laryngoscopy and intubation, dose of propofol required for anesthesia and sedative effect in adult patients posted for various laparoscopic surgeries under general anaesthesia, with single intravenous bolus dose of 0.6µg/kg body weight dexmedetomidine and midazolm 0.02mg/kg given 10 minutes prior to induction.

AIMS AND OBJECTIVES

1. To evaluate the efficacy of intravenous midazolam and dexmedetomidine in attenuating the haemodynamic responses to laryngoscopy and endotracheal intubation.
2. To compare the effects of midazolam and dexmedetomidine on the dose requirement of propofol for induction of anaesthesia.
3. To compare the sedative effects with intravenous midazolam and dexmedetoimidine.

REVIEW OF LITERATURE

Laryngoscopy and tracheal intubation are noxious stimuli that provoke a transient but marked sympathetic response, manifesting as tachycardia and hypertension. These haemodynamic responses to laryngoscopy and tracheal intubation were first recognized as early as in 1940s by Reid and Brace et al.[1] These facts were further confirmed by various investigators and were interpreted as a result of reflex sympathoadrenal response leading to an increase in plasma catecholamine levels.[2,3,4]

These responses are transitory, variable and are much more pronounced in hypertensive than in normotensive individuals.[5]

The haemodynamic response to laryngoscopy and tracheal intubations may not be of much significance in an otherwise normal individual, but in susceptible patients particularly those with systemic hypertension,[7] coronary artery disease, cerebrovascular disease or intracranial aneurysms, even these transient changes can result in potentially deleterious effect like LVF,[8] pulmonary edema, myocardial ischemia,[8] ventricular dysrrhythmias[9] and cerebral haemorrhage.[8]

Attempts were made as early as in 1960s by various investigators to reduce the pressor response to laryngoscopy and tracheal intubation using

1. Various inhalational anaesthetic agents and
2. Other pharmacological agents.

Inhalational anaesthetic agents like ether and cyclopropane, trichloroethylene, chloroform and ethyl chloride were used to obtund the laryngoscopic responses by increasing the depth of anaesthesia.[9,10]

As early as in 1970s, the investigators used low doses of opioids as premedications for blunting the laryngoscopic reactions and observed significant reduction in the haemodynamic responses to laryngoscopy and intubation. Use of fentanyl[15,16] effectively reduced tachycardia and hypertension associated with laryngoscopy and tracheal intubation. Though effective, these agents were associated with respiratory depression, chest wall rigidity and in addition, they prolonged the recovery time (Bedford, Marshall WK et al., 1984).

Robert K Stoelting,[14] noted that the best way to prevent laryngoscopic reaction was to minimize the duration of laryngoscopy and intubation. He noted that if laryngoscopy and intubation performed within 15 seconds, the haemodynamic responses were minimal. He also suggested that IV lidocaine given in the dose of 1.5 mg/kg body weight sufficiently attenuated the laryngoscopic reactions. However many authors have noted that lignocaine fails to attenuate the haemodynamic responses to laryngoscopy and intubation effectively.

Direct acting vasodilators like sodium nitroprusside[18] and nitroglycerine[19] were tried for obtunding the haemodynamic responses to laryngoscopy and intubation. The authors observed that, though they were powerful in attenuating these responses, the reflex tachycardia associated with their use limited their usefulness in blunting the laryngoscopic reaction and in addition their use needed invasive arterial pressure monitoring.

Calcium channel blockers like nifedipine[20,22] and verapamil[21] were studied widely to suppress the haemodynamic responses to laryngoscopy and tracheal intubation. Though these agents were effective in controlling the hypertensive response, they were ineffective in attenuating the tachycardic response to laryngoscopy and tracheal intubation. Another disadvantage, the authors observed with the drugs were exaggerated hypotensive responses in the presence of volatile anaesthetic agents by either causing reduction in systemic vascular resistance or by reduced myocardial contraction or by combination of these effects.

As the pressor response occurring during laryngoscopy and tracheal intubation was due to augmented sympathetic response, the investigators thought that by using pharmacological drugs with specific adrenergic blocking properties, they could reduce the haemodynamic responses to laryngoscopy and tracheal intubation.

As early as in 1960, alpha adrenergic blocker, phentolamine was used to attenuate the laryngoscopic reactions. However, these drugs had long duration of action and the authors observed exaggerated fall in blood pressure during perioperative period. Because of their property of extensive vasodilatation requiring rapid transfusion, this method employed for attenuating laryngoscopic reactions did not gain wide popularity.

In 1973, proctolol[23] was the first beta blocker used for attenuating the pressor response to laryngoscopy and tracheal intubation. Later many other drugs with beta blockade activity were tried to control the laryngoscopic reactions like acebutolol, propranolol[24] and labetolol.[25]

The authors noted that, though these agents were effective in blunting the laryngoscopic reactions, their onset of action was rather delayed and duration of action was prolonged, thereby increasing the risk of development of bradycardia in the perioperative period.

Esmolol,[17,26] a selective beta-1 blocker with an ultra short duration of action was introduced in 1986. With esmolol tachycardic response to laryngoscopy and intubation was effectively blunted and hypertensive response to laryngoscopy and intubation was less attenuated.

In **1989**, **Kallio et al.,**[66] studied the effects of dexmedetomidine on haemodynamic control mechanism. As part of a placebo controlled study Dexmedetomidine was administered to five healthy male volunteers in single intravenous doses of 12.5, 25, 50 and 75µg over 30 seconds. Blood pressure, heart rate, impairment of vigilance and sedation score were measured. Blood samples were collected at 15 min and 1 min before drug administration and at 15, 30, 45, 60, 90, 120, 180 and 240 min after administration of drug to assess the plasma concentrations of catecholamine, human growth hormone, cortisol, atrial natriuretic peptide (ANP) and arginine vasopressin (AVP).

Authors concluded that higher dose of dexmedetomidine (50 and 75 µg) decreased blood pressure and heart rate with initial small hypertensive response due to activation of postsynaptic α_2–receptors. The maximum hypotensive effect and inhibition of sympathetic activity was seen after administration of the 50 and 75µg dose. The administration of single intravenous doses of dexmedetomidine resulted in total inhibition of norepinephrine levels.

Limitation of the study: Dexmedetomidine in the above study has been given rapidly, taking only 30 sec which probably is the cause for hypertension in the early period.

In **1991**, **Aho M et al.,**[30] conducted a double blind randomised controlled study to evaluate the effects of dexmedetomidine 0.3 and 0.6 μg/kg body weight on haemodynamic responses to laryngoscopy and on requirements of isoflurane for maintenance of anaesthesia in patients undergoing abdominal hysterectomy under general endotracheal anaesthesia. The patients in fentanyl group were given fentanyl 2 μg/kg in 5ml saline. All patients received oral diazepam 0.1 mg/kg body weight before induction. The study drug dexmedetomidine 0.3 or 0.6μg/kg body weight, fentanyl 2μg/kg body weight diluted to 5 ml or 5 ml of saline were injected intravenously slowly over 1 min, 10 min prior to induction. Anaesthesia was induced after 10 min of test drug administration with thiopental and succinylcholine to facilitate laryngoscopy and intubation. Anaesthesia was maintained with isoflurane and fentanyl..

All patients were monitored for sedation, end tidal isoflurane concentration, time of awakening and postoperative analgesic requirement after test drug administration. Also the blood pressure and heart rate were recorded at 1 min interval after test drug administration until 10 min after intubation, at 2.5 min interval during first 15 min of operation and 5 min interval during rest of the operation.

The authors concluded that dexmedetomidine as a preanaesthetic medication at a dose of 0.6μg/kg body weight, blunted the tachycardiac and hypertensive

response to laryngoscopy and tracheal intubation. It also diminished isoflurane requirements during surgery demonstrating anaesthetic sparing effect. They also found a consistent feature of dexmedetomidine as the occurrence of bradycardia which was limited by glycopyrollate administration.

In **1992**, **Scheinin B et al.**,[28] conducted a study on 24 ASA I patients undergoing elective surgery under general endotracheal anaesthesia to know the effects of dexmedetomidine in attenuating sympathoadrenal responses to tracheal intubation and reduction of thiopentone requirements for induction. The study groups were allocated randomly in a double blind manner to receive either dexmedetomidine 0.6 µg/kg body weight diluted to 10 ml or 10 ml of saline 10 minutes before induction, over one minute. Both the groups were premedicated with glycopyrollate 3 minutes before the test drug. Then the dose of thiopentone sufficient to abolish eyelash reflex was injected (5 mg/sec) followed by vecuronium bromide. Laryngoscopy lasting for 10 sec was performed in both groups.

The authors observed that the mean sleep dose of thiopentone was significantly greater in control group ($p<0.001$) than in dexmedetomidine group. Also the total amount of fentanyl requirement for maintenance was greater in the control group than in dexmedetomidine group. They also observed that the maximal average increases (versus baseline) were 1% and 21% in systolic blood pressure, 23% and 46% in diastolic blood pressure and 6% and 29% in heart rate in dexmedetomidine group and saline group respectively. It was also noticed that during surgery arterial pressure and heart rate remained slightly less in dexmedetomidine group than control group.

The authors concluded that pretreatment with dexmedetomidine 0.6µg/kg body weight attenuated, but did not totally obtund the cardiovascular and catecholamine responses to tracheal intubation after induction of anaesthesia. Also the dose of thiopentone needed for induction was decreased significantly in patients receiving dexmedetomidine demonstrating the anaesthesia potentiating effects of drug.

In **1999**, **Talki et al.**, [94] conducted a study to evaluate the effect of dexmedetomidine on neuromuscular block and haemodynamics in 10 human volunteers. All patients received ringer lactate solution (10 ml/kg) before induction of anaesthesia. Anaesthesia was induced with intravenous alfentanyl and propofol and were maintained with same infusions. The twitch tension was measured 30 min after induction and value to T_1 response was taken as 100%. Rocuronium was administered as a bolus 200µg/kg body weight followed by an infusion of 200µg/kg/hr and was adjusted to target a stable T_1 response within the range of 50 ± 3% of pre-rocuronium value and then Dexmedetomidine was administered by a computer controlled infusion with target concentration of 0.6 ng/ml for 45 min.

All patients were monitored for evoked mechanical responses of adductor pollicis (T_1 response and T_4/T_1 ratio), systolic and diastolic blood pressure by an arterial cannula, heart rate and saturation at 10 sec interval. Arterial blood samples were collected to estimate the plasma dexmedetomidine and rocuronium concentration just before the start of infusions, 15, 30 and 45 min after dexmedetomidine infusion. The clearance of rocuronium was also estimated.

Authors observed that, the plasma rocuronium concentrations significantly increased after dexmedetomidine administration ($p<0.05$) compared to pre-dexmedetomidine values over 45 min. The increase was 7.6% and was associated with mean decrease in twitch tension from 51% to 44% after dexmedetomidine infusion. There was a significant increase in systolic blood pressure ($p<0.001$) and decrease in heart rate ($p<0.001$) 5 min after dexmedetomidine infusion.

Authors concluded that, dexmedetomidine infusion increased plasma rocuronium concentration, decreased T_1 response and significantly increased systolic blood pressure caused by dexmedetomidine induced peripheral vasoconstriction.

Limitation of the study: The authors do not mention whether any muscle relaxant was used for endotracheal intubation and the overall effect of the same on the study.

In **2006**, **Yildiz et al.**, [32] studied the effect of single preinduction intravenous dose of dexmedetomidine 1µg/kg body weight on cardiovascular response resulting from laryngoscopy and endotracheal intubation, need for anaesthetic agent and perioperative haemodynamic stability in fifty patients undergoing elective minor surgery under general endotracheal anaesthesia. Patients were randomized into two groups (dexmedetomidine and placebo group). All patients were premedicated with fentanyl and thiopental was given until eyelash reflex was lost. Anaesthesia was maintained with sevoflurane. All patients were connected to monitors to record heart rate, systolic blood pressure, diastolic blood pressure, before and after drug administration and after tracheal intubation. Patients were also monitored for sedation

by Ramsay sedation scale every 5 minutes after drug administration and after extubation. Steward awakening scale was applied at 5 and 10 min.

Authors observed that the need for thiopental and sevoflurane concentration was decreased by 39% and 92% respectively in dexmedetomidine group compared to placebo group. The increase in heart rate and blood pressure after intubation were significantly low in dexmedetomidine group ($p<0.05$) compared to placebo group. The fentanyl requirement in dexmedetomidine group was significantly lower compared to placebo group. The sedation score were ≥4 in all patients in dexmedetomidine group at 10 min ($p<0.05$) and the Steward awakening scores were >6 in 56% of dexmedetomidine group and in 4% of placebo group ($p<0.05$).

In **2008**, **Mowafi et al.**,[31] conducted a double blind randomized controlled study in 40 patients undergoing elective non-ophthalmic surgery under general endotracheal anaesthesia, to investigate the effect of dexmedetomidine premedication on intraocular pressure changes after succinylcholine and endotracheal intubation. All patients were randomly allocated into two groups to receive either single bolus intravenous dose of dexmedetomidine 0.6 µg/kg body weight or saline, over 10 min before induction. All patients were monitored with 3 lead ECG, pulse oximeter, capnometer and non invasive blood pressure. Intraocular pressure was measured with Schiotz tonometer. Anaesthesia was induced with thiopental sodium and fentanyl and trachea was intubated with succinylcholine. Anaesthesia was maintained with rocuronium and sevoflurane. Patients were monitored for heart rate, mean arterial pressure and intraocular pressure at following time periods:

T_1 – 5 min after arrival to operating room, before premedication, T_2 – 10 min after premedication, T_3 – 30 sec after thiopental, T_4 – 30 sec after succinylcholine and T_5 – every 2 min for 6 min after intubation.

Authors found that heart rate was significantly higher in control group than dexmedetomidine group after injection of thiopentone sodium, succinylcholine and intubation. Also the mean arterial pressure in the control group was higher than that of dexmedetomidine group after intubation (p=0.041). In dexmedetomidine group intraocular pressure was not different from baseline value (p=0.65) and was significantly lower than in saline group (p=0.003).

In **2010 Dere K et al.,**[101] conducted a comparative study of dexmedetomidine versus midazolam on perioperative hemodynamics, sedation, pain, satisfaction and recovery scores during colonoscopy. A total of 60 ASA I-II patients, between 20 and 80 years of age were included in the study. Patients were randomly assigned to two groups. Midazolam 0.05 mg/kg and fentanyl citrate 1 microg/ kg were administered intravenously to cases in Group I (n = 30). An initial loading dose of 1 microg/kg dexmedetomidine was administered intravenously in 10 min to cases in Group II (n = 30) before the procedure and as a continuous infusion dose of 0.5 microg/kg /h just before the procedure started. Also 1 microg/kg fentanyl citrate was administered intravenously immediately before the procedure. Peripheral oxygen saturation (SpO^2), mean arterial pressure (MAP), heart rate (HR), Ramsay Sedation Scale (RSS), Numeric Rating Scale (NRS) scores and colonoscopist satisfaction scores of the cases were recorded.

On observation, although statistically significant values were not detected between the two groups with regard to mean arterial pressure, in Group I heart rates were higher and SpO^2 scores were lower in a statistically significant manner. When the groups were compared with regard to RSS, the RSS scores of Group I at the 10th and 15th minutes were significantly lower than Group II. There was no statistically significant difference between the two groups when compared with regard to NRS scores. Satisfaction scores were significantly lower in Group II.

Authors concluded that dexmedetomidine provides more efficient hemodynamic stability, higher Ramsay sedation scale scores, higher satisfaction scores and lower NRS scores than midazolam in colonoscopies. And thus they believe that dexmedetomidine can be used safely as a sedoanalgesic agent in colonoscopies.

In **2008**, **Basar H et al.**,[33] conducted a randomized prospective double blind controlled study to investigate the haemodynamic, cardiovascular and recovery effects of dexmedetomidine used as single preanaesthetic dose. Patients were randomly divided into two groups to receive 0.5 µg/kg body weight dexmedetomidine or saline solution in a 10 ml solution by slow IV push over 60s. Anaesthesia was induced with thiopental sodium until loss of eyelid reflex and the dosage was recorded. Vecuronium was used for muscle relaxation and anaesthesia was maintained with desflurane. Monitors were connected to record heart rate (HR), oxygen saturation, mean arterial pressure (MAP) and end tidal carbon-dioxide continuously until extubation. In addition ejection fraction (EF), cardiac index (CI) and stroke volume index (SVI) were recorded for baseline, after dexmedetomidine

and saline injection, at thiopental administration, at intubation and at 10 min intervals. Also the recovery from anaesthesia was assessed by modified Alderete recovery score.

Authors observed that the induction dose of thiopental sodium was significantly lower (37%) than the placebo group after administration of 0.5µg/kg body weight of single dose of dexmedetomidine. HR was significantly lower in dexmedetomidine group after intubation (p=0.024) and on 10^{th} min (p=0.013). Also MAP was significantly lower in dexmedetomidine group (p=0.001). The EDI, CI, SVI, EF and Alderete score were similar in both the groups.

Authors concluded that a single dose of 0.5µg/kg body weight of dexmedetomidine given preoperatively 10 min before induction caused significant sedation, decreased thiopental dosage and blunted haemodynamics response to intubation with no change in recovery scores.

In **2009**, **Kunisawa T et al.**,[34] conducted a prospective, double blind, randomized controlled study in 30 patients with mild to moderate cardiovascular disease, to evaluate the effect of dexmedetomidine combined with fentanyl on haemodynamics. The study had two goals:

a. To confirm that dexmedetomidine suppresses the decrease in blood pressure during anaesthetic induction.
b. To confirm that dexmedetomidine blunts the cardiovascular responses to tracheal intubation.

All patients were assigned into three groups, group D-F_2 (dexmedetomidine and fentanyl), group F_2 (placebo and fentanyl effect site concentration 2 ng/ml) or

group F_4 (placebo and fentanyl effect site concentration 4 ng/ml). Patients received either dexmedetomidine as an infusion of 1µg/kg body weight for 10 min followed by a continuous infusion of 0.7µg/kg/hr or placebo saline 15 min before induction. Anaesthesia was induced with propofol and fentanyl. Monitors were connected to measure heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) before and after drug administration, before and after induction and before and after intubation.

Authors observed that, after inducing anaesthesia, SBP was significantly higher in group D-F_2 than group F_2 and F_4. The SBP in group F_2 and F_4 were significantly higher after intubation but no significant change was noted in group D-F_2. The percentage of increase in SBP due to tracheal intubation in group D-F_2 was 3%$\pm$4% and was significantly lower than group F_2 and F_4.

Authors concluded that, dexmedetomidine administration during anaesthetic induction may be useful because it suppresses the decrease in blood pressure due to induction and also blunts the cardiovascular responses to tracheal intubation.

In **2010**, **Ferdi et al.**,[35] conducted a prospective, randomized, double blind controlled study to investigate the haemodynamic effect of intravenous dexmedetomidine as an adjunct to anaesthetic induction to attenuate haemodynamic response to endotracheal intubation in patients undergoing fast track coronary artery bypass grafting. The patients were assigned into two groups: placebo (PLA n_1=15) and dexmedetomidine (DEX n_2=15). All patients received their cardiac medications two hours before and were premedicated with midazolam and prehydrated with 500 ml lactate ringer solution and were monitored with 12 lead ECG, invasive blood

pressure, pulse oximeter and neuromuscular blockade via train of four (TOF). DEX group received a total dose of 1µg/kg diluted in 100 ml normal saline over 15 min and PLA group received 100 ml normal saline over 15 min. Anaesthesia was induced with etomidate and fentanyl and endotracheal intubation was facilitated by rocuronium. Heart rate, blood pressure were monitored at baseline, after placebo or dexmedetomidine infusion, after induction and 1^{st}, 3^{rd} and 5^{th} min after tracheal intubation.

