Original Article:

Effect of intravenous dexmedetomidine on haemodynamic responses to laryngoscopy, tracheal intubation and anaesthetic and analgesic requirements: a randomized double-blind clinical efficacy study

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ABSTRACT

Background: Dexmedetomidine is an alpha 2-adrenergic receptor agonist that provides sedation, anxiolysis, hypnosis, analgesia, and sympatholysis. The present study is aimed to assess the efficacy of dexmedetomidine in attenuating sympathoadrenal response to laryngoscopy and tracheal intubation and to analyse its effect on intraoperative anaesthetic and analgesic requirements.

Methods: Sixty patients were randomized to receive either dexmedetomidine 1µg/kg (Group D) or 10 mL of 0.9% saline (Group S) over 10 minutes before induction of anaesthesia and after standard induction procedure the same study drug infusions were continued. Blood pressure, heart rate (HR) and Ramsay sedation score (RSS) were monitored at fixed time interval after study drug infusion and anaesthesia induction.

Results: After study drug administration the changes in HR and blood pressure was statistically significant between the groups (p = <0.001) at all-time intervals during study period. There was 50% reduction in thiopentone requirements in Group D in comparison to Group S (p<0.001). The intraoperative additional dose of morphine requirement was less in Group D in comparison to Group S to maintain the steady haemodynamics (p<0.001). Statistically significant difference was noticed in Group D regarding RSS at 5 min and 10 min after study drug infusion (p=0.025 and p=0.001 respectively) and again at 30 min after extubation (p= 0.002) when compared with Group S.

Conclusions: Our observations suggest that dexmedetomidine was effective in attenuating the heart rate and blood pressure rise during laryngoscopy and intubation, and decrease the thiopentone and morphine requirements intraoperatively.

Key words: *Dexmedetomidine, Laryngoscopy, Thiopentone, Morphine, Haemodynamics*

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INTRODUCTION

Laryngoscopy and tracheal intubation often provoke an undesirable increase in arterial blood pressure (BP) and/or heart rate (HR).[1] The haemodynamic response is exaggerated in hypertensive patients even though rendered normotensive pre-operatively by antihypertensive medication.[2] Intravenous anaesthetic induction agents do not adequately or predictably suppress the haemodynamic responses induced by laryngoscopy and tracheal intubation. The α_2-adrenergic agonists provide sedation, anxiolysis, hypnosis, analgesia, and sympatholysis. Dexmedetomidine belongs to the imidazole subclass of α_2-receptor agonists, similar to clonidine. Dexmedetomidine is the d-enantiomer of medetomidine, a substance that has been used for sedation and analgesia.[3] It shows a high ratio of specificity for the α_2 receptor (α_2/α_1 1600:1) compared with

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clonidine (α_2/α_1 200:1), making it a complete α_2-agonist.[4] The use of dexmedetomidine has dramatically increased now a days. This highly selective α_2 agonist has a set of unique effects that include titratable sedation, sympatholysis, and analgesia without significant respiratory depression. Originally approved as a sedative in the intensive care unit (ICU), it has found many off-label applications in the ICU, the operating room, and perioperative environment.[5,6] The present study was undertaken to assess the efficacy of dexmedetomidine in attenuating sympathoadrenal response to laryngoscopy and tracheal intubation and to analyze its effect on intraoperative anaesthetic and analgesic requirements.