Authors noted that in DEX group systolic, diastolic and mean arterial pressure were lower at all times in comparison to baseline values. In PLA group systolic, diastolic and mean arterial pressures decreased after the induction of general anaesthesia and five minutes after intubation compared to baseline values which was not significant between the groups. After the induction of general anaesthesia, the drop in heart rate was higher in DEX group compared to PLA group. One minute after intubation, heart rate significantly increased in PLA group ($p=0.03$) while it decreased in DEX group ($p=0.004$).

Authors concluded that dexmedetomidine can be safely used to attenuate the haemodynamic responses to endotracheal intubation in patients undergoing myocardial revascularization receiving beta blockers.

In **2011**, **Keniya et al.**,[96] conducted a double blind controlled study to assess the efficacy and safety of dexmedetomidine in attenuating sympathoadrenal responses to tracheal intubation and to analyse reduction in perioperative anaesthetic requirement. The patients were randomly assigned into two groups as

Group C – **Control**: isoflurane-opioid saline anaesthesia

Group D – **Dexmedetomidine**: isoflurane – opioid-dexmedetomidine anaesthesia.

All patients in group D received dexmedetomidine in a dose of 1 μg/kg over a period of 10 min prior to induction through infusion pump and in group C all the patients received saline through infusion pump. Anaesthesia was induced with thiopentone sufficient enough to abolish eyelash reflex followed by vecuronium to facilitate intubation. Anaesthesia was maintained with isoflurane, fentanyl and vecuronium. The dexmedetomidine infusion was continued after intubation at a dose of 0.2-0.7μg/kg/hr in group D, till the start of skin closure. All the patients were connected to monitors to record heart rate (HR), systolic and diastolic blood pressure (SBP and DBP) at 5 min and 10 min after dexmedetomidine administration, before induction, at induction, 0 min, and 1 min and 5 min after intubation. They also noted the dose requirement of thiopentone for induction of anaesthesia, perioperative fentanyl and isoflurane requirement and sedation score 5 min and 10 min after dexmedetomidine in both groups according to Ramsay sedation score.

Authors noted that after 10 min of dexmedetomidine administration patients were drowsy but arousable. The mean dose of thiopentone required in group C was 6 mg/kg body weight while it was 4.4 mg/kg body weight in group D. The decrease in dose requirement was by 30% in dexmedetomidine group as compared to control group (p=0.000). They also noted a decrease in the requirement of injection fentanyl and isoflurane concentration (32%) in group D which was statistically significant. After tracheal intubation, maximal average increase was 8% in systolic and 11% in diastolic blood pressure in group D, as compared to 40% and 25% respectively in

control group. Also the increase in heart rate was 7% and 21% in group D and group C respectively which was statistically significant.

Authors concluded that dexmedetomidine as a premedicant is effective in attenuating sympathoadrenal responses to tracheal intubation with significant anaesthetic and opioid sparing effect.

In **2012, Poonam S G et al**, studied dexmedetomidine as an anesthetic adjuvant in laparoscopic surgeries. 30 patients, ASA I and II, aged between 18 -50 years of either gender undergoing laparoscopic surgeries under general anesthesia were studied. Loading dose infusion of dexmedetomidine was started 1mcg/kg for 15 mins and patients were premedicated. Routine induction with propofol and fentanyl was carried out and maintenance infusion of dexmedetomidine0.2 mcg/kg/hr was given. Patients were monitored with standard monitoring and in addition the DOA was monitored with entropy.

They observed that there was a 62.5% reduction in the induction dose of propofol, with a 30% less end tidal concentration of isoflurane requirement for maintenance of anesthesia, while maintaining the adequate DOA.

The limitation of this study was lack of control group.

PHYSIOLOGY OF HAEMODYNAMIC RESPONSE[38, 39, 40]

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

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

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

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

It was concluded by the study of changes of plasma catecholamine concentration during laryngoscopy and endotracheal intubation by Russell WJ and Mortis RG[38] that a positive correlation existed between arterial pressure and plasma

noradrenaline concentration. The magnitude of increase in blood pressure paralleled the increase in plasma noradrenaline concentration. Plasma adrenaline did not change significantly.

This was further confirmed by Derbyshire[39] and Smith[40] who showed that the plasma noradrenaline concentration increased by 34% in samples obtained from central venous line and by 74% in samples obtained from radial artery. This can be explained by uptake of noradrenaline in lungs.

The adrenergic response was maximum by one minute and had diminished by 5 minutes. This haemodynamic response due to activation of sympathico-adrenal system increases heart rate, blood pressure and these serve as indirect indices to measure the response. Thus heart rate and blood pressure have been used as indirect indices to measure levels of sympathetic activity clinically.

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

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

Laryngoscopy, intubation and cardiac disease

The cardiovascular changes and catecholamine release should be divided into two phases, differentiating the act of laryngoscopy and its effects, from the act of tracheal insertion of an endotracheal tube (or of a catheter or bronchoscope). Laryngoscopy alone, without intubation provides a supraglottic pressure stimulus

with significant increases in both systolic and diastolic pressures[40] from a central level of stable anaesthetic state, as well as increases above the pre-induction control levels. Increases in heart rate are slight and are not significant from laryngoscopy alone.

The second phase, or the act of intubation and placement of an endotracheal tube in the trachea or a catheter, stimulates infraglottic receptors and evokes an additional cardiovascular response with a further increase in catecholamines. The pressor response is much greater, increasing by 36% from pre-induction control levels. The heart rate also now significantly increases by about 20% with the act of tracheal intubation, whereas as noted earlier, there is little rate response to laryngoscopy alone.

Neuroendocrine response to endotracheal intubation which leads to hypertension and tachycardia causes variety of complications in patients with cardiac disease. The most common adverse cardiovascular problem related to intubation is myocardial ischemia in patients with coronary artery insufficiency.

The major determinants of myocardial oxygen demand are heart rate and blood pressure and when endotracheal intubation causes marked increase in arterial pressure and heart rate, the increase in myocardial oxygen demand must be met by an increase in supply of oxygenated blood through coronary circulation. When one or more occlusive coronary lesions results in relatively fixed coronary blood flow, ability to increase myocardial oxygen supply during periods of increased demand is minimal and abrupt increase in myocardial demand results in tissue ischemia that can result in myocardial dysfunction or overt tissue infarction.

Furthermore, ischemia induced by arterial hypertension may be compounded by increase in left ventricular end-diastolic pressure resulting in further compromise of perfusion to subendocardial tissue. These circumstances are responsible for episodes of ST segment depression in ECG and increased pulmonary artery diastolic pressure in patients with atherosclerosis. Occasionally these episodes predispose to the occurrence of perioperative myocardial infarction.

Patients with vascular anomalies that cause weakening of lining of major arteries, are at risk during endotracheal intubation. Integrity of cerebral and aortic aneurysms is largely a function of transmural pressure; a sudden increase in blood pressure can lead to rupture of vessel and abrupt deterioration of patient's status. This results in significant blood loss for anaesthesiologists to replace and additional technical problems for surgeon trying to inspect the lesion and insert a vascular prosthesis.

PHYSIOLOGY OF ADRENORECEPTORS

α-2 receptors are found in many sites throughout the body. They are found in peripheral and central nervous system, in effector organs such as liver, kidney, pancreas, eye, vascular smooth muscles and platelets.[41] Physiologic responses mediated by α-2 adrenoceptors vary with location and can account for the diversity of their effects.[42]

The classification of α-2 receptors based on anatomical location is complicated since these receptors are found in presynaptic, postsynaptic and extrasynaptic locations.[43] They have been divided into three subtypes; each type is responsible uniquely for some actions of α-2 receptors. The subtype A, the predominant subtype in CNS, is responsible for the sedative, analgesic and sympatholytic effect; the subtype B, found mainly in the peripheral vasculature, is responsible for the short term hypertensive response and the subtype C, found in CNS, is responsible for anxiolytic effect.[44]

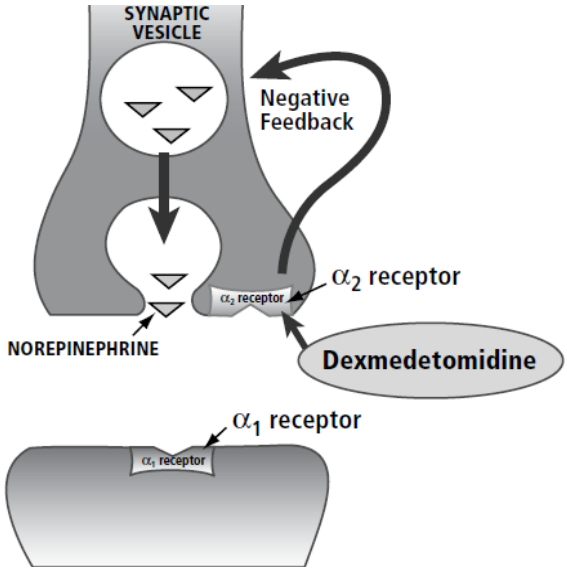


Figure 1: Physiology of α-2 adrenoceptors[27]

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

PHARMACOLOGY OF DEXMEDETOMIDINE

Dexmedetomidine hydrochloride, an imidazole compound is the pharmacologically active s-enantiomer of medetomidine, a veterinary anaesthetic agent. It is described chemically as (+)-4-(s)[2 3–(dimethylphenyl) ethyl]-11 H-imidazole monohyrochloride. Its empirical formula is $C_{13}H_{16}N_2HCl$ and its molecular weight is 236.7.[45]

Structural formula

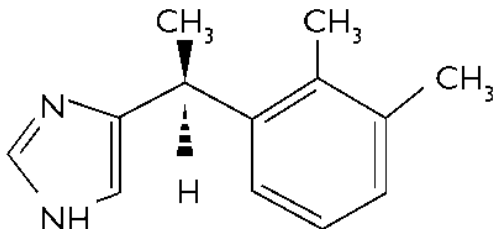


Figure 2: Chemical structure of dexmedetomidine[46]

PHYSIOCHEMICAL PROPERTIES

A white or almost white powder that is freely soluble in water with Pka of 7.1. Partition coefficient in octanol: water at pH 7.4 is 2.89. Preservative free dexmedetomidine is available in 2 ml ampoule as Dexmedetomidine Hydrochloride for intravenous use. It can also be used for intrathecal and epidural anaesthesia.

MECHANISM OF ACTION OF DEXMEDETOMIDINE

Dexmedetomidine is the dextro enantiomer of medetomidine, the methylated derivative of etomidine, its specificity for the α-2 receptor is 8 times that of clonidine, with an α-2: α-1 binding affinity ratio of 1620:1 and its effects are dose dependently reversed by administration of a selective α-2 antagonist such as atipamezole.[47]

Specific α-2 receptor subtypes mediate the varied pharmacodynamic effects of Dexmedetomidine. Agonism at α 2A receptor appears to promote sedation, hypnosis, analgesia, sympatholysis, neuroprotection[48] and inhibition of insulin secretion.[49] Agonism at the α -2B receptor suppresses shivering centrally, promotes analgesia at spinal cord sites and induces vasoconstriction in peripheral arteries. The α 2C receptors are associated with modulation of cognition, sensory processing, mood and stimulant-induced locomotor activity and regulation of epinephrine outflow from the adrenal medulla. Inhibition of nor epinephrine release appears to be equally affected by all three α-2 receptor subtypes.[50]

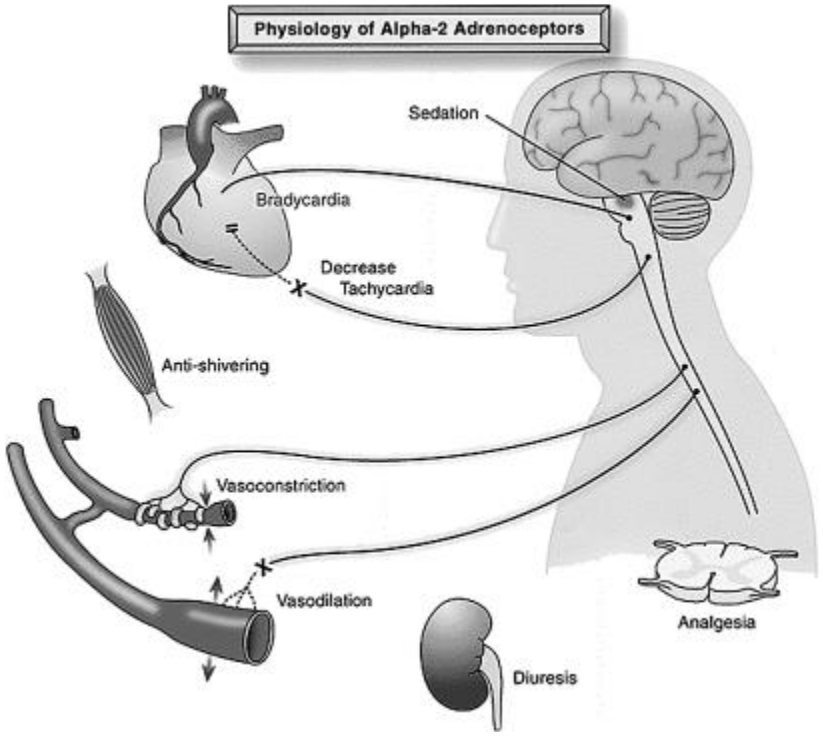


Figure 3: Responses that can be mediated by α-2 adrenergic receptors[27]

The mechanism of action of Dexmedetomidine is unique and differs from currently used sedative drugs. Alpha-2 adrenoceptors are found in CNS in highest

densities in the locus ceruleus, the predominant noradrenergic nuclei of the brainstem and an important modulator of vigilance. Presynaptic activation of alpha-2A adrenoceptor in the locus ceruleus inhibits the release of nor-epinephrine and results in the sedative and hypnotic effects.[51] In addition, the locus ceruleus is the site of origin for the descending medullospinal nor adrenergic pathway, known to be an important modulator of nociceptive neurotransmission. Stimulation of alpha-2 adrenoceptors in this area terminates the propagation of pain signals leading to analgesia. Postsynaptic activation of alpha-2 receptors in the CNS results in decrease in sympathetic activity leading to hypotension and bradycardia.[39]

At the spinal cord, stimulation of alpha-2 receptors at the substantia gelatinosa of the dorsal horn leads to inhibition of the firing of nociceptive neurons and inhibition of release of substance P. Also the alpha-2 adrenoceptors located at the nerve endings have a possible role in the analgesic mechanism by preventing norepinephrine release. The spinal mechanism is the principal mechanism for the analgesic action of Dexmedetomidine even though there is a clear evidence for both a supraspinal and peripheral sites of action.[52]

PERIPHERAL ACTION: Alpha-2 receptors are located on blood vessels where they mediate vasoconstriction and on sympathetic terminals, where they inhibit norepinephrine release. The responses of activation of alpha-2 receptors in other areas include contraction of vascular and other smooth muscles; decreased salivation and decreased bowel motility in the gastrointestinal tract, inhibition of renin release, increased glomerular filtration and increased secretion of sodium and water in the

kidney, decreased release of insulin from the pancreas, decreased intraocular pressure, decreased platelet aggregation and decreased shivering threshold by 2˚C.[27]

Pharmacodynamics of dexmedetomidine

Dexmedetomidine is considered as the full agonist at alpha-2 receptors compared to clonidine which is considered as a partial agonist at alpha-2 adrenoceptors. The selectivity of Dexmedetomidine to alpha-2 receptors compared to alpha-1 receptors is 1620:1, whereas with clonidine it is 200:1. The selectivity is dose dependant, at low to medium doses and on slow infusion, high levels of alpha-2 selectivity is observed, while high doses or rapid infusions of low doses are associated with both alpha-1 and alpha-2 activities.[27]

Central nervous system

1. Sedation, anxiolysis, hypnosis and amnesia

Dexmedetomidine provides dose dependant increase in anxiolysis and sedation. However, the quality of sedation appears to be unique in comparison with gamma-aminobutyric acid (GABAnergic) agents such as midazolam or propofol. Arousability is maintained at deep levels of sedation, with good correlation between the level of sedation and the bispectral EEG (BIS). Once aroused subjects performed well on tests of vigilance, such as the critical flicker-fusion frequency. Dexmedetomidine induced sedation qualitatively resembles normal sleep. Dexmedetomidine induces sleep by activating endogenous non-rapid eye movement pathways. Stimulation of alpha-2A receptors in the nucleus ceruleus inhibits nor adrenergic neurons and disinhibits GABAnergic neurons in the ventrolateral preoptic nucleus (VLPO). In contrast, GABAnergic agents such as propofol or

benzodiazepines, directly enhance the inhibitory effects of the GABAnergic system at the VLPO. As such norepinephrine release remains unaffected, thus leading to less restful sleep.[53]

The participation of non-rapid eye movement sleep pathways seems to explain why patients who appear to be deeply asleep from Dexmedetomidine are relatively easily aroused in much the same way as occurs with natural sleep. This type of sedation is branded "cooperative or arousable", to distinguish it from sedation induced by drugs acting on the GABA system, such as midazolam or propofol which produce a clouding of consciousness.[54] Sedation with Dexmedetomidine is dose dependant, however even low doses might be sufficient to produce sedation.[55] Dexmedetomidine may lack amnestic properties but amnesia is achieved with dexmedetomidine only at high plasma levels (>1.9 ng/ml) without retrograde amnesia.[56]

2. Analgesia

Dexmedetomidine appears to exert analgesic effects at the spinal cord level and at supraspinal sites. However there has been a considerable debate as to whether its analgesic effects are primary or simply opioid sparing. In comparison with hypnotic agents such as propofol or postoperative opioids used alone, Dexmedetomidine significantly decreases opioid requirement.[57,58]

Dexmedetomidine may also provide antinociception through nonspinal mechanisms. Intra-articular administration during knee surgery improves postoperative analgesia, with less sedation than IV route.[59] Suggested mechanisms are

activation of alpha-2A receptors, inhibition of the conduction of nerve signals through C and Aδ fibres and the local release of encephalin.[60]

Respiratory effects

Dexmedetomidine is able to achieve its sedative, hypnotic and analgesic effects without causing any clinically relevant respiratory depression unlike opioids. The changes in ventilation appeared similar to those observed during natural sleep. Dexmedetomidine do not cause any changes in arterial oxygenation, pH and respiratory rate.[56] It also exhibited a hypercarbic arousal phenomenon, which has been described during normal sleep and is a safety feature. The obstructive respiratory pattern and irregular breathing seen with high doses of 1-2µg/kg given over 2 minutes and are probably related more to deep sedation and anatomical features of the patient and this could be easily overcome by insertion of an oral airway.[61] Co-administration of dexmedetomidine with anaesthetic agents, sedatives, hypnotics or opioids is likely to cause additive effects.[58]

Intravenous or inhaled Dexmedetomidine has been implicated in blocking histamine induced bronchoconstriction in dogs.[62]

Dexmedetomidine is effective in achieving excellent sedation without respiratory depression during fibreoptic intubation or other difficult airway procedures.[63,64] Intubating conditions are further enhanced because Dexmedetomidine decreases saliva production and airway secretions.[47]

Cardiovascular effects

Dexmedetomidine does not appear to have any direct effects on the heart. A biphasic cardiovascular response has been described after the application of dexmedetomidine.[36, 55] The administration of a bolus of 1 μg/kg body weight, initially results in a transient increase of the blood pressure and a reflex decrease in heart rate, especially in young healthy patients. The initial reaction can be explained by the peripheral alpha 2B adrenoceptors stimulation of vascular smooth muscles and can be attenuated by a slow infusion over 10 or more minutes. Even at slower infusion rates however the increase in mean arterial pressure over the first 10 minutes was shown to be in the range of 7% with a decrease in heart rate between 16% and 18%.[55] The initial response lasts for 5-10 minutes and is followed by a decrease in blood pressure of approximately 10%-20% below baseline values; both these effects are caused by the inhibition of the central sympathetic outflow overriding the direct stimulant effects. Another possible explanation for the subsequent heart rate decrease is the stimulation of presynaptic alpha-2 adrenoceptors, leading to a decrease in norepinephrine release.[65]