MATERIAL AND METHODS

After obtaining approval from the Institutional Ethics Committee, a randomized, double-blind study was conducted. The study population comprised of 60 patients with American Society of Anesthesiologists (ASA) physical status[7] grade I aged between 18-65 years, scheduled for elective surgical procedures under general anaesthesia. Written informed consent was obtained from each patient. The exclusion criteria were, patients who do not belong to ASA physical status I, not willing to participate in the study, pregnant and nursing women, patients with morbid obesity, heart block, hypertensive, diabetes mellitus, and patients undergoing orthopaedic and paediatric surgical procedure. Patients with known allergic reaction to any of the study medications, patients recently using sedatives or analgesics, and patients with significant laboratory abnormalities were also excluded. Randomization into one of the two groups was done by using computer generated random numbers and sealed opaque envelope technique and randomization was done before initiating the study into two groups comprising of 30 patients in each group. After thorough preanaesthetic evaluation, each patient was explained about the study and the anaesthesia technique. All patients were premedicated with tablet ranitidine 150 mg and tablet alprazolam 0.5 mg orally with sips of water the night before surgery and in the morning before shifting to operating theatre. On arrival in the operating theatre, the patients were monitored by continuous electrocardiogram (ECG), noninvasive blood pressure (NIBP) monitor and pulse oximeter. The patients' baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), oxygen saturation by pulse oximetry (SpO_2), and Ramsay sedation score[8] (RSS) were recorded after 5 min of settling in the operative room by an anaesthesiologist who was blinded to the study. An 18G intravenous (IV) cannula was inserted for drugs and continuous intravenous fluid administration. Ondansetron 0.15 mg/kg was administered IV as premedication for both the groups. Patients received either dexmedetomidine 1 μg/kg in 0.9% NS to a total volume of 10 mL IV (Group D) or 10 mL of 0.9% normal saline (NS) IV (Group S) through a syringe infusion pump over 10 min. Both the drugs were prepared by an anaesthesiologist who was not involved in the study and syringes were labelled as study drug. After study drug infusion (at the end of 10 minutes) inj morphine 0.1mg/kg was given IV to both groups. Ten minutes after study drug infusion, all patients were induced with IV. thiopentone sodium in a dose sufficient to abolish eyelash reflex which was recorded followed by inj vecuronium 0.1 mg/kg to facilitate laryngoscopy and endotracheal intubation. Anaesthesia was maintained with oxygen, air, vecuronium top up doses and intermittent positive pressure ventilation in both groups. Sevoflurane was used to a maximum of 2% end-tidal concentration to maintain the heart rate and blood pressure within 30% of the baseline value.

Dexmedetomidine infusion in a dosage of 0.5 µg/kg/hour in group D (200 µg drug diluted with 0.9% NS to 50 mL volume) and normal saline infusion in group S (50 ml of 0.9% NS) were continued after intubation and the infusion was stopped 15-20 min before the start of skin closure in both groups. Intraoperatively IV morphine 0.05 mg/kg was repeated whenever there was rise in haemodynamic parameters of greater than 30% from the baseline which was not controlled with maximum end-tidal sevoflurane of 2% and the total extra dose of morphine required was calculated in all the patients and recorded. Intraoperative hypotension (30% fall in SBP from baseline value) was treated with simultaneous fluid bolus and vasopressors like phenylephrine (100 µg) or ephedrine (6 mg) bolus and repeated as necessary. Bradycardia was defined as a HR of less than 40 beats per minute and was treated with IV atropine 0.6 mg bolus dose and repeated as necessary. Hypertension was defined as increase in SBP 30% from the baseline value and was treated initially with increasing the sevoflurane concentration to a maximum end-tidal concentration of 2% in both groups and if still no response, additional doses of IV morphine 0.05 mg/kg was admistered. Sevoflurane was discontinued just before the end of skin closure. At the completion of surgery, residual neuromuscular blockade was reversed with IV neostigmine (0.05 mg/kg) and glycopyrolate (0.02 mg/kg) and patient was extubated after recovery of protective airway reflexes.

The HR, SBP, DBP, MAP, and SPO_2 were recorded at baseline, 5 min, 10 min after study drug infusion, before induction, after induction (just before laryngoscopy), 1 min, 3 min and 5 min after intubation in all the patients. The dose of thiopentone sodium required for abolishing eyelash reflex during induction and extra dose of morphine required intraoperatively were recorded in both groups. RSS was recorded at base line, 5 min, 10 min after study drug infusion, 5min, 30min and 60 min after extubation in all the patients.

Statistical analysis

Patient data variables were summarized as mean and standard deviations (SD). Comparison between two groups with respect to continuous variables such as age, weight, HR, SBP, DBP and MAP were compared with student's t-test. Continuous haemodynamic variables within the group were compared with baseline value by using repeated measures analysis of variance (ANOVA) with Bonferroni adjustment. After using repeated measure ANOVA test, a post-hoc test using Bonferroni adjustment was used to check for significant pair-wise differences. The RSS and categorical variables like gender distribution were compared using chi-square test. Statistical analysis was carried out using Microsoft Office 2010, Statistical Packages for Social Sciences version 20 (SPSS 20) software (SPSS Inc; Chicago, IL, USA) for windows. A p-value of less than 0.05 was considered as statistically significant.