The application of a single high dose of Dexmedetomidine reduced norepinephrine release by as much as 92% in young healthy volunteers. The release of epinephrine is also reduced by the same amount. The baroreceptor reflex is well preserved in patients who received dexmedetomidine, and the reflex heart rate response to a pressor stimulus is augmented. These results illustrate that

cardiovascular response is evoked mainly by decrease in central sympathetic outflow.[66]

Dexmedetomidine could result in cardiovascular depression i.e. bradycardia and hypotension. The incidence of postoperative bradycardia has been reported as high as 40% in healthy surgical patients who received Dexmedetomidine, especially high doses. Usually these temporary effects were successfully treated with atropine or ephedrine and volume infusions.[67]

Effect on adrenocorticotrophic hormone (ACTH) secretion

Although Dexmedetomidine has no significant effect on ACTH secretion at therapeutic doses, cortisol's response to ACTH may be reduced after prolonged use or high doses. The ratio of levels of inhibition caused by etomidate and Dexmedetomidine was shown to be in the order of 100:1, suggesting that the biologic effects of the inhibitory activities of Dexmedetomidine are not clinically important.[68]

Effect on renin release

Renin release is stimulated by β-adrenoceptor mechanisms, whereas alpha-2 adrenoceptor agonists directly inhibit renin release.[27]

Effect on insulin release

Stimulation of alpha-2 adrenoceptors on islet cells directly inhibits the release of insulin; this effect has unproven clinical importance, because hyperglycemia has never been reported to be significant in patients receiving clonidine.[27]

Effect on thermoregulation

Like clonidine, Dexmedetomidine is associated with lower rates of shivering. Intravenous infusion of Dexmedetomidine reduced the vasoconstriction and

shivering threshold but do not change the sweating threshold. Therefore with Dexmedetomidine, thermoregulatory response were inhibited within a wider range of temperature.[69] Dexmedetomidine and other alpha-2 agonists suppress shivering, possibly by their activity at alpha-2B receptors in the hypothalamic thermoregulatory centre of the brain. Low dose Dexmedetomidine has an additive effect with meperidine on lowering the shivering threshold, and Dexmedetomidine may be beneficial in decreasing patient discomfort from postanaesthetic shivering.[53]

Effects on renal function

Alpha-2 agonists exert a diuretic effect by inhibiting the antidiuretic action of arginine vasopressin at the collecting duct, resulting in decreased expression of aquaporin-2 receptors and decreased salt and water absorption.[27]

Organ protective effects

The ability of alpha-2 agonists to decrease tachycardia and hypertension suggests that they may play a role in cardioprotection by enhancing myocardial oxygen balance. There is considerably more experimental evidence that dexmedetomidine has neuroprotective effects by several mechanisms. These include sympatholysis, preconditioning and attenuation of ischemic reperfusion injury.[70] There is also evidence that dexmedetomidine decreases cerebral blood flow. But its ratio with cerebral metabolic rate i.e. flow metabolism coupling appears to be preserved.[71]

Pharmacokinetics

After intravenous injection, Dexmedetomidine has an onset of action after approximately 15 minutes. Peak concentrations are usually achieved within 1 hr after

continuous infusion. It has a rapid distribution half life ($t_{1/2}\alpha$) of 6 minutes and a terminal elimination half life ($t_{1/2}\beta$) of between 2 and 2.5 hrs. The drug is highly protein bound (94%) with a 6% free fraction. It has a steady state volume of distribution (Vdss, 1.33 l/kg). Dexmedetomidine is rapidly distributed and extensively metabolized in the liver. It undergoes conjugation (41%), n-methylation (21%) or hydroxylation followed by conjugation. Dexmedetomidine is 94% protein bound and its concentration ratio between blood and plasma is 0.66. The elimination half life is 2 to 3 hrs with a context sensitive half time ranging from 4 minutes after a 10 minute infusion to 250 minutes after an 8 hr infusion.[72] Total plasma clearance is age independent, thus similar rates of infusion can be used in children and adults to effect a steady state plasma concentration. Plasma protein binding is similar to adults.[73]

Dexmedetomidine is also absorbed systematically through transdermal, buccal or intramuscular routes, with a mean bioavailability from the latter 2 routes of 82% and 104% respectively. After intramuscular administration, the time to maximum concentration (T_{max}) in the blood is 1.6 to 1.7 hrs, with an absolute bioavailability of 73%. After transdermal administration, the T_{max} is six hours with an absolute bioavailability of 88%.[74]

Perioperative uses of Dexmedetomidine

1. Premedication

Dexmedetomidine has anxiolytic, sedative, analgesic, antisialogogue and sympatholytic properties which render it suitable as a premedication agent. As a premedicant, Dexmedetomidine, at IV doses 0.33 to 0.67μg/kg given 15 minutes

before surgery, seems efficacious, while minimizing the cardiovascular side effects of hypotension and bradycardia.

a. It reduces thiopental and propofol requirements.[28, 29, 33 and 103]

b. Reduces the requirements of volatile anaesthetics.[30, 75, 76]

c. More effectively attenuates the haemodynamic responses to endotracheal intubation.[28, 29,30,31,32,33,34,35]

d. Decreases plasma catecholamine concentrations.[66]

e. Improves perioperative haemodynamic and sympathoadrenal stability.

2. Use of dexmedetomidine for regional anaesthesia

a. Epidural dexmedetomidine at a dose of 100µg decreased the incidence of postoperative shivering.[77]

b. Intrathecal dexmedetomidine at a dose of 3µg causes significant prolongation of sensory and motor blockade.[78]

c. Addition of 0.5µg/kg body weight of dexmedetomidine to lidocaine for intravenous regional anaesthesia improves the quality of anaesthesia and perioperative analgesia.[79]

3. Use in monitored anaesthesia care (MAC): Dexmedetomidine confers arousable sedation with ease of orientation, anxiolysis and mild analgesia without respiratory depression.[42]

4. Dexmedetomidine has also been used as **sole anaesthetic agent** upto doses of 10µg/kg/hr.[64]

5. Use of dexmedetomidine in postoperative period: infusion can be continued in extubated and spontaneously breathing patients. The ongoing sedation and sympatholytic effect is beneficial in reducing postoperative myocardial ischemic events in high risk patients undergoing non-cardiac surgery.[42]

6. Use of dexmedetomidine in paediatric age group:[80] addition of dexmedetomidine 2μg/kg body weight to bupivacaine for caudal analgesia promotes analgesia after anaesthetic recovery without increasing the incidence of side effects.

7. Use of dexmedetomidine in intensive care unit (ICU): it provides adequate sedation with minimal respiratory depression and can be used for weaning patients from ventilator.[81]

Adverse effects

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

Withdrawal phenomenon is reported after abrupt discontinuation with prolonged administration of dexmedetomidine, leading to development of hypertension, tachycardia, emesis, agitation, dilated pupils, diarrhea, increased muscle tone and tonic clonic seizures.[82,83]

Dosage and administration

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

It is not necessary to discontinue Dexmedetomidine before, during or after extubation. Dose up to 2.5μg/kg/hr for up to seven days, with no rebound effect on withdrawal and no compromise in haemodynamics stability have been used in clinical trials.[84]

Drug interactions

Dexmedetomidine has shown to inhibit CYP2 D6 in vitro, but the clinical significance of this inhibition is not well established. Dexmedetomidine appears to have little potential for interactions with drugs metabolized by the cytochrome p450 system.

Co-administration of Dexmedetomidine with sevoflurane, isoflurane, propofol, alfentanil and midazolam may result in enhancement of sedative, hypnotic or anaesthetic effects.[85]

PHARMACOLOGY OF MIDAZOLAM [9]

Fryer and Walser's in 1976 synthesised midazolam (Versed), the first clinically used water-soluble benzodiazepine. Midazolam was the first benzodiazepine that was produced primarily for use in anesthesia.

The benzodiazepines have many of the characteristics sought by anesthesiologists. Specific benzodiazepine receptors were described when ligands were found to interact with a central receptor. The discovery and understanding of the mechanism of the benzodiazepine receptor have enabled chemists to develop many agonist compounds and to produce a specific antagonist for clinical use.

Physicochemical Characteristics

Three benzodiazepine receptor agonists are commonly used in anesthesia: midazolam, diazepam, and lorazepam . All these molecules are relatively small and are lipid soluble at physiologic pH. Midazolam solution (1 or 5 mg/mL) contains 0.8% sodium chloride and 0.01% disodium edetate, with 1% benzyl alcohol as a preservative. The pH is adjusted to 3 with hydrochloric acid and sodium hydroxide. Midazolam is the most lipid soluble of the benzodiazepine drugs in vivo, but because of its pH-dependent solubility, it is water soluble as formulated in a buffered acidic medium (pH 3.5). The imidazole ring of midazolam accounts for its stability in solution and rapid metabolism. The high lipophilicity accounts for the rapid CNS effect and relatively large volumes of distribution.

Metabolism

Biotransformation of the midazolam occurs in the liver. The two principal pathways involve either hepatic microsomal oxidation (*N*-dealkylation or aliphatic hydroxylation) or glucuronide conjugation. The difference in the two pathways is significant because oxidation is susceptible to outside influences and can be impaired by certain population characteristics (e.g., old age), disease states (e.g., hepatic cirrhosis), or the coadministration of other drugs that can impair oxidizing capacity (e.g., cimetidine). Conjugation is less susceptible to these factors. Midazolam undergo oxidation reduction or phase I reactions in the liver. The fused imidazole ring of midazolam is oxidized rapidly by the liver.

Midazolam is biotransformed to hydroxymidazolams, which have activity, and when given over a longer time can accumulate. These metabolites are rapidly conjugated and excreted in the urine, however. The α-hydroxymidazolam has an estimated clinical potency 20% to 30% of midazolam. It is excreted largely by the kidneys and can cause profound sedation in patients with renal impairment. The primary hydroxymetabolite is cleared more rapidly than midazolam in healthy patients. The metabolites are less potent and normally cleared more rapidly than midazolam, making them of little concern in patients with normal hepatic and renal function.

Pharmacokinetics

The midazolam is classified as short-lasting according to its metabolism and plasma clearance. The plasma disappearance curve of midazolam can be fitted to a two-compartment or three-compartment model. The clearance rate of midazolam ranges from 6 to 11 mL/kg/min. Although the termination of action of these drugs is primarily a result of redistribution of the drug from the CNS to other tissues after use in anesthesia, after daily (long-term) repeated administration, or after prolonged continuous infusion, midazolam blood levels decrease more rapidly than blood levels of the other drugs because of greater hepatic clearance.

Factors that may influence the pharmacokinetics of midazolam are age, gender, race, enzyme induction, and hepatic and renal disease. Increasing age tends to reduce the clearance of midazolam to a lesser degree. Midazolam is affected by obesity. The volume of distribution is increased as drug goes from the plasma into the adipose tissue. Although clearance is not altered, elimination half-life is prolonged, owing to the delayed return of the drug to the plasma in obese patients. Generally, sensitivity to midazolam in some groups, such as elderly patients, is greater despite relatively modest pharmacokinetic effects; factors other than pharmacokinetics must be considered when midazolam is used.

Pharmacology

Midazolam is hypnotic, sedative, anxiolytic, amnesic, anticonvulsant, and centrally produced muscle-relaxing properties. The binding of midazolam to its receptor is of high affinity and is stereospecific and saturable. Midazolam is approximately 3 to 6 times, and lorazepam 5 to 10 times, as potent as diazepam.

The mechanism of action of midazolam is reasonably well understood. More recent genetic studies have found the $GABA_A$ subtypes mediate the different effects (amnesic, anticonvulsant, anxiolytic, and sleep). Sedation, anterograde amnesia, and anticonvulsant properties are mediated via $\alpha 1$ receptors, and anxiolysis and muscle relaxation are mediated by the $\alpha 2$ $GABA_A$ receptor. Drug effect is a function of blood level. By using plasma concentration data and pharmacokinetic simulations, it has been estimated that benzodiazepine receptor occupancy of less than 20% may be sufficient to produce the anxiolytic effect, sedation is observed with 30% to 50% receptor occupancy, and unconsciousness requires 60% or greater occupation of benzodiazepine agonist receptors.

The midazolam receptors are found in highest densities in the olfactory bulb, cerebral cortex, cerebellum, hippocampus, substantia nigra, and inferior colliculus, but lower densities are found in the striatum, lower brainstem, and spinal cord. Spinal cord benzodiazepine receptors can play an important role in analgesia, however, further elucidating the mechanism of action of this drug class. Intrathecal midazolam reduces excitatory GABA-mediated neurotransmission in interneurons, leading to a

decrease in the excitability of spinal dorsal horn neurons. Intrathecal midazolam added to a bupivacaine spinal increases analgesia and shortens the time to return of motor function.

A fascinating and therapeutically significant discovery regarding the benzodiazepine receptor is that the pharmacologic spectrum of ligands includes three different types or classes, which have been termed *agonists, antagonists,* and *inverse agonists,* names that connote their actions. Agonists (e.g., midazolam) alter the conformation of the $GABA_A$ receptor complex so that binding affinity for GABA is increased, with a resultant opening of the chloride channel. Agonist and antagonist bind to a common (or at least overlapping) area of the receptor by forming differing reversible bonds with the receptor. The well-known effects of an agonist then occur (anxiolysis, hypnosis, and anticonvulsant action). Antagonists (e.g., flumazenil) occupy the benzodiazepine receptor, but they produce no activity and block the actions of the agonists and inverse agonists. Inverse agonists reduce the efficiency of GABA-adrenergic synaptic transmission, and because GABA is inhibitory, the result of decreased GABA is CNS stimulation. The potency of the ligand is dictated by its affinity for the benzodiazepine receptor and the duration of effect by the rate of clearance of the drug from the receptor.

The onset and duration of action of a bolus IV administration of a midazolam depend on the lipid solubility of the drug. Midazolam has a rapid onset (usually within 30 to 60 seconds). The half-life of equilibrium between plasma concentration and EEG effect of midazolam is approximately 2 to 3 minutes and is not affected by

age. Similar to onset, the duration of effect also is related to lipid solubility and blood level. The more rapid redistribution of midazolam accounts for the shorter duration of its action.

Effects on the Central Nervous System

The midazolam, in a dose-related manner, reduce the $CMRO_2$ and CBF. In healthy human volunteers, midazolam, 0.15 mg/kg, induces sleep and reduces CBF by 34%, despite a slight increase in $PaCO_2$ from 34 to 39 mm Hg. Midazolam increase the seizure initiation threshold to local anesthetics. Midazolam cause a dose-related protective effect against cerebral hypoxia. Antiemetic effects are not a prominent action of the benzodiazepines.

Effects on the Respiratory System

Midazolam produces dose-related central respiratory system depression. The slopes of the ventilatory response curves to carbon dioxide are flatter than normal (control), but not shifted to the right, as with opioids.

The peak onset of ventilatory depression with midazolam (0.13 to 0.2 mg/kg) is rapid (about 3 minutes), and significant depression remains for about 60 to 120 minutes. The rate of midazolam administration affects the onset time of peak ventilatory depression; the faster the drug is given, the more quickly this peak depression occurs.

Apnea occurs with benzodiazepines in a dose-dependent manner. The incidence of apnea after thiopental or midazolam when these drugs are given for induction of anesthesia is similar. Apnea is more likely to occur in the presence of opioids. Old age, debilitating disease and other respiratory depressant drugs probably also increases the incidence and degree of respiratory depression and apnea with benzodiazepines.

Effects on the Cardiovascular System

The midazolam used alone have modest hemodynamic effects. The predominant hemodynamic change is a slight reduction in arterial blood pressure, resulting from a decrease in systemic vascular resistance. The mechanism by which benzodiazepines maintain relatively stable hemodynamics involves the preservation of homeostatic reflex mechanisms, but there is evidence that the baroreflex is impaired by midazolam. Midazolam causes a slightly larger decrease in arterial blood pressure than the other benzodiazepines, but the hypotensive effect is minimal. Despite the hypotension, midazolam, even in doses of 0.2 mg/kg, is safe and effective for induction of anesthesia.

The stresses of endotracheal intubation and surgery are not blocked by midazolam. Adjuvant anesthetics, usually opioids, are often combined with benzodiazepines. The combinations of benzodiazepines with opiates produce greater decreases in systemic blood pressure than does each drug alone. The mechanism for

this synergistic hemodynamic effect is not completely understood, but it is probably related to a reduction in sympathetic tone when the drugs are given together.

Uses

Intravenous Sedation:

Midazolam is used for sedation as preoperative premedication, intraoperatively during regional or local anesthesia, and postoperatively. The anxiolysis, amnesia, and elevation of the local anesthetic seizure threshold are desirable benzodiazepine actions. The onset of action is more rapid with midazolam, usually with peak effect reached within 2 to 3 minutes of administration.

Induction dose → 0.05-0.15 mg/kg

Maintenance dose → 1 µg/kg/min

Sedation dose → 0.5-1 mg repeated

Oral Sedation:

An oral formulation of midazolam has been used primarily for oral premedication in pediatric patients. The dose is 0.5 mg/kg, and one preparation of 0.5 mg/mL mixed in with 10 mg/kg of oral acetaminophen. Other reparations have been developed, including strawberry-flavored glucose (pH 4.5), which is stable for 8 weeks. The 0.5 mg/kg oral dose is rapid-acting, providing reliable amnesia within 10 minutes and rendering children effectively sedated for anesthesia induction.

Induction and Maintenance of Anesthesia:

Midazolam is the benzodiazepine of choice to induce anesthesia. When midazolam is used in appropriate doses induction occurs less rapidly than with thiopental, but the amnesia is more reliable. Numerous factors influence the rapidity of action of midazolam when used for induction of general anesthesia, including dose, speed of injection, degree of premedication, age, ASA physical status, and concurrent anesthetic drugs. In a well-premedicated, healthy patient, midazolam (0.2 mg/kg given in 5 to 15 seconds) induces anesthesia in 28 seconds. The usual induction dose of midazolam in premedicated patients is 0.05 to 0.15 mg/kg. When midazolam is used with other anesthetic drugs (coinduction), there is a synergistic interaction, and the induction dose is less than 0.1 mg/kg. The synergy is seen when midazolam is used with opioids or other hypnotics, such as thiopental and propofol.

Side Effects and Contraindications

The most significant problem with midazolam is respiratory depression. When used as sedative or for induction and maintenance of anesthesia, midazolam can produce an undesirable degree or prolonged interval of postoperative amnesia, sedation, and, rarely, respiratory depression. These residual effects can be reversed with flumazenil.

METHODOLOGY

A study entitled "A comparative study of intravenous dexmedetomidine and midazolam used as a premedication for laparoscopic surgeries under general anesthesia – a prospective randomized double blind controlled clinical study" was undertaken in B.L.D.E.U.'s Shri B.M. Patil Medical College Hospital and Research Centre – 586103 Karnataka, during the period 18 months from Nov 2011 to April 2013. The study was undertaken after obtaining ethical committee clearance as well as informed consent from all patients.

Fifty patients, scheduled for various elective laparoscopic surgical procedures belonging to ASA class I and II were included in the study. The patients were normotensive with age varying from 18 to 55 years.

INCLUSION CRITERIA

1) Adult patients aged between 18 and 55 years of both sex
2) Patients belonging to ASA class I and II
3) Mallampatti grade I and II
4) Elective laparoscopic surgeries under general endotracheal anaesthesia

EXCLUSION CRITERIA

1) Patients with cardiac, coronary, renal, hepatic, cerebral diseases and peripheral vascular diseases.
2) Patients with hypertension.

3) Patients with heart rate less than 60 bpm, systolic blood pressure less than 100 mm of Hg.
4) Presence of 1st, 2nd or 3rd degree heart block.
5) Patients with difficult airway and obese patients (BMI>30).
6) Patients with endocrinal diseases like hyperthyroidism, hypothyroidism and diabetes mellitus.

The study population was randomly divided into two groups with 25 patients in each group using sealed envelopes containing the name of the group and patient was asked to pick up the envelope. The envelope was opened by senior anaesthesiologist who was assigned to prepare the solutions and not involved with the study.

Group A- Midazolam group (n=25): received injection midazolam 0.02mg/kg intravenously over 10 min, 10 minutes prior to induction using syringe pump.

Group D – Dexmedetomidine (n=25): received injection dexmedetomidine 0.6µg/kg (Dexem, Themis Medicare Limited, 200µg in 2 ml ampoule) diluted with 10 ml normal saline intravenously over 10 min, 10 minutes prior to induction using syringe pump.

Pre-anaesthetic evaluation was done on the day before surgery. A routine pre-anaesthetic examination was conducted assessing;

- General condition of the patient
- Airway assessment by Mallampatti grading and rule of 1-2-3
- Nutritional status and body weight of the patient
- A detailed examination of the Cardiovascular system

- A detailed examination of the Respiratory system

The following investigations were done in all patients

- Haemoglobin estimation
- Urine examination for albumin, sugar and microscopy
- Standard 12-lead electrocardiogram
- X-ray chest/Screening of chest
- Blood sugar
- Blood urea, Serum creatinine.

All patients included in the study were premedicated with tablet alprazolam 0.5 mg and tablet ranitidine 150 mg orally at bed time the previous night before surgery. They were kept nil orally 10 pm onwards on the previous night.

On arrival of the patient in the operating room, an 18-gauge intravenous cannula was inserted under local anaesthetic infiltration and an infusion of normal saline was started. The patients were connected to BPL SC-7000, multiparameter monitor which records Heart rate, non-invasive measurements of SBP, DBP, MAP, EtCO2 and continuous ECG monitoring and oxygen saturation. The baseline systolic, diastolic blood pressure, mean arterial pressure, heart rate and SpO2 were recorded. The cardiac rate and rhythm were also monitored from a continuous visual display of electrocardiogram from lead II.

After recording the baseline reading, patients in group A received midazolam 0.02mg/kg intravenously over 10 min, 10 min before induction using syringe pump and patients in group B received dexmedetomidine 0.6µg/kg body weight diluted in

10 ml normal saline intravenously over 10 min, 10 min before induction using syringe pump. The study drug was prepared by the senior anaesthesiologist who was not involved with the study and observer as well as patient was blinded for the study. 50 μg of dexmedetomidine (0.5 ml) was added to 9.5 ml of normal saline and made to 10 ml with each ml containing 5 μg of dexmedetomidine. Based on the body weight, volume of the diluted drug in normal saline is infused through a syringe pump.

All the patients were premedicated with injection ondansetron 0.08mg/kg, injection glycopyrrolate 0.01mg/kg and injection Pentazocine 0.3mg/kg body weight IV after test drug administration. Then patients were preoxygenated for 3 minutes via a face mask with Bain's circuit. Anaesthesia was induced with injection propofol, till loss of eye lash reflex occurred and dose of propofol required for loss of eye lash reflex recorded. Endotracheal intubation was facilitated with 1.5mg/kg IV succinylcholine one minute prior to laryngoscopy and intubation. Laryngoscopy and intubation was performed using Macintosh no.3 blade lasting for not more than 15 seconds and after confirmation of bilateral equal air entry, the endotracheal tube was fixed. If time for laryngoscopy and intubation exceeds 15 seconds, such patients were excluded from the study.

Anaesthesia was maintained using 66% nitrous oxide and 33% of oxygen with 0.2-1% isoflurane. After the patients recovered from succinylcholine further neuromuscular blockade was maintained with vecuronium 0.02 mg/ kg . No surgical or any other stimulus was applied during 10 minutes of study period and vecuronium was the only additional drug given during this 10 minutes period. At the end of the

procedure total dose of vecuronium required for the surgery recorded and patients were reversed with neostigmine 0.05 mg/kg body weight and glycopyrrolate 0.01 mg/ kg IV. Sedation at the end of the surgery was assessed using Ramsay sedation score.

MONITORING

The following cardiovascular parameters were recorded in all patients.

- Heart rate [HR] in beats per minute
- Systolic blood pressure [SBP] in mm of Hg
- Diastolic blood pressure [DBP] in mm of Hg
- Mean arterial pressure [MAP] in mm of Hg

The above cardiovascular parameters were monitored in the following time interval –

1. Basal before giving study drug

   After administering study drug:

2. 2 minutes
3. 5 minutes
4. 8 minutes
5. Before induction of anesthesia.
6. After induction of anesthesia.

   After laryngoscopy and intubation:

7. 1 minute
8. 3 minutes
9. 5 minutes
10. 10 minutes

SIDE EFFECTS

1) Hypertension was defined as SBP $\geq$ 20% of baseline value.[29]
2) Tachycardia was defined as HR > 25% of baseline value.[66]
3) Bradycardia was defined as HR < 45 beats/ minute.[29,51]
4) Any dysrrhythmia was defined as any ventricular or supra ventricular beat or any rhythm other than sinus.[66]

All these parameters were recorded in both the groups.

The side effects of the study drug like hypotension, bradycardia and sedation were noted.

Sedation scoring as per Ramsay sedation scale.

RAMSAY SEDATION SCORING[97]

Score	Response
1	Anxious or restless or both
2	Cooperative, oriented and tranquil
3	Responding to commands
4	Brisk response to stimulus
5	Sluggish response to stimulus
6	No response to stimulus

STATISTICAL METHODS

- Descriptive statistics (to measure mean, standard deviation)
- Independent sample ‘t’ test (to measure difference between two groups i.e. inter group comparison)
- Contingency table analysis (for association between the rows and columns)
- Statistical software used was SPSS version 15.

RESULTS

Table no. 1(a) : Showing the age distribution between Group A and Group B

	A		B	
Age	**Frequency**	**Percentage**	**Frequency**	**Percentage**
15-25	4	16.0	11	44.0
25-35	3	12.0	5	20.0
35-45	8	32.0	5	20.0
45-55	7	28.0	1	4.0
55-65	3	12.0	3	12.0
Total	25	100.0	25	100.0

Graph no. 1: Showing the age distribution between Group A and Group B

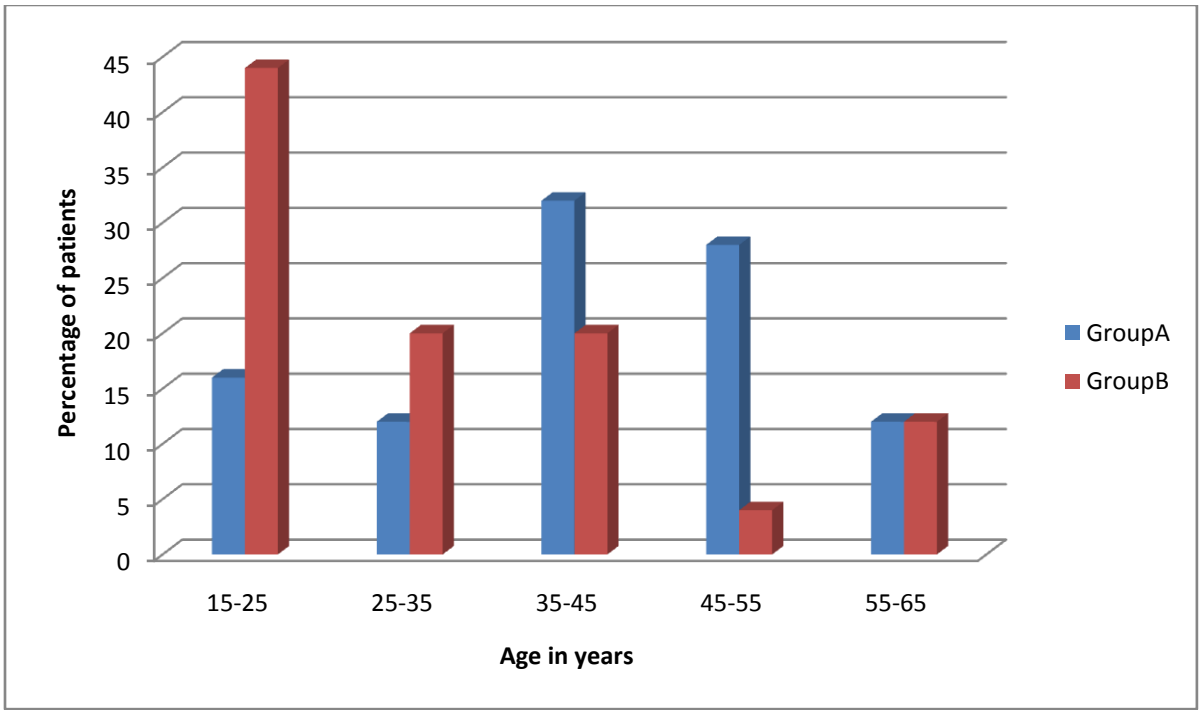


Table no. 1 (b) : Showing the age distribution between Group A and Group B

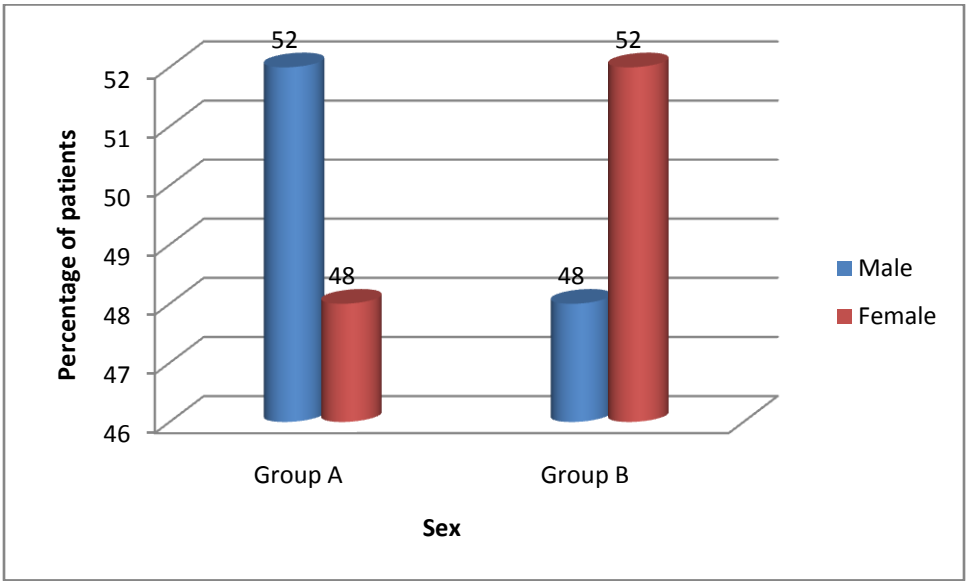
	Mean	S.D	S.E	p-value
Group A	36.83	12.4376	2.48752	**0.455**
Group B	36.42	13.3832	2.67664	

Table 1 (a) and 1 (b) shows age distribution of the patients in both the groups. The minimum age in groups A and B were 20 and 18 years respectively. The maximum age in both groups was 55 years. The mean age in group A and B were 36.8±12.43 and 36.42± 13.38 respectively. There was no significant difference in the age of patients between the Group A and Group B. Both groups were similar with respect to age distribution (p=0.455).

Table No. 2 : Showing the sex distribution between Group A and Group B

	A		B		
Sex	**Frequency**	**Percentage**	**Frequency**	**Percentage**	**p-value**
Male	13	52.0	12	48.0	**0.777**
Female	12	48.0	13	52.0	
Total	25	100	25	100	

Graph No. 2: Showing the sex distribution between Group A and Group B



From the above table it is seen that statistically there is no significant change in the gender between the two groups (p=0.777).

Table No. 3 (a) : Showing the body weight distribution between Group A and Group B

	A		B	
Weight in Kg	**Frequency**	**Percentage**	**Frequency**	**Percentage**
43-53	12	48.0	11	44.0
53-63	12	48.0	10	40.0
63-73	1	4.0	4	16.0
Total	25	100	25	100

Graph no. 3: Showing the body weight distribution between Group A and Group B

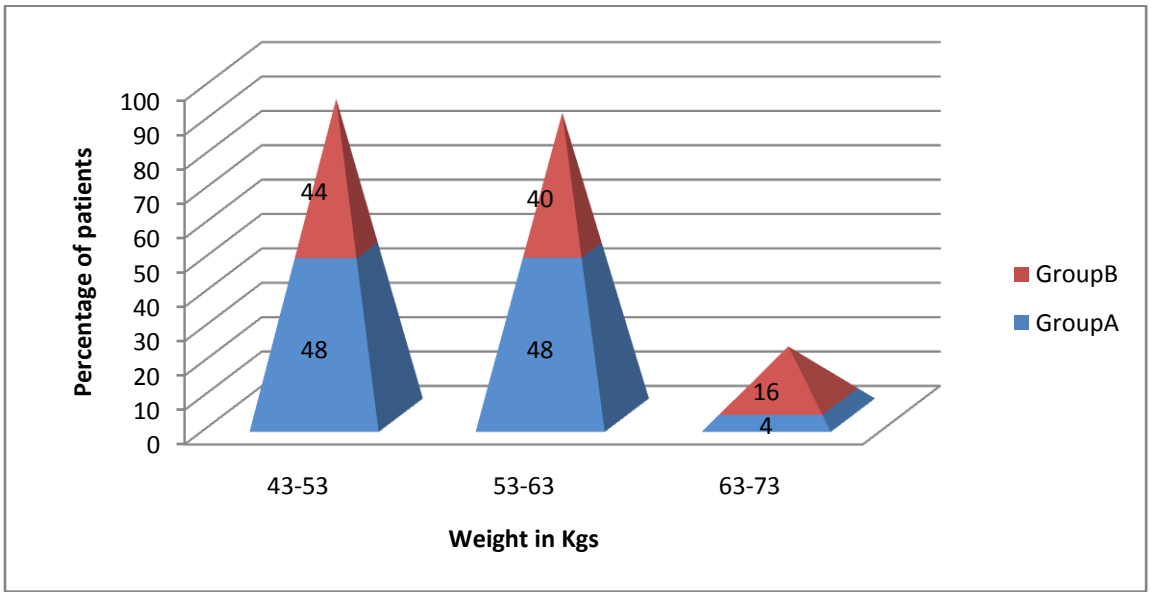


Table no. 3 (b) : Showing the body weight distribution between Group A and Group B

	Mean	S.D	S.E	p-value
Group A	54.0800	5.80890	1.16178	**0.107**
Group B	55.0400	7.74317	1.54863	

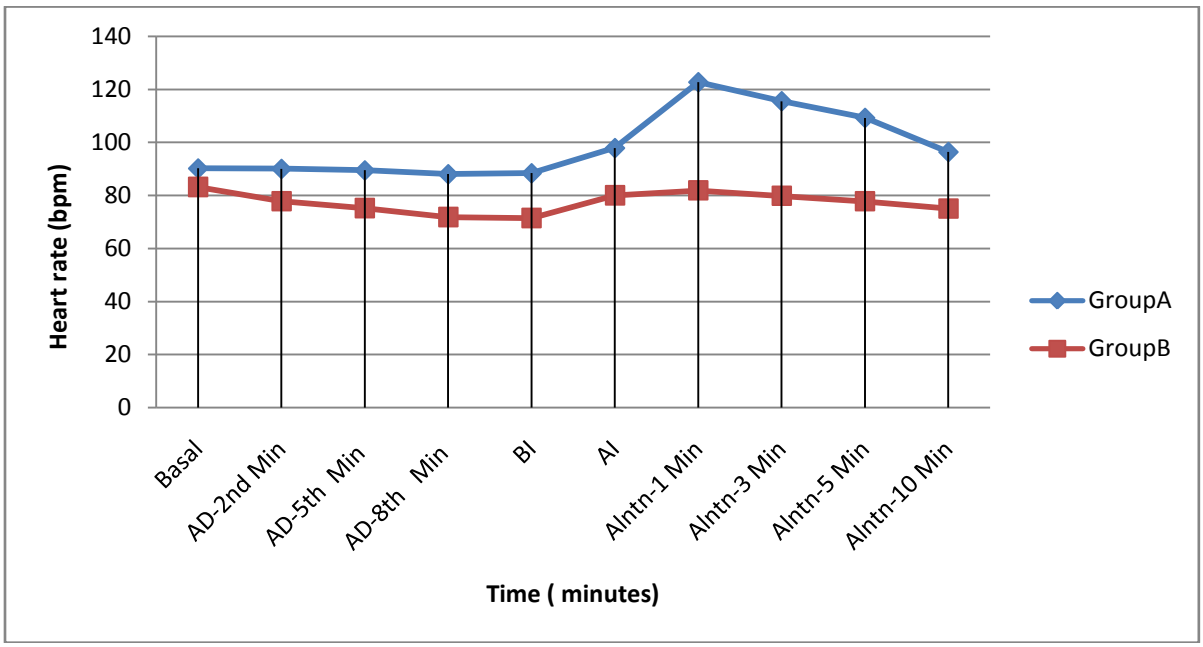
Table 3 (a) and (b) shows the body weight distribution of the patients. The minimum body weight in groups A and B were 45 kg and 43 kg respectively. The maximum body weight in groups A and B were 68 kg and 72 kg respectively. The mean body weight in Group A was 54.080 ± 5.808 and in Group B it was 55.040 ± 7.743. There was no significant difference in the body weight of patients between the Group A and Group B (p=0.107).