RESULTS

A total of 250 patients posted for various elective surgical procedures under general endotracheal anaesthesia were screened for inclusion in the study during the period. Out of these 190 patients who did not meet the inclusion criteria were excluded. Remaining 60 patients were randomized into Group D and Group S. After randomization, one patient discontinued from intervention in group D due to urticarial rash over the infused IV line. Finally 29 patients in group D and 30 patients in group S were analyzed (Figure1).

The two groups were comparable regarding age, sex and weight (Table 1). Pre-induction heart rate, SBP, DBP and MAP were comparable between the two groups (p=NS).

Table 2: Comparison of thiopentone and morphine requirements

	Group D	Group S	p-value
Thiopentone (mg/kg)	1.95±0.9	4.10±0.5	<0.001
Morphine (mg)	0.15±0.6	2.10±1.3	<0.001

Data are presented as mean ± standard deviation

Table 3: Ramsay sedation score

	Ramsey sedation score						p-value
	1	2	3	4	5	6	
At baseline							
Group D	3	27	0	0	0	0	
Group S	4	26	0	0	0	0	0.694
5 minutes after study drug infusion							
Group D	0	27	3	0	0	0	
Group S	2	28	0	0	0	0	0.025
10 minutes after study drug infusion							
Group D	0	22	8	0	0	0	
Group S	1	29	0	0	0	0	0.001
5 minutes after extubation							
Group D	0	17	9	4	0	0	
Group S	1	18	11	0	0	0	0.166
30 minutes after extubation							
Group D	0	24	6	0	0	0	
Group S	3	27	0	0	0	0	0.002
60 minutes after extubation							
Group D	4	26	0	0	0	0	
Group S	6	24	0	0	0	0	0.497

Data are presented as no. of subjects

When compared with base line, the change in HR (Figure 2) was statistically significant ($p< 0.001$) at all-time intervals in group D patients whereas in group S, the change in HR was statistically significant ($p< 0.001$) only at 1 min after intubation. The change in HR was statistically significant ($p< 0.001$) between the groups at all-time intervals during study period.

With regard to blood pressure both groups were comparable before study drug administration (Figures 3, 4 and 5). After study drug administration the change in SBP, DBP and MAP was statistically significant between two groups ($p< 0.001$) at all-time intervals during study period. When compared with base line, change in SBP, DBP and MAP was statistically significant ($p< 0.001$) in group D except in DBP ($p = 1.000$) and MAP ($p = 0.258$) at 1 min after intubation in which there was rise in HR due to pressor response to laryngoscopy and intubation. Whereas in Group S the change in SBP, DBP and MAP was statistically significant only after induction and intubation in which there was fall in SBP, DBP and MAP followed by rise in SBP, DBP and MAP.

The mean dose of IV thiopentone in abolishing eyelash reflex was 2mg/kg and 4 mg/kg in Group D and Group S respectively (Table 2). This means that there was 50% reduction in thiopentone requirements in group D in comparison to group S ($p< 0.001$). The intraoperative additional dose of morphine requirements (Table 2) on average 0.15 mg of inj morphine was required in only 2 patients in group D, whereas in group S, 23 out of 30 patients received on an average 2 mg of additional dose of IV morphine to maintain the haemodynamics ($p< 0.001$). Statistically significant difference was noticed in group D regarding RSS (Table 3) at 5 min and 10 min after study drug infusion ($p = 0.025$ and $p = 0.001$ respectively) and again at 30 min after extubation ($p=0.002$) when compared with group S. After extubation, patients in Group D had higher sedation score compared to Group S, which persisted till 30 min after extubation and had comparable sedation score at the end of 60 min. But none of the patients in Group D had airway obstruction and respiratory depression even though they had higher sedation score compared to Group S.

DISCUSSION

In our study, after tracheal intubation, the HR, SBP, DBP and MAP was decreased by 7%, 6%, 1% and 3% respectively from baseline value in the dexmedetomidine group compared to saline group where it was raised by 15%,10%,14% and 14% respectively from baseline **(**Figures 1,2,3 and 4) and our study

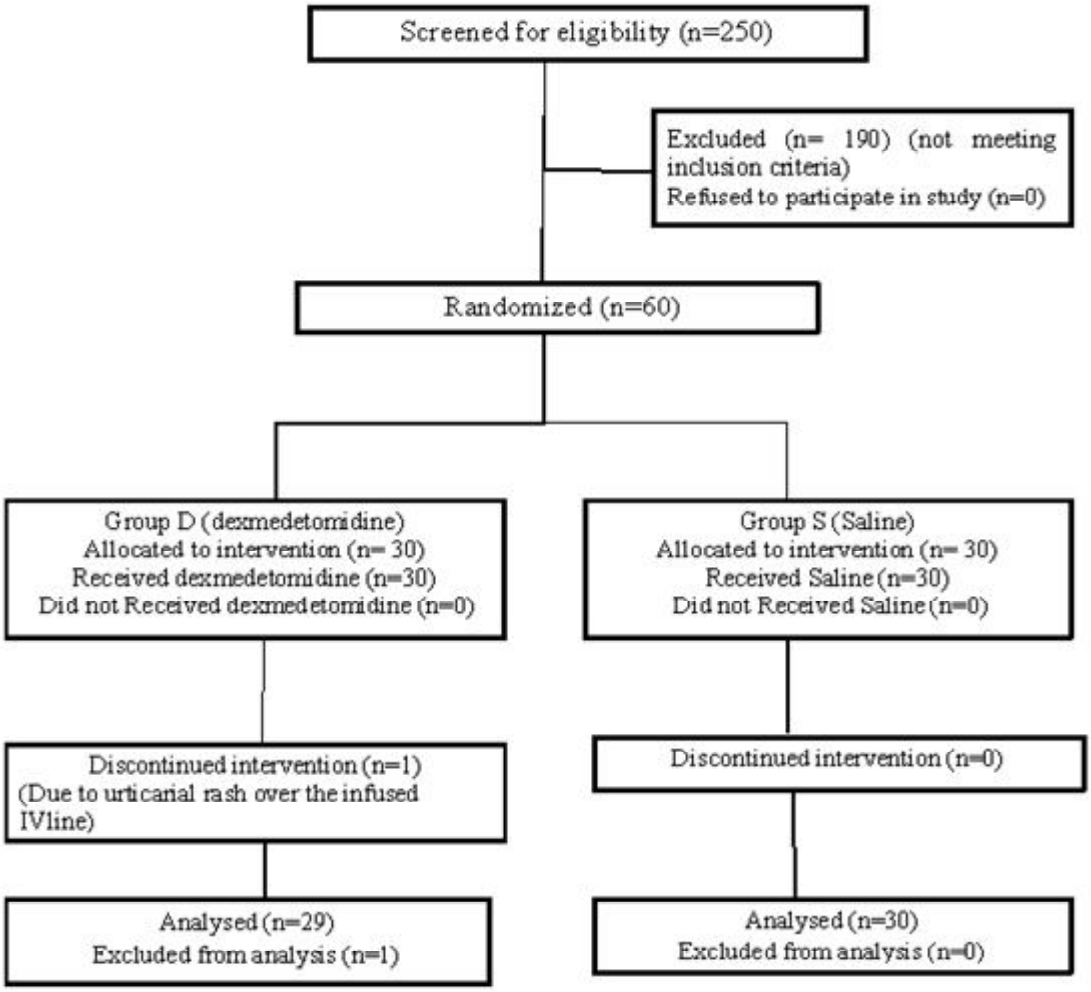

Figure 1: Study plan

Table 1: Demographic data

	Group D	**Group S**	**p-value**
Age (years)*	41±8.9	44±7.4	0.140
Weight (kg)*	56±10	58±10	0.500
Gender (male/ female)	14/16	12/18	0.600