Table no. 4 : Showing the intergroup comparison of mean heart rate (bpm) changes in response to laryngoscopy and intubation between midazolam(A) group and dexmedetomidine(B) group

		Mean	S.D	S.E	P-value
Basal	**Group A**	90.2000	9.21954	1.84391	**0.298**
	Group B	89.1200	10.85633	2.17548	
AD-2nd Min	**Group A**	90.0400	8.91852	1.78370	**0.338**
	Group B	80.6800	12.07518	2.41504	
AD-5th Min	**Group A**	89.4800	9.25167	1.85033	**0.031***
	Group B	75.2400	12.97202	2.59440	
AD-8th Min	**Group A**	88.0400	9.80850	1.96170	**0.0002***
	Group B	69.4000	10.06231	2.01246	
BI	**Group A**	88.4000	9.47804	1.89561	**0.0001***
	Group B	71.4800	10.66193	2.13239	
AI	**Group A**	97.8800	10.09257	2.01851	**0.0001***
	Group B	80.0400	10.26515	2.05303	
A lntn-1 Min	**Group A**	122.6800	10.32683	2.06537	**< 0.0001***
	Group B	81.8800	9.41329	1.88266	
A lntn-3 Min	**Group A**	115.5200	9.17478	1.83496	**< 0.0001***
	Group B	79.8400	8.86792	1.77358	
A lntn-5 Min	**Group A**	109.2400	7.23579	1.44716	**0.0001**
	Group B	77.8000	10.86278	2.17256	
A lntn-10 Min	**Group A**	96.4000	8.17517	1.63503	**0.521**
	Group B	75.0800	7.70238	1.54048	

*** Significant**

Graph No. 4: Showing the intergroup comparison of mean heart rate (bpm) changes in response to laryngoscopy and intubation between midazolam(A) group and dexmedetomidine(B) group



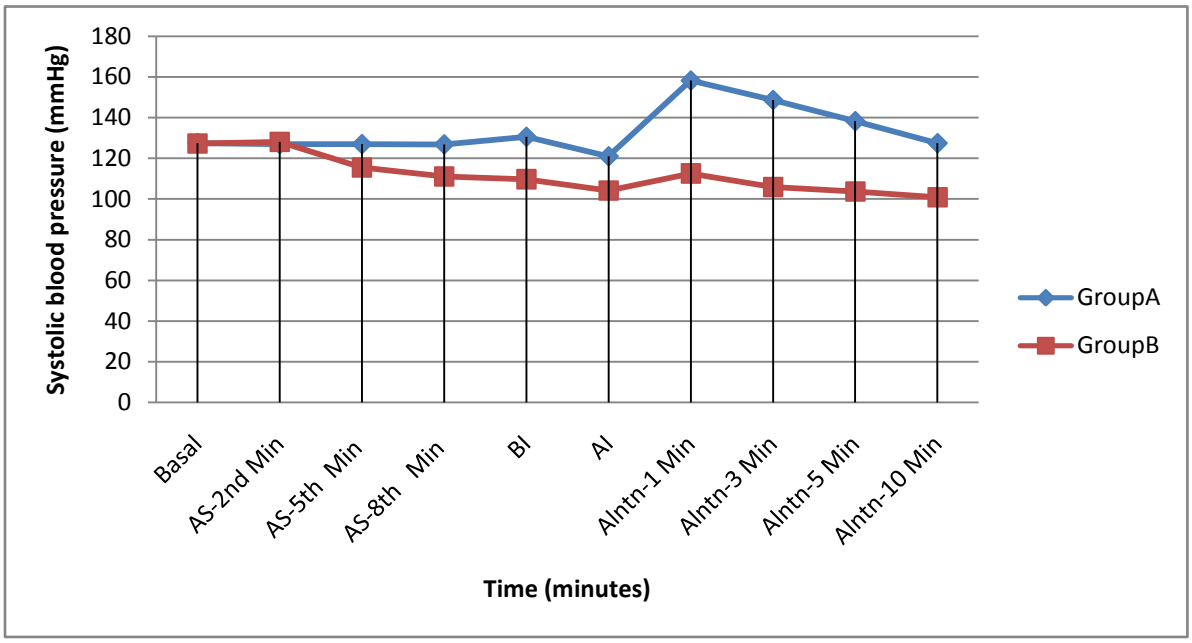
Statistical evaluation between the groups showed a significant fall in HR in group B at 2, 5 and 8 minutes of drug administration and before and after induction. The mean HR increase observed at 1, 3, 5 and 10 minutes after intubation in group A was statistically highly significant compared to mean HR in group B (p=0.000).

Table no. 5: Showing intergroup comparison of mean systolic blood pressure (SBP in mmHg) changes in response to laryngoscopy and intubation between midazolam(A) group and dexmedetomidine(B) group

		Mean	S.D	S.E	P-value
Basal	**Group A**	127.4400	7.38850	1.47770	**0.410**
	Group B	127.3200	11.36779	2.27356	
AD-2nd Min	**Group A**	126.9600	5.62346	1.12469	**0.705**
	Group B	128.0400	13.03355	2.60671	
AD-5th Min	**Group A**	126.9200	6.38957	1.27791	**0.037***
	Group B	115.4400	11.08332	2.21666	
AD-8th Min	**Group A**	126.8000	5.65685	1.13137	**0.030***
	Group B	111.0400	10.39022	2.07804	
BI	**Group A**	130.5200	6.23244	1.24649	**0.410**
	Group B	109.6800	7.16891	1.43378	
AI	**Group A**	120.9200	6.68905	1.33781	**0.025***
	Group B	104.1200	10.62356	2.12471	
A lntn-1 Min	**Group A**	158.2000	4.62781	.92556	**0.007***
	Group B	112.5200	7.92738	1.58548	
A lntn-3 Min	**Group A**	148.6400	8.04094	1.60819	**< 0.005***
	Group B	105.8000	10.29158	2.05832	
A lntn-5 Min	**Group A**	138.2000	8.37158	1.67432	**0.323**
	Group B	103.6400	10.06181	2.01236	
A lntn-10 Min	**Group A**	127.3600	5.98526	1.19705	**0.055**
	Group B	100.8000	9.75534	1.95107	

*** Significant**

Graph No. 5: Showing intergroup comparison of mean systolic blood pressure (SBP in mmHg) changes in response to laryngoscopy and intubation between midazolam(A) group and dexmedetomidine(B) group



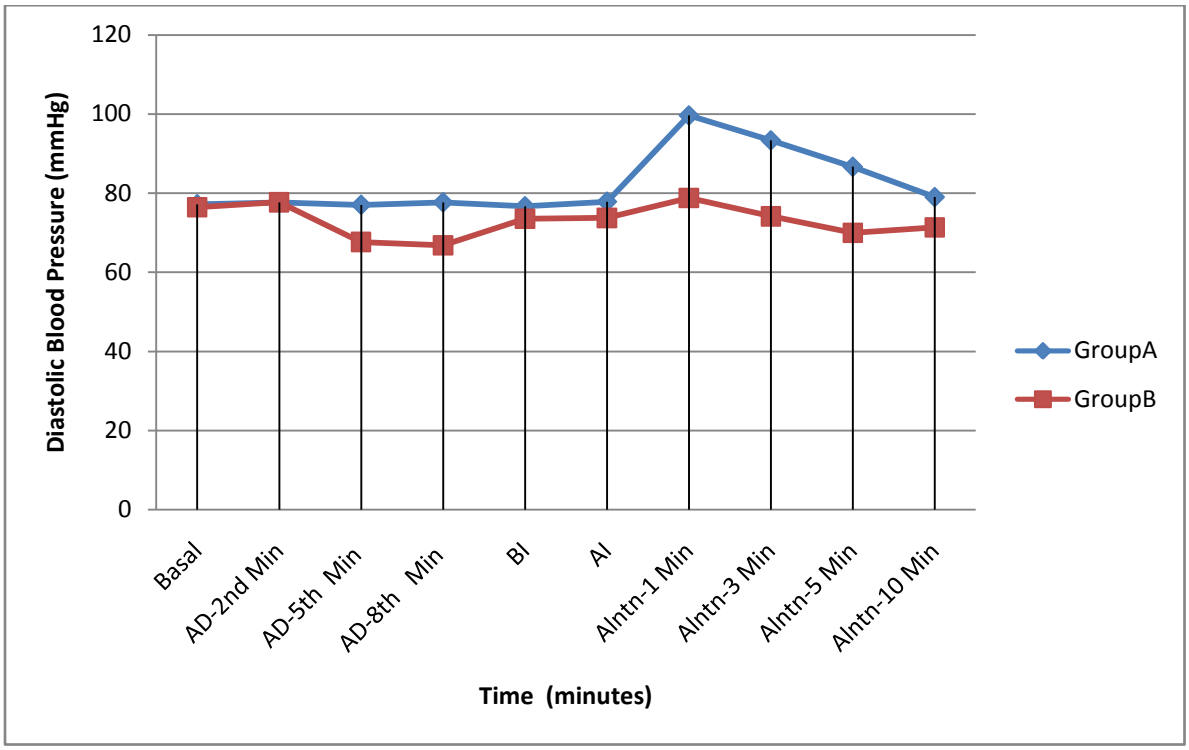
The mean SBP were comparable in both groups. After 2 min of drug administration the change in SBP was not significant (0.456). The mean SBP values at 5 and 8 minutes of drug administration, before and after induction were significantly low (p=0.00) compared to group A. The increase in SBP in group A at 1, 3, 5 and 10 minutes after intubation was statistically highly significant (p=0.00) compared to group B.

Table no. 6: Showing intergroup comparison of mean diastolic blood pressure (DBP in mmHg) changes in response to laryngoscopy and intubation between midazolam(A) and dexmedetomidine(B) group

		Mean	S.D	S.E	P-value
Basal	**Group A**	77.2000	6.33114	1.26623	**0.483**
	Group B	76.4400	6.02135	1.20427	
AD-2nd Min	**Group A**	77.6800	6.15576	1.23115	**0.283**
	Group B	77.6800	5.12933	1.02587	
AD-5th Min	**Group A**	77.0400	9.16733	1.83347	**0.0001***
	Group B	67.6400	6.68880	1.33776	
AD-8th Min	**Group A**	77.6800	6.15576	1.23115	**0.0001**
	Group B	66.8000	6.26498	1.25300	
BI	**Group A**	79.0800	6.12318	1.22464	**0.04***
	Group B	73.4800	6.83813	1.36763	
AI	**Group A**	77.8400	6.76190	1.35238	**0.034***
	Group B	73.7200	6.61135	1.32227	
Alntn-1 Min	**Group A**	99.6800	4.68793	.93759	**0.001***
	Group B	78.7600	9.22533	1.84507	
Alntn-3 Min	**Group A**	93.3600	8.13880	1.62776	**0.0001***
	Group B	74.1200	7.52396	1.50479	
Alntn-5 Min	**Group A**	86.6800	7.60329	1.52066	**0.440**
	Group B	69.9600	7.49155	1.49831	
Alntn-10 Min	**Group A**	79.0000	8.57807	1.71561	**0.980**
	Group B	71.3200	8.76888	1.75378	

*** Significant**

Graph No. 6: Showing intergroup comparison of mean diastolic blood pressure (DBP in mmHg) changes in response to laryngoscopy and intubation between midazolam(A) and dexmedetomidine(B) group



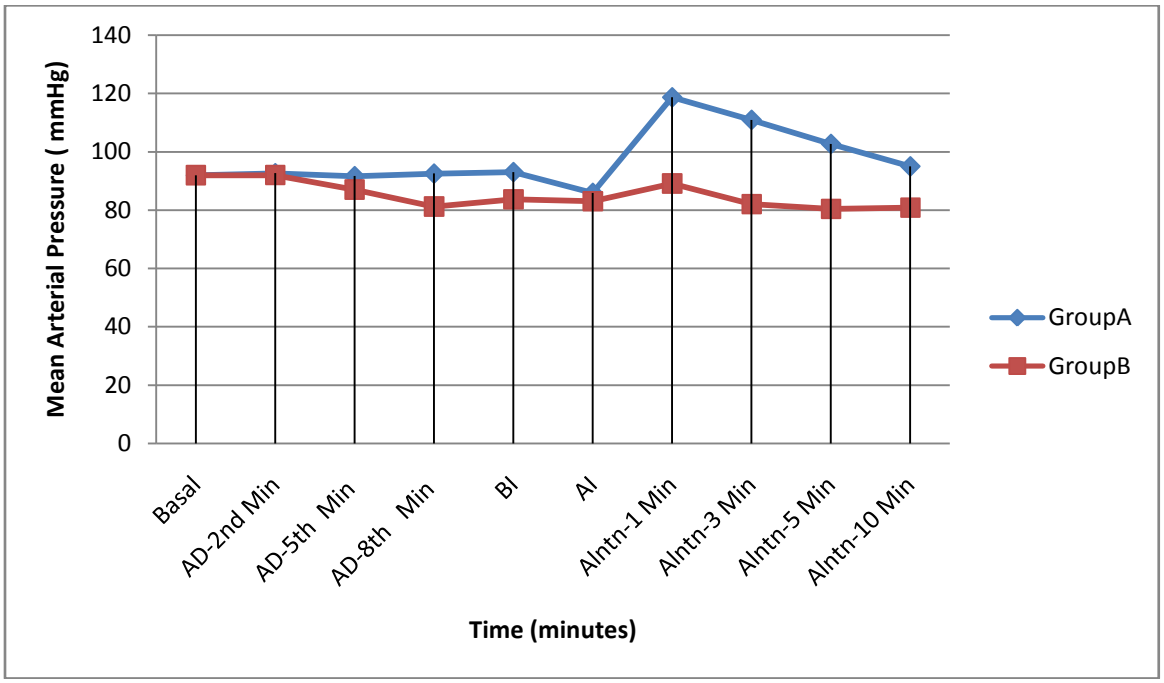
The mean basal DBP are comparable in both groups (p=0.223). The mean DBP at 2nd min after drug administration was statistically not significant (p=0.674). The mean DBP values at 5 and 8 minutes of drug administration, before and after induction were significantly low (p=0.000) in group B compared to group A. The increase in DBP in group A at 1, 3, 5 and 10 minutes after intubation was statistically highly significant (p=0.000) compared to group B.

Table no. 7: Showing intergroup comparison of mean arterial pressure (MAP in mmHg) changes in response to laryngoscopy and intubation between midazolam (A) and dexmedetomidine (B) group.

		Mean	S.D	S.E	P-value
Basal	**Group A**	91.9200	3.99917	.79983	**1.000**
	Group B	91.9200	3.99917	.79983	
AD-2nd Min	**Group A**	92.6400	4.47102	.89420	**0.183**
	Group B	91.9600	3.93150	.78630	
AD-5th Min	**Group A**	91.6400	3.75144	.75029	**0.0001***
	Group B	87.0000	4.49073	.89815	
AD-8th Min	**Group A**	92.5200	4.61086	.92217	**<.0005***
	Group B	81.2000	5.23609	1.04722	
BI	**Group A**	93.0400	3.69098	.73820	**<0.005***
	Group B	83.6800	4.71452	.94290	
AI	**Group A**	88.6000	5.67891	1.13578	**0.002***
	Group B	83.0000	6.44851	1.28970	
A lntn-1 Min	**Group A**	118.6400	4.36730	.87346	**0.009***
	Group B	89.0800	6.44800	1.28960	
A lntn-3 Min	**Group A**	110.9200	6.92772	1.38554	**<0.0001***
	Group B	82.0400	6.76067	1.35213	
A lntn-5 Min	**Group A**	102.6800	6.99238	1.39848	**0.032***
	Group B	80.4000	5.16398	1.03280	
A lntn-10 Min	**Group A**	95.0000	6.33114	1.26623	**0.208**
	Group B	80.8400	8.80189	1.76038	

*** Significant**

Graph No. 7: Showing intergroup comparison of mean arterial pressure (MAP in mmHg) changes in response to laryngoscopy and intubation between midazolam(A) and dexmedetomidine (B)

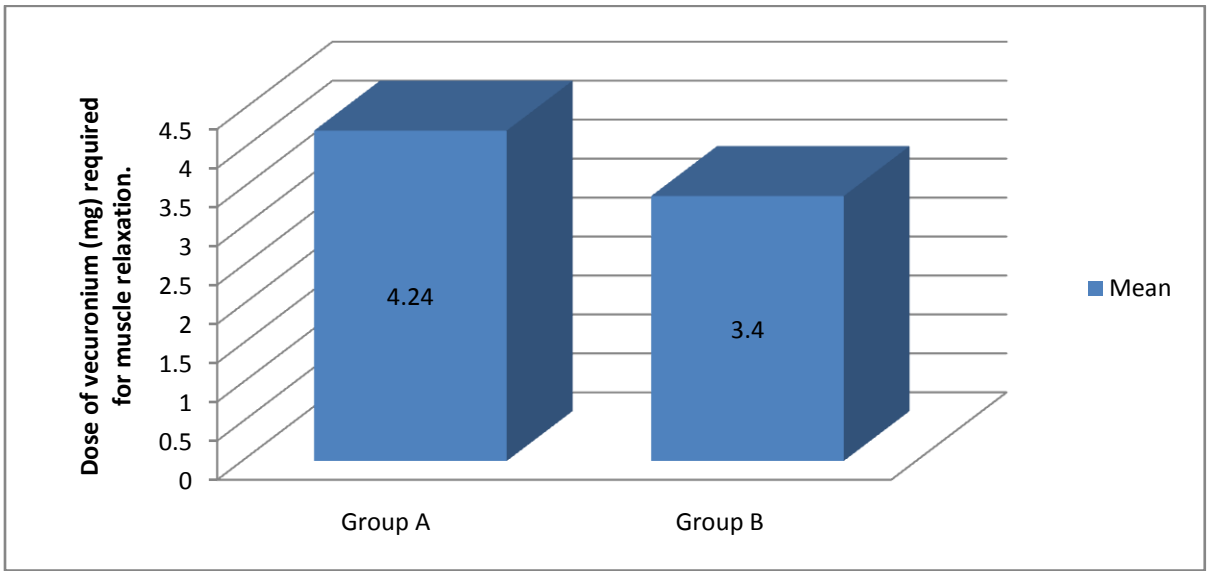


The mean basal MAP are comparable in both groups (p=1.000). After 2 min of drug administration the change in MAP was statistically not significant (p=0.183). There was a significant difference in MAP values at 5^{th} min, 8^{th} min after drug administration and before and after induction which was statistically highly significant (p=0.000). The increase in MAP in group A was statistically highly significant at 1 min and 3, 5 and 10 minutes after intubation (p=0.000) compared to group A.

Table no. 8: Showing the total dose of vecuronium bromide required for muscle relaxation in midazolam(A) and dexmedetomidine group.

	Mean	S.D	S.E	p-value
Group A	4.2440	1.00709	0.20142	**0.0392***
Group B	3.4000	1.24499	0.24900	

Graph no. 8: Showing the total dose of vecuronium bromide required for muscle relaxation in midazolam (A) and dexmedetomidine (B) group.



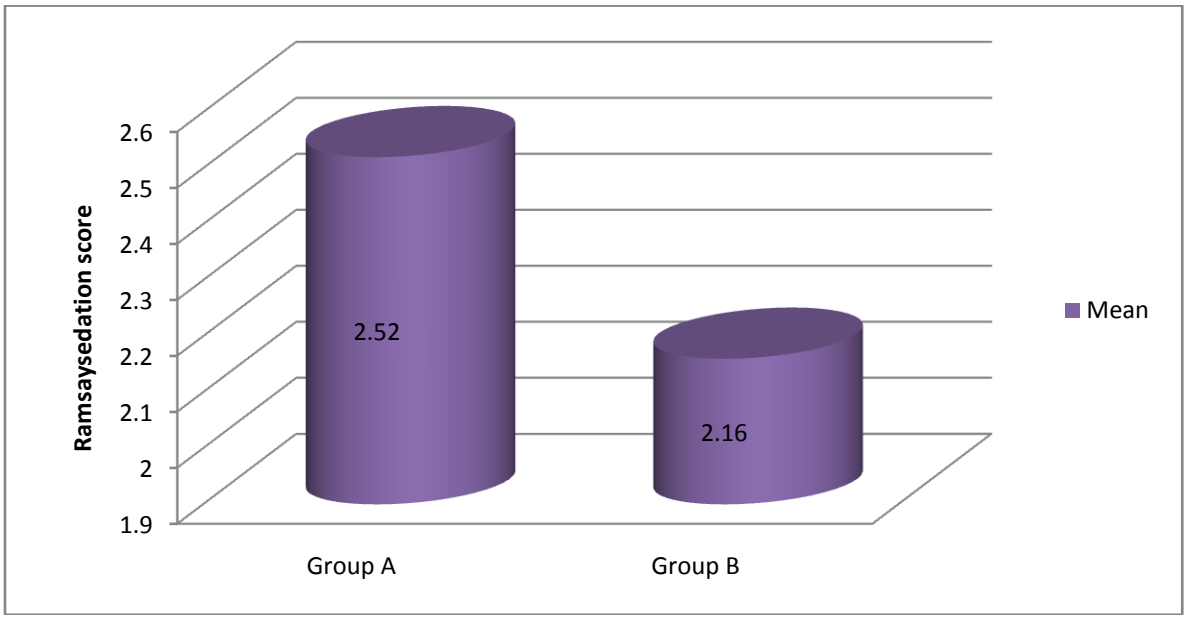
The mean dose of vecuronium bromide required for muscle relaxation in group A and group B were 4.24±1.36 and 3.4±1.22 respectively.

Statistical evaluation between the groups showed a statistical significant reduction in dose of vecuronium bromide for muscle relaxation.

Table no. 9: Showing the Ramsay sedation score between midazolam (A) and dexmedetomidine (B) group

	Mean	S.D	S.E	p-value
Group A	2.5200	.50990	.10198	**0.202**
Group B	2.1600	.55377	.11075	

Graph no. 9: Showing the Ramsay sedation score between midazolam (A) and dexmedetomidine (B) group.

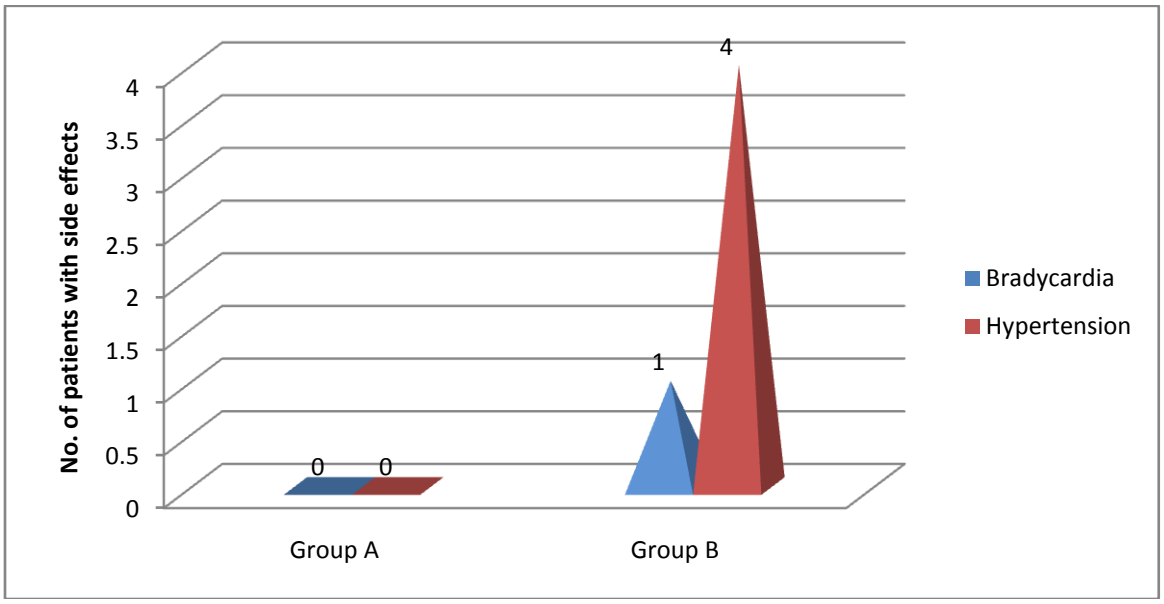


In group A sedation score was 2.52±0.49 and in group B the score was 2.16±0.43. Statistical evaluation showed no difference in the sedation score between the two groups.

Table no. 10: Showing the side effects between midazolam (A) and dexmedetomidine (B) group.

Side effects	Group A	Group B	Total
Bradycardia	0	01	01
Hypertension	0	04	04
Total	0	05	05

Graph no. 10: Showing the side effects between midazolam (A) and Dexmedetomidine (B) group



In group A, none of the patients had side effects like bradycardia and hypotension. In group B, 4 patients had hypertension, 1 had bradycardia and one patient had both bradycardia and hypertension.

Table no. 11 (a): Showing the dose of propofol (mg) required for induction in Midazolam(A) and dexmedetomidine(B) group.

	Group A		Group B	
Propofol in mg	**Frequency**	**Percentage**	**Frequency**	**Percentage**
100-110	2	8.0	1	4.0
110-120	4	16.0	0	0
120-130	1	4.0	0	0
60-80	2	8.0	13	52.0
80-90	2	8.0	8	32.0
90-100	14	56.0	3	12.0
Total	25	100.0	25	100.0

Graph no. 11: Showing the dose of propofol (mg) required for induction in Midazolam(A) and dexmedetomidine(B) group.

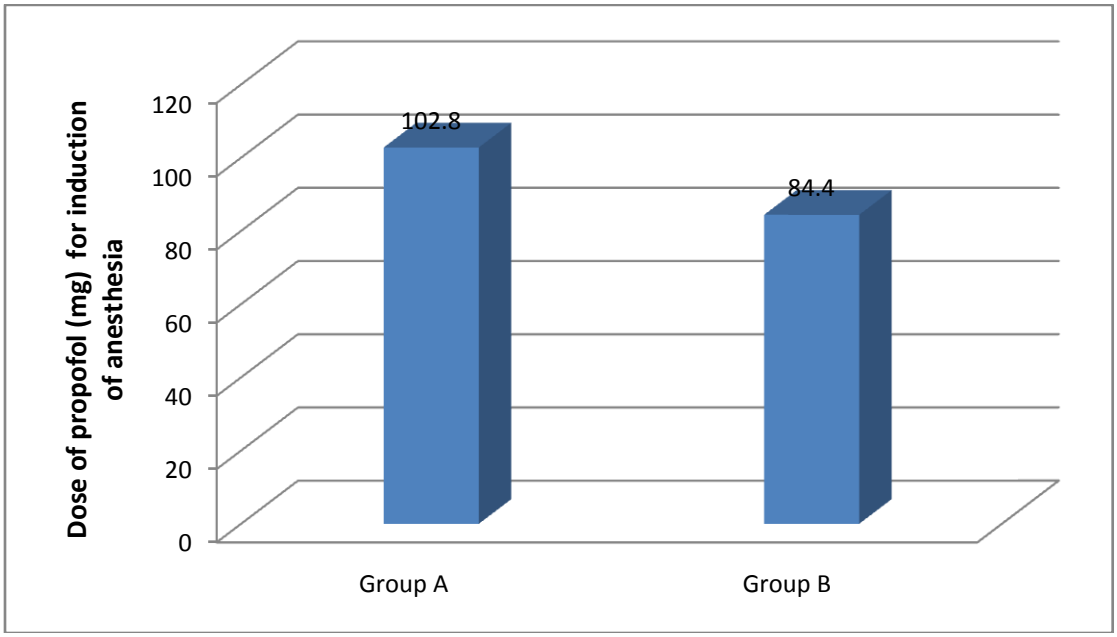


Table no. 11 (b) : Showing the dose of propofol (mg) required for induction in midazolam(A) and dexmedetomidine(B) group.

	Mean	S.D	S.E	P-value
Group A	102.8000	12.08305	2.41661	**< 0.0001***
Group B	84.4000	10.83205	2.16641	

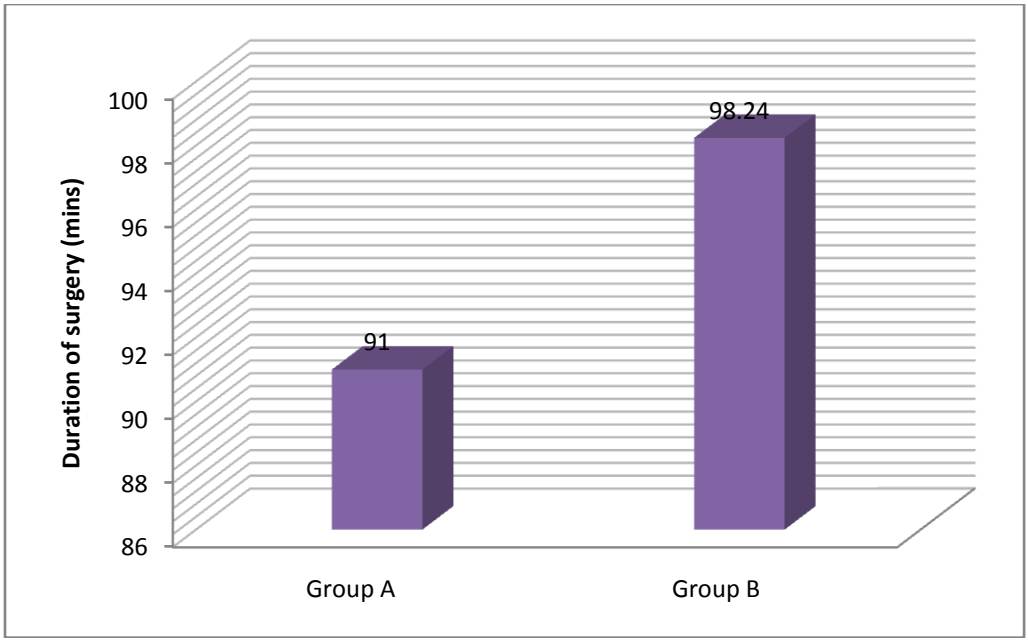
The mean dose of propofol (mg) required for loss of eye lash reflex in group A and group B were 102.80 and 84.40 respectively.

Statistical evaluation between the groups showed a statistically highly significant reduction in dose of propofol (mg) required for induction (p=0.000) in Group B.

Table no. 12: Showing the mean duration of surgery.

	Mean	S.D	S.E	p-value
Group A	91.0000	33.26034	6.65207	**0.071**
Group B	98.2400	49.55912	9.91182	

Graph No. 12: Showing the mean duration of surgery



From the above table it is seen that statistically there is no significant change in the duration of the surgical procedure between the two groups (p=0.071).

DISCUSSION

Most of the general anaesthetic procedures in the modern anaesthetic practice are carried out with endotracheal intubation. Laryngoscopy and tracheal intubation are considered as the most critical events during administration of general anaesthesia as they provoke transient but marked sympathoadrenal response manifesting as hypertension and tachycardia.[5]

These responses are transitory, variable and may not be significant in otherwise normal individuals. But in patients with cardiovascular compromise like hypertension, ischemic heart disease, cerebrovascular disease and in patients with intracranial aneurysms, even these transient changes in haemodynamics can result in potentially harmful effects like left ventricular failure, [8] pulmonary edema, myocardial ischemia, [8] ventricular dysrhythmias[9] and cerebral haemorrhage.[8]

This is by far the most important indication for attenuation of haemodynamic response to laryngoscopy and tracheal intubation.[11]

Many methods like use of inhalational anaesthetic agents, lidocaine,[12,13,14] opioids,[15,16,17] direct acting vasodilators,[18,19] calcium channel blockers[20,21,22] and β-blockers[23,24,25] have been tried by various authors for blunting haemodynamic responses to laryngoscopy and intubation. But all such maneuvers had their own limitations. For example, with opioids respiratory depression and chest wall rigidity were potential problems, use of halothane was associated with dysrrhythmias, calcium channel blockers produced reflex tachycardia, direct acting vasodilators needed

invasive haemodynamic monitoring and lidocaine did not give consistent results in blunting the haemodynamic responses to laryngoscopy and intubation.

Beta blockers are also one group of pharmacological agents employed for blunting haemodynamic response to laryngoscopy and intubation. But they blunt the heart rate response better than blood pressure response.[23,24]

Hence a drug which can blunt both the heart rate response and blood pressure response of laryngoscopy and intubation, without having any adverse effects like respiratory depression and post operative nausea and vomiting (PONV), was required for the purpose.

Recently α-2 agonists like clonidine[26] and dexmedetomidine[27] have been tried for suppressing the response to intubation and have been found to have better effects compared to all the drugs mentioned above, without any of the side effects like respiratory depression or increased incidence of PONV. Clonidine being less potent (α-1: α-2=1:220) compared to dexmedetomidine (α-1: α-2=1:1620) in its agonism to α-2 receptors.[27] Hence dexmedetomidine may be a better drug among α-2 agonists for suppressing the haemodynamic responses to laryngoscopy and intubation.

Dexmedetomidine has been found by various authors[28, 29, 30, 31, 32, 33,34,35,96] to blunt the haemodynamic response for laryngoscopy and intubation. Dexmedetomidine is recently introduced in India (only in 2009) and available as 200 µg/2ml ampoule (Dexem, Themis Medicare Limited) and not many studies have been done using dexmedetomidine for suppression of intubation response. Hence the effects of dexmedetomidine and midazolam as premedicative agents were compared and taken up as our study topic.

The present study was undertaken to study the efficacy of dexmedetomidine and midazolam in blunting the haemodynamic response to laryngoscopy and intubation and also to know the sedative effect and requirement of dose of propofol. The study was conducted in B.L.D.E.U.'s Shri B.M. Patil Medical College Hospital and Research Centre – 586103 Karnataka, during the period 18 months from Nov 2011 to April 2013. The study population consisted of 50 patients divided into two groups with 25 patients in each group. Group A consisted of 25 patients served as midazolam group who were given injection midazolam 0.02mg/kg intravenously over 10 min, 10 minutes before induction and group B consisted of 25 patients who were given dexmedetomidine in the dose of 0.6µg/kg body weight in 10 ml normal saline intravenously over 10 min, 10 minutes before induction using syringe pump as pretreatment to blunt the haemodynamic response to laryngoscopy and intubation.

Demographic criteria

Both the groups were comparable and there was no statistically significant difference with regards to mean age, weight, sex and duration of surgery.

Dose of dexmedetomidine employed and administration

Various authors have employed IV dexmedetomidine for blunting haemodynamic responses to laryngoscopy and intubation in different doses as shown in the table below.

Table 13: Showing dose of dexmedetomidine employed in various studies

Sl.No.	Authors and year	Dose of dexmedetomidine employed
1.	Yildize et al.[32] – 2006	1µg/kg body weight infusion
2.	Mowafi et al.[31] – 2008	0.6µg/kg body weight 50 ml saline 10 min before induction
3.	Basar et al.[33] – 2008	0.5µg/kg body weight in 10 ml saline over 60 sec
4.	Kunisawa et al.[34] – 2009	1µg/kg body weight over 10 min, 15 min before induction followed by 0.7µg/kg/hr infusion
5.	Ferdi et al.[35] – 2010	1µg/kg body weight in 100 ml saline over 15 min
6.	Esra et al.[98] – 2010	0.5 and 1µg/kg body weight infusion 5 min and 10 min respectively before induction
7.	Keniya et al.[96] – 2011	1µg/kg body weight infusion 10 min before induction

Kunisawa et al.[34] used 1µg/kg body weight of dexmedetomidine with fentanyl and found that, though there was a decrease in HR, the decrease in blood pressure was suppressed and the authors opined that vasoconstrictive effects of dexmedetomidine through α-2 adrenoceptors which are located in vascular smooth muscle might be responsible for this suppression as a result of administration of higher dose.

Ferdi et al.[35] used 1µg/kg body weight of dexmedetomidine for patients posted for CABG surgeries. They found that dexmedetomidine was effective in suppressing haemodynamic response to intubation. However, all the patients studied were on beta blockers.

Esra et al.[98] used 0.5 and 1µg/kg body weight of dexmedetomidine for suppression of intubation response and found that there was no significant change regarding HR in both doses.

Since most of the authors found dexmedetomidine effective at the dose of 0.6µg/kg body weight in attenuating stress response to intubation, 0.6µg/kg body weight dose was chosen for our study.

Method of administration

In the present study dexmedetomidine was diluted in 10 ml of normal saline and given intravenously over 10 minutes using syringe pump. Rapid administration of bolus dose of dexmedetomidine, initially results in transient increase in blood pressure and reflex decrease in HR. The initial reaction is due to peripheral α-2 adrenoceptors stimulation of vascular smooth muscle and can be attenuated by a slow infusion over 10 minutes. Hence in our study we administered the bolus dose over 10 minutes.[27]

The administration of dexmedetomidine as 10 ml in the present study is similar to the administration by Scheinin et al.[28] and Basar et al.[33] The administration of drug over 10 minutes is similar to Mowafi et al.,[31] Basar et al.[33] and Kunisawa et al.[34] study.

Timing of administration of dexmedetomidine

From the pharmacokinetic profile, it is seen that the distribution half life of intravenous dexmedetomidine is approximately 6 minutes.[27]

Various authors Aho et al.,[30] Scheinin et al.,[28] Jaakola et al.,[29] Mowafi et al.[31] and Keniya et al.[96] have employed dexmedetomidine 10 minutes before induction.

In view of the above, in the present study dexmedetomidine was employed 10 minutes before induction to blunt the haemodynamic response to laryngoscopy and intubation.

Comparative analysis of haemodynamic data between the dexmedetomidine and control groups at various intervals.

I. Changes in heart rate

After dexmedetomidine administration

Table 14: Showing mean HR changes in various studies following Dexmedetomidine administration

Sl. No.	Authors and year	Dose employed	Mean Change in HR after dexmedetomidine administration				Maximum decrease
			2 min	5 min	8 min	BI/10 min	
1.	Talke et al.[94]-1999	Target plasma concentration 6 ng/ml	-	-11	-11	-	-11
2.	Basar et al.[33]-2008	1μg/kg	-	-	-	-9	-
3.	Kunisawa et al.[34]-2009	1μg/kg	-	-	-	-14	-
4.	Ferdi et al.[35]-2010	1μg/kg	-	-	-4	-	-
5.	Keniya et al.[96] – 2011	1μg/kg	-	-	-	-10	-
6.	**Present study**	**0.6μg/kg**	**-9**	**-14**	**-20**	**-16**	**-**

The sign (-) denotes decrease and (+) denotes increase in HR. The spaces which have been left blank ('–'), are the parameters not studied by the authors.

As per table 14, it has been found by various authors[30,92,28,29,94,33,34,35,96] that dexmedetomidine has decreased the HR at various intervals of 2,5,8 and 10 minutes. Our study also found similar change in HR which is statistically highly significant.

Comparative value of HR between control and dexmedetomidine group

Table 15: Showing mean HR changes in Midazolam and Dexmedetomidine group in present study following drug administration

Mean change in HR in midazolam group				Mean change in HR in dexmedetomidine group			
2 min	**5 min**	**8 min**	**BI/10 min**	**2 min**	**5 min**	**8 min**	**BI/10 min**
+1	-1	-2	-2	-9	-14	-20	-16

The sign (-) denotes decrease and (+) denotes increase in HR.

As per table 15, in the midazolam group, initially there is not much of variation in HR after the administration of midazolam in the first 10 minutes whereas in dexmedetomidine group there was a continuous decrease in HR at 2, 5, 8 and 10 minutes which is statistically highly significant. Four patients in dexmedetomidine group developed bradycardia and one patient required inj. Atropine for the correction. No patient in midazolam group developed any bradycardia.

After induction

After induction of anaesthesia, compared to preinduction values, as per table 4, it was found that there was an increase of nearly 10 bpm in the midazolam group compared to 8 bpm in dexmedetomidine group which is statistically significant.

Compared to the basal values in the midazolam group, there is an increase of 7 bpm compared to dexmedetomidine group where there is a decrease of 9 bpm which is statistically highly significant. Our present study compares with the findings of the study done by Kunisawa et al.[34]

After laryngoscopy and intubation

Table 16: Showing changes in HR after tracheal intubation at various intervals in Control and Dexmedetomidine group

Sl. No.	Author and year	Mean change in HR following intubation in control group				Mean change in HR following intubation in dexmedetomidine group			
		1 min	3 min	5 min	10 min	1 min	3 min	5 min	10 min
1.	Basar et al.[33]- 2008	+10	-	-	+5	-8	-	-	-5
2.	Kunisawa et al.[34]- 2009	+12	-	-	-	-7	-	-	-
3.	Ferdi et al.[35]- 2010	+19	+14	+9	-	-3	-5	-6	-
4.	Keniya et al.[96] - 2011	+17		+10		-2	-	-4	
5.	**Present study**	**+32.24**	**+25.04**	**+19.26**	**+6.94**	**-7.86**	**-10.98**	**-12.48**	**-14.46**

The sign (-) denotes decrease and (+) denotes increase in HR. The spaces which have been left blank ('– '), are the parameters not studied by the authors.