*data are presented as mean ± standard deviation

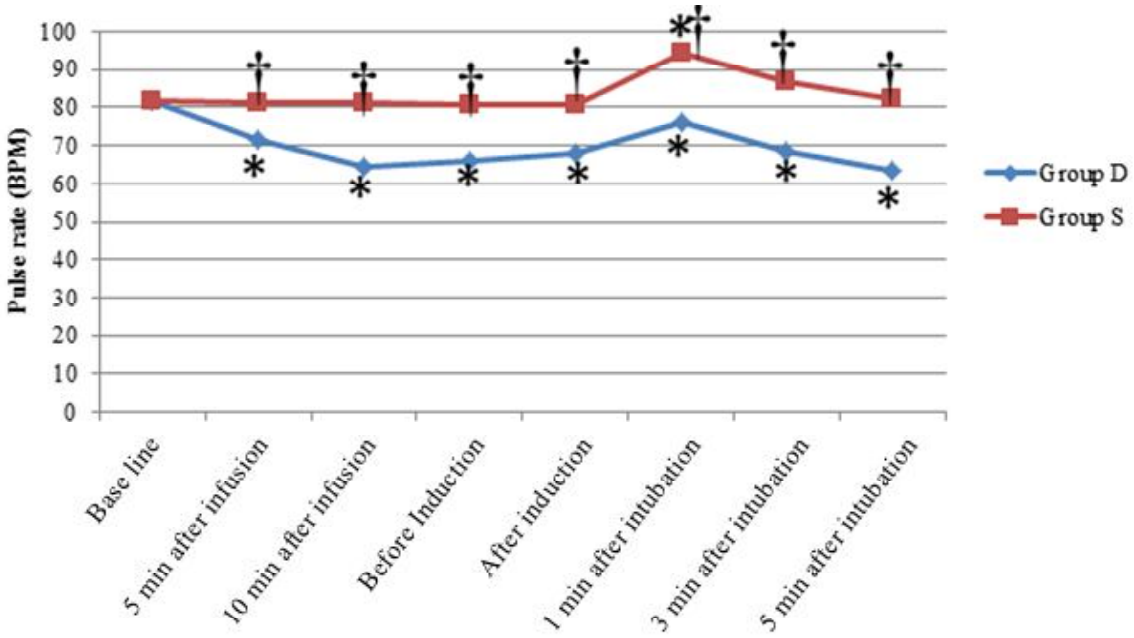

Figure 2: Comparison of pulse rate in Group D and Group S patients at various time points
∗ $p < 0.05$ within the group; † $p < 0.05$ between the groups

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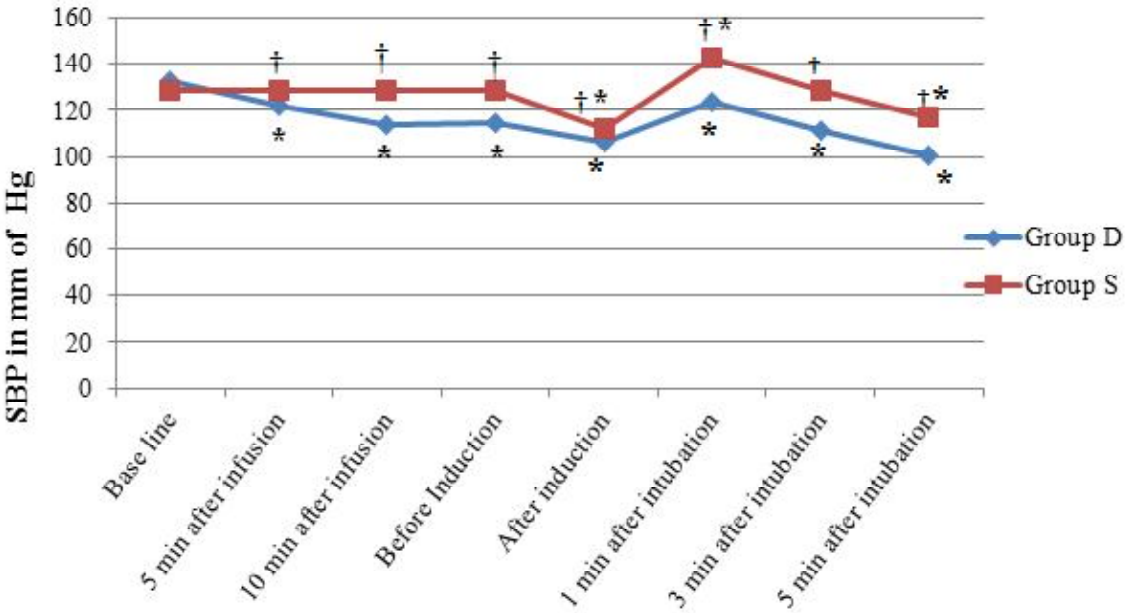