At 1st min

In the present study, following laryngoscopy and intubation at 1 minute, the mean HR increased by 32.48 bpm in the midazolam group whereas in dexmedetomidine group the mean HR decreased by 7.86 bpm which is statistically

highly significant (p=0.000). Various authors have found similar response to IV dexmedetomidine at 1 min after intubation.

Basar et al.[33] noted that following laryngoscopy and intubation HR increased by 10 bpm in control group and in dexmedetomidine group the HR decreased by 8 bpm which is statistically highly significant.

Mowafi et al.[31] noted the increase in HR at 2 min following intubation in control group by 6 bpm and by 1 bpm in dexmedetomidine which is statistically highly significant.

Above authors have found a statistically significant ($p<0.05$) obtundation of heart rate response to intubation at 1 min which concurs with our study.

At 3rd min

The increase in mean HR at 3rd minute in midazolam group was 25.32 bpm whereas in dexmedetomidine group the HR decreased by 4.98 bpm which is statistically highly significant (p=0.000). We could not compare our results with other authors as they have not noted the haemodynamic parameters at 3rd minute.

At 5th min

The increase in mean heart rate in midazolam group sustained even at 5th minute and it was 19.04 bpm whereas in dexmedetomidine there was further decrease in HR by 11.32 bpm which is statistically highly significant(p=0.000).

Scheinin et al.[28] and Jaakola et al.[29] noted a increase in HR by 10 and 24 bpm respectively in control group. There was a decrease in HR by 10 bpm noted by Scheinin et al.[28] in dexmedetomidine group which is similar to our present study and Jaakola et al.[29] noted increase in HR by only 7 bpm in dexmedetomidine group.

At 10th minute

In our study even at 10th minute, there was increase in HR by 6.2 bpm in midazolam group compared to basal group and in dexmedetomidine group, the HR remained low by 14.04 bpm.

We could not compare our results with other authors as they have not studied the haemodynamic parameters at 10th minute.

Basar et al.[33] observed a increase in HR by 5 bpm in control group and decrease in HR by 5 bpm in dexmedetomidine group.

In the midazolam group, statistically highly significant increase in HR occurred at various intervals after intubation at 1, 3, 5 and 10 minutes with maximum rise of 32.48 bpm (1 min after intubation). Similar findings were also noted by Aho et al.[30] and Basar et al.[33]

In dexmedetomidine group there was a decrease in HR at 1 min after intubation and maximum decrease in HR was sustained till 10th minute after intubation also (-10.46) which is statistically highly significant (p=0.000).

II. Changes in systolic blood pressure (SBP)

<u>After dexmedetomidine administration</u>

After administration of dexmedetomidine at 2nd minute there was a marginal increase of 2 mmHg of SBP which is statistically not significant. Similar observation was made by Bloor BC et al.[36] and Aho et al.[30] where in they found initially transient increase in SBP which was attributed to peripheral α-2 adrenoceptor stimulation of vascular smooth muscle.

From the 5th minute onwards, there is a gradual reduction in blood pressure till induction which was statistically highly significant. Aho et al.,[30] Ralph Getler et al.[27] and Keniya et al.[96] found a continuous gradual reduction of SBP as in our study.

There was no reduction in SBP in midazolam group till induction which was statistically not significant.

After induction

After induction there was a reduction of 7 mmHg of SBP in midazolam group compared to 24 mmHg in dexmedetomidine group to basal value which is statistically significant. Similar observations were made by Kunisawa et al.[34] where in there was decrease in SBP by 12 mmHg in dexmedetomidine group.

After laryngoscopy and intubation

Table 17: Showing mean changes in SBP following laryngoscopy and intubation in Control and Dexmedetomidine group at various intervals

Sl. No.	Author and year	Mean change in SBP following intubation in control group				Mean change in SBP following intubation in dexmedetomidine group			
		1 min	3 min	5 min	10 min	1 min	3 min	5 min	10 min
1	Jaakola et al.[29]-1992	-	-	+	-	-	-	-17	-
2	Kunisawa et al.[34]-2009	+10	-	-	-	-15	-	-	-
3	Keniya et al.[96] – 2011	+30	-	10	-	-10	-	-20	-
4	**Present study**	**+30.02**	**+21.02**	**+10.7**	**+0.78**	**-15.86**	**-22.34**	**-24.34**	**-26.08**

The sign (-) denotes decrease and (+) denotes increase in SBP. The spaces which have been left blank (‘ – ’), are the parameters not studied by the authors.

From table 17, it is seen that dexmedetomidine blunts the increase in systolic blood pressure at 1, 3, 5 and 10 minutes following laryngoscopy and intubation compared to control group (p=0.000) which is statistically highly significant.

At the 1st minute, there is an increase of 9 mmHg of SBP compared to the values immediately after induction, but compared to the basal value the reduction in SBP is 15 mmHg. Even at 10th minute the SBP did not reach the basal value and it was 26 mmHg lower than the basal value. In the midazolam group, the increase in SBP was maximum at 1st minute but reached the basal value by 10th minute.

Scheinin et al.[28] observed increase in SBP by 18 mmHg immediately after intubation compared to the values after induction, but the SBP was less than the basal values. This compares with our study. They also observed an increase in SBP by 25 mmHg in control group compared to basal value which returned to below the basal value by 10th minute.

Jaakola et al.[29] have observed a fall of 17 mmHg in SBP 5 minutes after intubation in dexmedetomidine group and in control group an increase of SBP by 10 mmHg, compared to the basal values. This again concurs with our study.

Aho et al.[30] noted a increase in SBP by 48 mmHg and 18 mmHg in control group and dexmedetomidine group respectively at 1 min after intubation which was statistically significant.

Ferdi et al.[35] and Keniya et al.[96] noted a reduction of 20 mmHg of SBP compared to the basal value at 5th minute which concurs with our study.

III. Changes in diastolic blood pressure (DBP)

After dexmedetomidine administration

At the 2nd minute, there is a marginal increase of DBP like that occurred with SBP. After 2nd minute there is a gradual decrease of DBP till induction which is statistically significant. In midazolam group there is not much of variation in DBP till induction.

Aho et al.[30] observed a continuous decrease of DBP in dexmedetomidine group till induction which concurs with our study.

Similar observations were also found by Kunisawa et al.[34] and Keniya et al.[96] where there was a decrease in DBP in dexmedetomidine group and no change in control group.

After induction

In the present study, there was a reduction of 6 mmHg in the midazolam group and 18 mmHg in dexmedetomidine group compared to basal value.

Jaakola et al.[29] found a decrease in DBP by 3 mmHg in control group and 15 mmHg in dexmedetomidine group which compares with the present study.

After laryngoscopy and intubation

Table 18: Showing comparison of mean increase in DBP in Control and Dexmedetomidine group following intubation at various intervals

	Mean changes in DBP following intubation (mmHg)			
	1 min	**3 min**	**5 min**	**10 min**
Midazolam	+22.34	+15.42	+10.16	+3.12
Dexmedetomidine	-2.54	-2.12	-6.64	-5.72
p-value	0.001	0.0005	0.440	0.980

From the above table, in our study there is an increase of DBP by 22 mmHg in midazolam group which gradually decreased to near basal values by 10th minute. In dexmedetomidine group, there is a decrease in DBP by 9 mmHg in 1st minute and 17 mmHg by 10th minute compared to basal values which is statistically highly significant. However there is an increase of 28 mmHg in midazolam group compared with 8 mmHg increase in the dexmedetomidine group in comparison with the values of DBP immediately after induction. This is also statistically highly significant.

Jaakola et al.[29] observed a fall of DBP by 10 mmHg in dexmedetomidine group compared with an increase of 16 mmHg in control group compared to basal values which concurs with our study. There is an increase of 5 mmHg compared to postinduction value in dexmedetomidine group compared with 17 mmHg of increase in control group which again compares with our study.

Ferdi et al.[35] also noticed a fall in DBP by 10 mmHg at 1st minute and at 5th minute 13 mmHg which concurs with our study.

In the study done by Kunisawa et al.,[34] there is a fall of DBP by 5 mmHg after intubation. Scheinin et al.[28] found an increase of 15 mmHg after intubation compared with the postinduction value in dexmedetomidine group compared with an increase of 20 mmHg in control group which is statistically significant and concurs without study.

IV. Changes in mean arterial pressure (MAP)

After dexmedetomidine administration

After administration of dexmedetomidine at 2nd min there was a marginal increase in MAP by 1 mmHg which is statistically not significant. From 5th minute onwards there is a continuous fall in MAP in dexmedetomidine group till induction which is statistically significant. In midazolam group not much of variation was observed regarding MAP till induction compared to basal values and to dexmedetomidine group.

Ferdi et al.[35] found a decrease in MAP by 13 mmHg and 3 mmHg in dexmedetomidine and control group respectively, compared to basal value which concurs with our study.

Basar et al.[33] and Mowafi et al.[31] also noted a decrease in MAP by 7 mmHg in dexmedetomidine group which compares with our study. In control group there was not much of reduction in MAP till induction which was statistically significant.

After induction

After induction, there was a reduction in MAP by 9 mmHg in dexmedetomidine group and 7 mmHg in midazolam group which is statistically significant.

Similarly Mowafi et al.[31] observed a decrease in MAP by 13 mmHg in dexmedetomidine group which concurs with our study.

After laryngoscopy and intubation

Table 19: Showing comparison of mean increase in MAP in Control and Dexmedetomidine group following intubation at various intervals

	Mean changes in MAP following intubation (mmHg)			
	1 min	**3 min**	**5 min**	**10 min**
Midazolam	+26.42	+18.34	+11	+4.12
Dexmedetomidine	-1.98	-10.4	-11.5	-10.3
p-value	0.009	0.000	0.022	0.208

At 1st minute, in dexmedetomidine group, there is an increase of MAP by 7 mmHg compared to the values immediately after induction, but compared to the basal values there is a reduction in MAP by 2 mmHg. Even at 10th minute the MAP was lower by 10 mmHg, compared to the basal values in dexmedetomidine group which is statistically highly significant.

However in midazolam group there is an increase in MAP by 24 mmHg compared with 7 mmHg of increase in dexmedetomidine group comparison with the values of MAP immediately after induction which is statistically significant.

At 1st minute after intubation, the increase in MAP in control group 26 mmHg whereas in dexmedetomidine group there is a fall in MAP by 2 mmHg which is statistically highly significant. The MAP value did not reach to basal values even after 10th minute in midazolam group.

Basar et al.[33] found a decrease in MAP by 10 mmHg in dexmedetomidine group at 10th minute which concurs with our study. Similarly Mowafi et al.[31] observed

an increase in MAP by 5 mmHg immediately after intubation in dexmedetomidine group compared to an increase of 12 mmHg in control group in comparison with values after induction.

Dose of propofol required for induction

We studied the total dose of propofol required for induction in each group. The target dose for induction was upto the loss of eyelash reflex. In midazolam group the mean dose of propofol required for induction was 102.8 mg (2mg/ kg body weight) and in dexmedetomidine group dose required was 84.40 mg (1.4 mg /kg body weight) showing reduction of 0.6 mg/ kg body weight (16.66%) which is statistically highly significant (p=0.000).

Various authors have studied the effect of dexmedetomidine on induction agent requirements for induction of anaesthesia.

Aanta et al.,[65] studied the effect of intravenous dexmedetomidine on the dose of thiopentone requirement for induction. In this study the dose of thiopentone required for induction in control group and dexmedetomidine group was 329±100 mg and 207±49 mg respectively showing a reduction by 37%.

C. J. Peden et al [98] also studied the dose of required for induction with propofol which was 120 mg and 90 mg in control and dexmedetomidine group respectively showing a reduction by 23%.

Basar et al.[33] also noted a significant decrease in dose of propofol for induction in control group (110±62 mg) and dexmedetomidine group (80 ±72 mg) which was statistically highly significant (p=0.000). The induction dose of propofol was lower by 37% compared to control group.

Above authors have found statistically significant reduction of propofol for induction in dexmedetomidine group ($p<0.05$) which concurs with our study.

The anaesthetic sparing effect of dexmedetomidine is due to decrease in central noradrenergic transmission and also due to α-2 receptor specificity mediating analgesic and sedative properties.[27]

Dose of vecuronium bromide required for muscle relaxation

We also studied the total dose of vecuronium required in each group. We found the total dose of vecuronium required in midazolam and dexmedetomidine group for muscle relaxation was 4.70$\pm$1.36 mg (90.08.92 minutes) and 3.74$\pm$1.22 mg (88.92 minutes) respectively which was statistically highly significant ($p=0.000$).

Talke et al.[94] studied the effect of dexmedetomidine on neuromuscular blockade and noted that dexmedetomidine increased the plasma concentration of rocuronium significantly ($p<0.05$). The authors could not find a definitive reason for this effect. They hypothesized that dexmedetomidine might have influenced the pharmacokinetics of rocuronium by decreasing both renal and hepatic blood flow. Similar observation was made by Ghada Ahmad et al.[99]

Sedation scoring

In group A mean sedation score immediately after extubation was 2.62 and 2.52 in control group and dexmedetomidine group which was statistically not significant ($p=0.087$).

There was no difference found in both groups with respect to sedation and recovery which was similar to observation noted by Aanta et al.[65]

Side effects

In dexmedetomidine group, 4 patients developed bradycardia which was after 30 minutes of the drug administration and significant hypotension in 3 patients which was 20 minutes after intubation. One patient required inj. Atropine for bradycardia and no patient required vasopressors for correction of blood pressure. Hypotension was managed by decreasing volatile anaesthetic concentration and infusing intravenous fluids.

SUMMARY

A prospective double blind controlled study entitled "A comparative study of intravenous dexmedetomidine and midazolam used as a premedication for laparoscopic surgeries under general anesthesia – a prospective randomized double blind controlled clinical study" was undertaken in B.L.D.E.U.'s Shri B.M. Patil Medical College Hospital and Research Centre – 586103 Karnataka, during the period 18 months from Nov 2011 to April 2013. Fifty patients scheduled for various elective surgical procedures belonging to ASA class I and II and Mallampatti grade I and II, in the age group of 18 to 55 years were included in the study. The patients with hypertension, difficult airway, obesity and any other systemic disorders were excluded from the study. The study population was divided randomly into two groups.

Group A – Control group (n=25) – received midazolam 0.02mg/kg intravenously over 10 minutes, 10 minutes before induction using syringe pump.

Group B – Dexmedetomidine group (n=25) – received dexmedetomidine in the dose of 0.6 µg/kg body weight diluted in 10 ml normal saline intravenously over 10 minutes, 10 minutes before induction using syringe pump.

All the patients were premedicated with, inj. ondansetron0.08mg/kg, inj. glycopyrrolate 0.02mg/kg and inj Pentazocine 0.3mg/kg body weight, given IV just before induction. Anaesthesia was induced 10 minutes after the study drug with inj. propofol till the eye lash reflex is lost and dose noted. This is followed by succinylcholine 1.5 mg/kg body weight IV to facilitate laryngoscopy and intubation

lasting for not more than 15 seconds. The heart rate, systolic, diastolic and mean arterial pressures were recorded, before the test drug, after the test drug at 2, 5 and 8 minutes, before induction, after induction and after intubation at 1,3,5 and 10 minutes.

The following table shows the results obtained in the present study.

Table 20: Showing the results obtained in the present study

	GROUP A (Midazolam)	**GROUP B (Dexmedetomidine)**
Mean age in years	36.83	36.42
Sex ratio M:F	13:12	12:13
Mean weight in kgs	54.o8o	55.040
Variation in HR (bpm) 2 min after drug administration	-0.002	-8.08
Variation in HR (bpm) 5 min after drug administration	- 0.74	-8.72
Variation in HR (bpm) 8 min after drug administration	-2.54	-12.1
Variation in HR (bpm) before induction	-2.06	-13.28
Variation in HR (bpm) after induction	+8.88	-6.1
Variation in HR (bpm) 1 min postintubation	+36.24	-2.86
Variation in SBP (mmHg)1 min postintubation	+30.02	-15.86
Variation in DBP (mmHg) 1 min postintubation	+22.34	-9.64
Variation in MAP (mmHg) 1 min postintubation	+26.42	-1.98

There was marked decrease in HR 10 minutes after dexmedetomidine administration. HR, SBP, DBP and MAP markedly increased at 1 minute following laryngoscopy and intubation in the midazolam group where as in dexmedetomidine group there was a fall in HR, SBP, DBP and MAP at all times which was statistically significant.

There was also a noted reduction in propofol requirement in dexmedetomidine group 1.4 mg/ kg body weight compared to midazolam group 2 mg/ kg body weight.

There was also a reduction in the requirement of vecuronium bromide in the dexmedetomidine group which was statistically significant.

There was no variation in sedation scoring in patients belonging to dexmedetomidine group (2.52) compared to midazolam group (2.62) which was statistically not significant.

There were minimal side effects like bradycardia in 1 patient and hypertension in 4 patients noted with the administration of dexmedetomidine which were managed with routine medications.

CONCLUSION

Dexmedetomidine at a dose of 0.6μ/kg body weight diluted in 10 ml saline given 10 minutes before induction significantly obtunded the haemodynamic responses to laryngoscopy and tracheal intubation when compared with midazolam. It also decreased requirement of induction dose of propofol and also the requirement of the total dose of vecuronium bromide for muscle relaxation without significant side effects when compared with midazolam in laparoscopic surgeries.

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ANNEXURE I

Ethical Committee
BIJAPUR-586103
OUT WARD
No 27/2011
Date 21-10-11
Shri B. M. PATIL Medical College

B.L.D.E. UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 20-10-2011 *at* 10-30 am *to scrutinize the Synopsis/Research projects of postgraduate/undergraduate student/Faculty members of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis/Research project has been accorded Ethical Clearance.*

Title "A comparative study of intravenous dexmedetomidine & midazolam used as a premedication for Laparoscopic Surgeries under general Anesthesia"

Name of P.G./U.G. student/Faculty member Dr. Shivakumar Mutnal
Dept of Anaesthesiology

Name of Guide/Co-investigator Dr. Vidya Patil Prof Anaesthesiology

DR.M.S.BIRADAR,
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Chairman
Ethical Committee
BLDEA'S Shri. B.M. Patil
Medical College
Bijapur-586103

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

ANNEXURE II

CONSENT FORM

B.L.D.E.U.'s SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, BIJAPUR – 586103, KARNATAKA

TITLE OF THE PROJECT: A comparative study of intravenous dexmedetomidine versus midazolam used as a premedicant in laparoscopic surgeries under general anesthesia.

PRINCIPAL INVESTEGATOR: Dr.Shivakumar Mutnal
Department of Anesthesiology
Email: mutnal.shivkumar@gmail.com

PG GUIDE: Dr.Vidya Patil$_{M.D.}$
Professor of Anesthesiology
B.L.D.E. University's
Shri B.M. Patil Medical College & Research Centre, Sholapur Road, BIJAPUR - 586103

PURPOSE OF RESEARCH:

I have been informed that this study will comparatively evaluate the efficacy of premedication between intravenous dexmedetomidine versus midazolam in patients undergoing laparoscopic surgeries. I have been explained about the reason for doing this study and selecting me/my ward as a subject for this study. I have also been given free choice for either being included or not in the study.

PROCEDURE:

I have been explained that depending upon the group allocated to me/my ward, I'll/my ward will either be given intravenous dexmedetomidine/ midazolam.

RISKS AND DISCOMFORTS:

I understand that I/my ward may experience some pain and discomfort during this study period. This is mainly the result of my/my ward's conditions and the procedure of this study arenot expected to exaggerate these feelings which are associated with the usual course of procedure.

BENEFITS:

I understand that my/my ward's participation in this study will help in finding out the efficacy of intravenous dexmedetomidine versus midazolam for premedication in patients undergoing laparoscopic surgeries.