Figure 3: Comparison of systolic blood pressure in Group D and Group S patients at various time points
∗ $p < 0.05$ within the group; † $p < 0.05$ between the groups

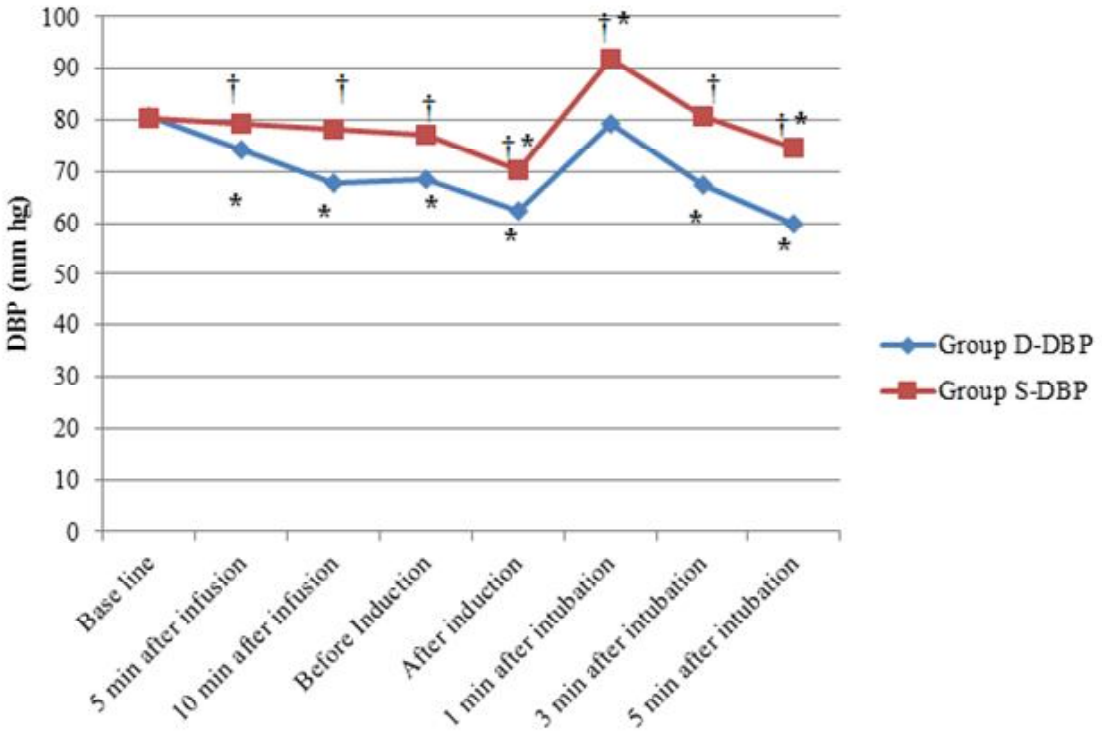

Figure 4: Comparison of changes in diastolic blood pressure in Group D and Group S patients at various time points

∗ $p < 0.05$ within the group; † $p < 0.05$ between the groups

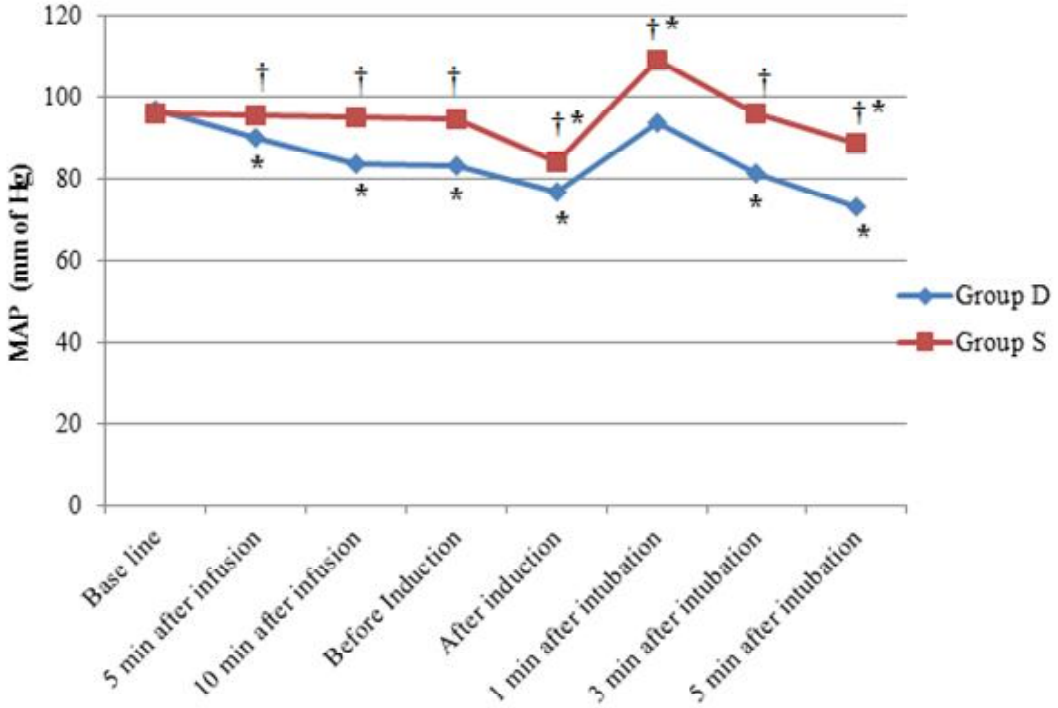

Figure 5: Comparison of changes in mean arterial pressure in Group D and Group S patients at various time points

∗ $p < 0.05$ within the group; † $p < 0.05$ between the groups

results were comparable with the previous study results.[9,10]

In our study when compared with NS group (Table 2) in dexmedetomidine group the thiopentone requirement was decreased by 50% and intraoperative requirement of morphine by 92.5% and our results were consistent with the earlier studies.[11-14]

Contrary to the previous study,[15] in our study all patients were extubated on the operating table and there was no delayed recovery and also patients who received dexmedetomidine had higher sedation score (Table 3) as assessed by RSS after extubation but all patients had normal and regular respiratory pattern without any airway obstruction and respiratory depression even though patients had higher sedation scores.

One retrospective[16] study and two prospective, randomized controlled trials[17-19] in bariatric surgical patients have found that a balanced anaesthetic with desflurane or propofol plus dexmedetomidine reduces postoperative morphine consumption, and improves haemodynamics compared with desflurane-fentanyl or propofol-fentanyl anesthetics. In our study, we have used morphine for analgesia in both groups but the requirement of additional dose of morphine was decreased in patients who received dexmedetomidine compared to those who received saline.

The limitations of our study was, firstly we have not measured the depth of anaesthesia which could be more helpful in titrating the sevoflurane dial setting according to the depth of anaesthesia because of the unavailability of (BIS) monitor. Secondly, we have not calculated the sevoflurane requirements separately in both groups to maintain haemodynamic parameters within acceptable range which could be more helpful in this study.

The significant changes in haemodynamic parameters between two groups is probably due to Group D patients received dexmedetomidine initially 1 μg/kg as bolus followed by 0.5 μg/kg/ hour as an infusion compared to Group S patients who received 0.9% NS both as bolus and infusion. Due to its central sympatholytic action, dexmedetomidine causes decrease in haemodynamic parameters thereby prevents the stress response to laryngoscopy and intubation. The decrease in anaesthetic dose requirements is due to Group D patients received dexmedetomidine, an α_2-adrenergic agonists had central sedative, anxiolytic, hypnotic, analgesic, and sympatholytic properties which leads to decrease in the anaesthetic and analgesic requirements intraoperatively compared to Group S, who received 0.9% NS.

We conclude that dexmedetomidine was effective in attenuating the heart rate and blood pressure from rising during laryngoscopy and intubation, and decrease the thiopentone and morphine requirements intraoperatively. Thus dexmedetomidine infusion had perioperative haemodynamic stability and also had the anaesthetic and analgesic sparing effect. Patients who received dexmedetomidine infusion intraoperatively had higher sedation scores during early recovery phase; one should be careful while monitoring these patients to identify any adverse events like airway obstruction because of higher sedation score.

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