CONFIDENTIALITY:

I understand that medical information produced by this study will become a part of this Hospital records and will be subjected to the confidentiality and privacy regulation of this hospital. Information of a sensitive, personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by a code number.

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

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time Dr.Shivakumar Mutnal is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation. And that a copy of this consent form will be given to me for keep for careful reading.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

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

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

INJURY STATEMENT:

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

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

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

Date: Dr. Vidya Patil (Guide) Dr. Shivakumar Mutnal (Investigator)

STUDY SUBJECT CONSENT STATEMENT:

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

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

_____ _____

(Participant) Date

_____ _____

(Witness to above signature) Date

ANNEXURE III

CASE PROFORMA

Patient name :

I.P. No :

Age :

Sex :

Weight of the patient :

Address :

Preoperative diagnosis and Indication for surgery :

Pre-anaesthetic evaluation

History :

General Physical Examination :

Pulse rate :

Blood pressure :

Cardiovascular system :

Respiratory System :

Oral cavity :

Airway assessment

Mallampatti grade :

Thyromental distance :

Neck extension :

Spine :

RELEVANT LABORATORY INVESTIGATIONS

Hb%	:	RBS	:
BT	:	Blood Urea	:
CT	:	Serum Creatinine	:
Urine: Albumin	:	CXR	:
Sugar	:	ECG	:
Microscopy	:		

OTHER RELEVANT INVESTIGATIONS

Thyroid function tests:

Liver function tests :

Neck X-ray: AP view

Lateral view

Case has been evaluated and accepted under ASA grade _____ physical status.

ANAESTHETIC MANAGEMENT

IVL secured in _____ with 20G vasofix and 1 pint ringer lactate started.

Basal haemodynamic parameters recorded.

Inj. Dexmedetomidine given at 0.6 µg/kg body weight diluted in 10 ml normal saline over 10 minutes, 10 minutes prior to induction using syringe pump in dexmedetomidine group.

In midazolam group, 0.02mg/kg midazolam given over 10 minutes, 10 minutes prior to induction using syringe pump.

Premedication: inj. Glycopyrrolate 0.2 mg + inj. Pentazocine 0.3mg/kg IV+ inj. Ondansetron 0.08mg/kg IV.

Pre oxygenation done with 100% oxygen by mask for 3 minutes.

Induction- Inj.Propofol _____ mg IV

+ Inj. Suxamethonium 1.5 mg kg^{-1} _____ mg IV

Intubation- With oral endotracheal tube (cuffed) and connected to Bain's circuit.

Time of intubation : Duration :

Maintenance – O_2+N_2O + 0.2-1% Isoflurane + Inj. Vecuronium IV with IPPV using Bain's circuit

Parameters noted

	HR	**SBP**	**DBP**	**MAP**	**Dose of propofol required**	**Dose of Vecuronium required**	**Sedation scoring**	**Side effects**	**SPO_2**
Basal									
After test drug									
2^{nd} min									
5^{th} min									
8^{th} min									
Before induction									
After induction									
After intubation									
1 min									
3 min									
5 min									
10 min									

Reversal

Inj. Neostigmine 0.05 mg/body weight kg IV and Inj. Glycopyrrolate 0.01 mg /kg body weight IV

Reversal and extubation:

Postoperative

Patient is conscious and oriented

Respiration is spontaneous with adequate tidal volume

Pulse :

BP :

Muscle power : Reflexes:

SPO_2 :

Sedation score :

Side effects if any :

Patient monitored and shifted to post-operative ward.

ANNEXURE V

MASTER CHART

GROUP A

						HEART RATE (bpm)										SYSTOLIC BLOOD PRESSURE (mmHg)										Diastollic pressure (mmHg)										Mean Arterial Pressure (mmHg)														
							AD					Alntn					AD					Alntn					AD					Alntn					AD					Alntn								
SL NO	I.P. NO.	AGE (YEARS)	SEX	Wt (kg)	SURGICAL PR	BASAL	2nd min	5th min	8th min	BI	a1	1 min	3 min	5 min	10 min	1Basal	2nd min	5th min	8th min	BI	AI	1 min	3 min	5 min	10 min	2Basal	2nd min	5th min	8th min	BI	AI	1 min	3 min	5 min	10 min	3Basal	2nd min	5th min	8th min	BI	AI	1 min	3 min	5 min	10 min	SpO2	propofol	Veecuroniumdose	Ramsay sedation	Duration	Sideeffecs
1	19123	43	M	55	Lap. Appendix	98	96	96	92	100	98	95	99	99	98	128	130	129	130	128	106	158	132	125	138	74	80	86	80	89	72	98	89	77	80	92	92	86	94	95	90	118	103	93	99	99%	100	4.5	3	45	-
2	21837	28	M	68	Lap. Appendix	104	102	99	102	100	112	129	124	108	90	120	126	120	125	129	120	150	136	124	120	73	70	70	70	89	90	102	78	73	70	88	90	94	98	90	95	118	96	90	86	99%	120	2.5	2	45	-
3	23780	55	M	55	Lap. Chole	90	92	88	90	100	97	112	108	96	92	124	128	125	127	128	121	159	142	140	134	70	76	72	76	76	88	100	98	90	80	98	96	90	88	93	95	119	112	108	98	99%	100	5	3	110	-
4	25618	40	M	60	Lap. Appendix	84	84	86	86	82	93	129	122	118	119	128	128	130	128	130	124	160	145	138	130	70	75	73	75	76	86	112	108	96	88	89	90	93	88	89	85	128	120	110	102	99%	100	4.2	3	90	-
5	911	40	M	48	Lap. Chole	76	76	74	72	100	79	96	90	99	92	122	130	123	123	120	130	142	136	122	118	70	78	88	78	77	88	89	80	70	80	87	85	95	98	98	95	104	104	89	90	99%	90	3.5	3	120	-
6	5404	50	M	45	Lap. Chole	108	106	105	102	107	112	128	118	114	108	143	140	140	142	137	130	161	151	130	118	83	77	77	77	77	73	96	80	80	70	93	90	93	97	96	85	117	103	96	86	99%	100	3.7	2	90	-
7	9249	42	M	54	Lap. Appendix	104	101	102	100	108	116	132	126	118	103	136	130	134	133	140	130	162	150	146	128	80	80	78	80	82	71	110	100	90	76	98	96	87	88	90	88	127	116	108	93	99%	100	6	3	130	-
8	13178	56	F	50	Lap. Appendix	84	85	82	82	86	98	129	120	112	92	128	124	128	124	129	120	161	159	136	139	76	77	75	77	70	70	99	96	84	80	93	90	89	96	90	83	119	115	101	98	99%	100	4	2	90	-
9	17112	25	M	62	Lap. Appendix	86	88	86	85	84	99	126	118	106	108	126	130	125	128	122	120	153	148	130	120	80	85	90	85	80	72	103	89	80	82	95	92	98	98	99	88	116	105	96	99	99%	90	4	2	60	-
10	17719	26	F	56	Lap. Chole	94	94	99	94	89	98	128	118	116	103	146	130	140	130	148	132	164	160	151	136	82	93	92	93	89	87	106	108	92	80	93	99	88	99	90	90	125	125	111	98	99%	110	3.2	3	45	-
11	19107	50	M	54	Lap. Hernia	90	90	87	86	100	90	116	104	99	90	128	130	129	130	126	120	156	146	138	123	86	70	68	70	88	80	100	96	94	80	90	98	92	92	88	85	116	112	108	94	99%	80	3.5	2	75	-
12	19468	55	F	45	Lap. Adhesiolysis	92	92	88	76	78	75	129	118	114	86	126	120	125	122	126	120	160	153	148	128	78	70	73	70	70	80	100	100	84	72	94	96	95	90	95	88	120	115	105	92	99%	120	4.5	2	120	-
13	4518	42	M	60	Lap. Chole	80	80	82	80	82	96	128	117	108	96	118	120	118	121	124	110	163	148	138	118	70	71	69	71	70	65	94	84	94	62	88	88	90	96	99	80	117	101	108	84	99%	100	4	2	45	-
14	5932	63	F	52	Lap. Adhesiolysis	96	86	96	106	98	96	130	118	102	88	136	130	130	132	138	130	159	155	136	126	90	89	103	89	84	70	102	96	90	82	90	100	88	90	92	98	121	115	105	96	99%	100	3.5	2	90	-
15	5842	43	F	60	Lap. Chole	106	103	101	104	104	114	132	126	118	108	130	132	130	130	128	123	158	150	148	128	84	84	83	84	84	80	98	90	84	80	99	98	89	85	93	88	118	110	105	93	99%	100	3.7	2	50	-
16	21437	50	F	48	Lap. Chole	87	90	87	88	86	98	118	108	112	94	128	128	126	127	132	120	155	152	135	128	72	73	71	73	70	79	98	84	95	89	90	88	98	90	95	98	117	105	108	98	99%	100	4.4	3	60	-
17	22802	50	F	60	Lap. Chole	90	95	97	90	91	99	122	108	108	94	124	122	124	122	128	120	160	156	146	128	74	78	77	78	78	80	97	93	94	72	90	88	96	96	98	86	118	114	111	90	99%	120	7	3	180	-
18	23040	22	F	48	Lap. Appendix	100	102	104	99	96	108	120	120	116	98	128	128	133	128	130	120	158	130	126	120	80	83	81	83	79	79	101	92	80	70	96	98	92	92	93	90	120	104	95	86	99%	130	2.4	2	90	-
19	23143	60	F	51	Lap. Chole	82	80	82	84	80	88	129	118	106	94	124	125	124	125	130	120	157	152	148	128	86	80	69	80	80	76	97	91	84	71	98	96	90	90	89	90	117	110	105	90	99%	120	5.5	3	130	-
20	25251	35	F	50	Lap. Fundopl.	80	87	80	77	86	92	128	118	106	88	128	130	128	130	130	120	161	158	136	132	70	70	65	70	72	80	100	96	78	73	89	88	99	91	87	98	120	116	96	96	99%	100	4	2	90	-
21	27129	20	F	53	Lap. Appendix	86	86	85	83	90	99	128	120	116	86	128	129	127	128	128	118	162	155	142	130	70	76	77	76	77	70	98	102	96	88	89	88	90	90	88	80	119	119	111	102	99%	80	4	2	60	-
22	16781	45	M	58	Lap. Appendix	94	96	96	90	89	109	128	126	118	98	130	132	129	131	138	125	159	151	138	128	86	80	69	80	85	80	98	96	94	88	90	98	86	97	98	90	118	114	108	101	99%	100	4.5	3	85	-
23	20857	41	F	50	Lap. Chole	86	86	80	80	88	98	130	126	116	98	126	120	126	122	138	120	162	153	144	128	80	81	79	81	80	80	98	100	90	88	95	94	94	98	93	90	119	115	101	101	99%	100	5	3	75	-
24	19786	50	M	60	Lap Appendix	80	84	80	77	76	96	116	114	108	88	110	112	110	112	126	106	159	147	142	130	70	69	66	69	80	70	100	88	94	102	83	88	90	90	95	80	119	107	94	111	99%	100	4.5	3	90	-
25	23077	22	M	50	Lap. Chole.	78	70	75	76	80	87	109	104	98	99	121	120	120	120	130	118	156	151	148	128	76	77	75	77	75	80	96	100	84	72	91	90	89	82	93	80	116	117	105	92	99%	110	5	3	110	-

GROUP B

						HEART RATE (bpm)										SYSTOLIC BLOOD PRESSURE (mmHg)										Diastollic pressure (mmHg)										Mean Arterial Pressure (mmHg)															
							AD					Alntn					AD					Alntn					AD					Alntn					AD					Alntn									
SL NO	I.P. NO.	AGE (YEARS)	SEX	Wt (kg)	SURGICAL PROCEDUCE	BASAL	2nd min	5th min	8th min	BI	a1	1 min	3 min	5 min	10 min	Basal	2nd min	5th min	8th min	BI	AI	1 min	3 min	5 min	10 min	Basal	2nd min	5th min	8th min	BI	AI	1 min	3 min	5 min	10 min	Basal	2nd min	5th min	8th min	BI	AI	1 min	3 min	5 min	10 min	SpO_2	propofol	vecuronium dose	Ramsay sedation	Duration	Side effecs
1	7679	28	F	51	Lap. Appendicectomy	77	80	65	64	65	77	80	84	78	76	138	142	110	111	110	112	115	99	93	92	83	80	77	73	75	80	83	70	65	66	92	91	90	85	86	90	93	79	74	74	99%	80	2.5	2	45	-
2	8363	24	M	58	Lap. Hernia repair	85	85	87	64	76	71	85	70	70	69	131	133	119	116	113	85	120	101	90	88	88	86	84	78	80	69	90	66	64	62	88	83	97	90	90	74	100	77	78	70	99%	70	4	2	110	-
3	13018	60	M	51	Lap. Cholecystectomy	78	59	62	58	62	65	70	67	66	67	127	146	106	98	97	108	109	91	93	94	78	80	74	84	65	82	84	72	69	70	98	95	88	88	75	90	92	78	77	78	99%	65	3.5	2	125	Bradyacardia
4	22523	55	M	61	Lap. Fundoplication	84	76	68	64	80	88	74	83	80	76	106	110	90	90	99	84	100	110	100	102	70	78	60	60	73	67	80	85	75	78	89	90	82	70	81	78	94	80	83	86	99%	90	2	3	30	-
5	5053	20	F	54	Lap. Appendicectomy	82	76	77	71	77	75	82	76	71	76	145	123	115	106	116	110	116	103	93	94	72	77	70	62	82	80	84	75	61	66	87	89	90	76	90	80	94	80	71	75	99%	100	4.4	3	110	-
6	491	26	M	48	Lap. Appendicectomy	88	80	78	70	82	90	95	98	89	80	127	125	120	110	112	100	106	111	108	109	70	70	68	62	68	82	88	80	70	72	93	89	86	78	82	88	94	90	82	84	99%	90	3.5	3	45	-
7	8760	24	M	63	Lap. Appendicectomy	67	78	66	68	70	76	79	73	67	77	127	131	125	111	113	113	120	108	99	126	65	70	60	66	76	77	70	77	71	94	98	98	88	81	78	89	86	87	80	104	99%	80	4.5	2	138	-
8	9	36	F	60	Lap. Cholecystectomy	99	86	86	78	77	82	88	80	81	77	123	128	113	115	102	96	122	102	101	101	76	77	70	66	74	60	91	77	77	76	93	96	89	82	87	72	90	85	85	84	99%	80	4	2	75	-
9	614	25	M	55	Lap. Appendicectomy	68	78	59	57	55	59	68	70	70	71	127	125	115	106	109	117	126	122	95	105	74	78	70	64	76	85	93	83	65	80	95	90	90	78	88	90	92	80	75	88	99%	90	2	2	65	-
10	24420	26	M	72	Lap. Appendicectomy	97	93	86	77	79	84	90	92	83	79	122	120	111	114	114	107	114	112	118	110	72	80	61	63	83	82	86	80	78	80	93	90	90	80	84	90	95	90	90	90	99%	100	4.6	1	180	-
11	530	23	M	45	Lap. Appendicectomy	68	64	64	60	59	78	70	76	60	63	107	98	95	94	95	84	110	80	99	100	71	70	60	60	68	62	70	63	73	74	90	99	78	71	78	69	83	68	80	82	99%	90	2	2	60	-
12	2889	43	F	49	Lap. Appendicectomy	108	98	96	64	89	94	99	90	102	98	118	129	110	110	112	106	114	108	129	102	75	75	65	65	70	71	74	67	55	66	94	90	88	80	85	80	87	80	78	78	99%	70	2.5	2	60	-
13	3620	60	F	58	Lap. Cholecystectomy	101	89	89	77	72	80	92	90	74	73	106	109	109	108	112	111	118	120	97	93	78	76	68	68	78	75	82	89	70	66	88	88	87	81	90	87	94	80	79	75	99%	80	7	2	98	Hypertension
14	3446	24	F	48	Lap. Appendicectomy	106	100	97	88	93	97	92	87	110	92	130	138	115	126	114	107	110	102	110	98	73	67	63	63	72	69	78	70	72	70	90	95	83	84	88	81	88	80	84	79	99%	75	6	2	136	Hypertension
15	1467	19	F	45	Lap. Appendicectomy	110	106	98	90	87	92	90	86	70	77	140	142	130	118	109	100	110	108	112	98	70	74	60	60	76	70	76	70	66	60	99	90	92	79	80	80	87	82	80	72	99%	110	3.2	3	138	-
16	3037	45	F	58	Lap. Cholecystectomy	89	82	71	67	67	78	79	79	72	68	140	149	136	130	120	125	129	102	101	98	83	88	70	73	58	74	60	68	65	68	90	93	90	92	78	91	83	77	77	78	99%	100	2.5	2	65	-
17	15228	35	M	64	Lap. Appendicectomy	84	81	80	76	77	76	82	77	81	77	138	111	106	104	104	97	98	96	101	98	83	80	80	73	71	69	66	70	67	67	90	93	88	83	83	78	76	78	78	77	99%	80	3.5	2	136	Hypertension
18	14564	58	M	56	Lap. Cholecystectomy	70	80	62	62	60	78	80	86	80	78	142	150	133	125	120	118	120	128	122	114	78	80	70	68	75	78	82	80	70	72	96	95	90	87	90	90	94	96	80	86	99%	70	3.8	3	140	-
19	14254	21	F	68	Lap. Appendicectomy	98	97	92	89	78	80	83	77	78	65	142	133	134	130	121	104	113	111	108	100	75	78	65	65	87	78	92	81	78	73	98	97	90	86	80	86	99	91	88	82	99%	80	3	2	65	-
20	13568	35	F	59	Lap. Appendicectomy	70	69	69	70	73	70	72	74	70	68	120	125	125	119	111	100	104	99	97	95	75	78	65	63	65	71	65	61	60	62	89	93	83	80	81	80	78	72	72	73	99%	85	2	1	50	-
21	13832	24	F	64	Lap. Appendicectomy	79	82	78	80	70	88	90	73	78	78	122	131	114	112	117	90	108	115	101	97	75	77	65	65	84	73	74	80	67	70	89	87	88	80	90	78	85	90	78	79	99%	80	3	2	200	-
22	9621	45	F	48	Lap. Cholecystectomy	68	64	69	60	57	90	95	96	86	69	122	129	119	104	103	102	103	95	105	83	86	88	66	76	66	65	64	65	77	57	90	89	80	85	79	77	77	75	86	65	99%	90	3	2	120	Hypertension
23	13772	25	M	46	Lap. Appendicectomy	68	80	64	65	66	73	70	72	79	76	138	112	110	111	110	112	115	99	93	92	73	77	63	63	75	80	83	70	65	66	95	98	88	79	86	90	93	79	78	74	99%	90	3	3	175	-
24	11693	42	M	52	Lap. Hernia repair	60	62	58	56	57	63	70	70	79	70	117	130	110	96	109	104	111	111	117	116	88	80	77	70	74	72	78	84	91	91	83	89	80	78	85	82	89	93	89	99	99%	80	3.5	2	170	-
25	2481	24	F	43	Lap. Appendicectomy	76	72	60	60	59	97	72	70	71	77	128	132	116	112	100	111	102	112	109	115	80	78	60	60	66	72	76	70	78	77	91	92	80	77	78	85	84	84	88	89	99%	85	2	2	45	-

ANNEXURE IV

KEY TO MASTER CHART

A Intn	–	After intubation
AD	–	After drug administration
AI	–	After induction of anesthesia
BI	–	Before induction of anesthesia
F	–	Female
I.P. No.	–	Inpatient number
M	–	Male
Wt.	–	Weight
Lap.	-	Laparoscopy
Chole.	-	Cholecystectomy
Appendix	-	Appendicectomy