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RESEARCH ARTICLE

A PROSPECTIVE RANDOMIZED DOUBLE BLIND STUDY TO FIND OUT THE EFFICACY OF DEXMEDETOMIDINE 1MCG/KG SINGLE INFUSION AS AN ADJUVANT FOR GENERAL ANAESTHESIA

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ABSTRACT

Background: Dexmedetomidine is an α2-adrenoreceptor agonist with sedative, analgesic and anxiolytic effects. We evaluate the effect of preanaesthetic dexmedetomidine 1 μg/kg single infusion on sedation, haemodynamics, anaesthetic consumption, and recovery profiles during anaesthesia.

Methods: Sixty patients of both gender with American Society of Anaesthesiologists physical status I or II undergoing surgery with anticipated operation time of 2 h, were randomly assigned to receive dexmedetomidine 1 μg/kg (study group) or normal saline (control group) intravenously over 10 min before anaesthetic induction. After tracheal intubation with Inj. thiopentone sodium 5 mg/kg intravenous (i.v.), vecuronium 0.12 mg/kg i.v., anaesthesia was maintained with sevoflurane, O2 50%, N2O 50% around a BIS value of 40.

Results: After infusion of the study drug was completed, BIS of study group was significantly lower than that of control group (57.36±3.88 vs 96.66±1.51, $p < 0.0001$). After tracheal intubation, HR, SBP, DBP, MAP was significantly higher ($p < 0.05$) in control group than the study group. During maintenance, HR, SBP, DBP and MAP remained significantly lower ($p < 0.05$) in study group than control group. Sevoflurane consumption for 2 hours duration of surgery was significantly less in study group than control group (25.05±2.67 vs 33.14±3.70,$p<0.0001$). Patients in study group took significantly more time to respond to suction catheter, to obey verbal commands and for complete extubation than the control group ($p < 0.05$).

Conclusion: Preanesthetic dexmetomidine 1 μg/kg single infusion is an economical and useful adjuvant to general anaesthesia that maintains stable haemodynamics, decrease anaesthetic consumption and provides good post-operative analgesia.

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INTRODUCTION

Intubation has been practiced following its description by Rowbatham and Magill in 1921. Till today, laryngoscopy and intubation is the Gold standard for airway management. In 1940, Reid and Brace (Reid, 1940), first described hemodynamic response to laryngoscopy and intubation which is exhibited in the form of changes in heart rate, blood pressure and arrhythmias. The pressure response, which is part of a huge spectrum of stress response, results from the increase in sympathetic and sympathoadrenal activity, as evidenced by increased plasma catecholamines concentration in patients undergoing surgery under general anaesthesia. The major cause of this sympathoadrenal response is the stimulation of the supraglottic region by the laryngoscope blade.

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Increase in mean arterial pressure of an average of 25mm Hg was observed in normotensive patients following laryngoscopy and intubation under anaesthesia with thiopentone, nitrous oxide, oxygen and suxamethonium. 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, pulmonary edema, myocardial ischemia, ventricular dysrhythmias and cerebral haemorrhage. (Fox et al., 1977) Convulsions may be precipitated in pre-eclamptic patients. To blunt this pressor response, various methods have been tried including,

- Deeper plane of anaesthesia with intravenous or inhalation agent

- Use of Propofol
- Curtailing the duration of laryngoscopy to less than 15 seconds
- Sympathetic blockage
- Lidocaine spray or gargles 3 minutes prior to intubation
- Use of intravenous lidocaine to blunt the pressor response
- Use of ACE inhibitors e.g. Captopril, Enalapril 45 minutes prior to intubation
- Use of Magnesium sulphate
- Various antihypertensive and vasodilators e.g. I.V. Hydralazine, Ca^{+2} channel blocker like Nifedipine, betablockers like Esmolol
- Use of Nicardipine
- Use of Opioids prior to induction e.g. Fentanyl, Sufentanyl or Alfentanyl
- Use of Nitroglycerine ointment, intravenous, sublingual spray, intranasal spray
- Use of Gabapentin
- Alpha -2 agonists like Clonidine, Dexmedetomidine

Alpha-2 receptors are a subgroup of noradrenergic receptors that mediate the function of the sympathetic nervous system. The alpha-2 receptor activation results in reduction in nor-epinephrine release, which can be used therapeutically to induce sympatholysis. Dexmedetomidine was first marketed for Intensive Care Unit (ICU) sedation, to make use of highly selective adrenergic alpha-2 receptor agonist activity. Unlike commonly used sedatives such as propofol or midazolam, dexmedetomidine produces an "interactive" form of sedation, in which patients can be aroused easily with stimulation, and are co-operative once aroused. Because of its sympatholytic properties, dexmedetomidine was gradually developed as anaesthetic premedication, with the goal of attenuating the sympathetic response to perioperative stresses such as laryngoscopy and intubation. Dexmedetomidine when co-administered with opioids has no depressant effects on respiration, but its analgesic effects offer a significant advantage for patients at risk for respiratory decompensation. Several studies have indicated that administration of intravenous dexmedetomidine during general anaesthesia can decrease the minimum alveolar anaesthetic concentration (MAC) of sevoflurane and thus decrease the total consumption of sevoflurane. With this in background, we planned a prospective, randomized, double blind study to investigate the effects of preanesthetic dexmedetomdine 1 µg/kg on sedation, haemodynamics, anaesthetic consumption and recovery profiles during surgeries with an anaesthesia time of 2 hours.

MATERIALS AND METHODS

The study entitled "A prospective randomized double blind study to find out the efficacy of dexmedetomidine 1µg/kg single infusion as an adjuvant for general anaesthesia" was carried out in our tertiary care hospital. The study was conducted after the approval of ethical committee of the institution and with the informed consent given by the patient.
It was a prospective, randomized, double blind, comparative study involving 60 patients, distributed equally 30 each in Group N (control group-Normal saline) and Group D (study group-Dexmedetomidine). Initially we did a pilot study of 20 patients. 10 in each Group N and D as an open drug study. From the pilot study, a sample size of 21 patients per study group was determined to be sufficient for identifying a 20% difference in the hemodynamic changes between the two groups' with a power of 0.8 and α value of 0.05. However, we included 30 patients in each group. Sixty patients of both gender (age range 18-50 years) scheduled for surgery requiring general anaesthesia with an anticipated operation time of 2 h and classified as American Society of Anaesthesiologists (ASA) physical status I or II were enrolled in the study. Patients with a history of severe cardiac or pulmonary diseases, neurologic dysfunction, psychiatric illness, bleeding or coagulation disorder, known drug allergy, chronic renal failure, alcohol or drug abuse, chronic analgesic abuse, pregnant and lactating females were excluded. This study was controlled, double-blinded, and randomized using a sealed envelope technique that placed patients into one of two groups. The envelope was opened by an independent anaesthetist who prepared the study drugs but was not otherwise involved in the study.

General physical and systemic examination was carried out. Pre-operative investigations were done which included complete haemogram with platelet count, bleeding time, clotting time, blood sugar & urea, x-ray chest PA view and ECG. Accordingly patients were assigned into ASA groups. All patients were kept fasting 8 hours prior to surgery. Tab. diazepam 5 mg was given orally to provide a nice sleep on the previous night of surgery. On arrival of patient to holding area of O.T in the morning intravenous (i.v.) line was secured with 20G cannula. Ringer Lactate infusion was started at 10ml/ kg/ hr rate and Inj. metoclopramide 10 mg i.v. and Inj. ranitidine 50 mg i.v. was administered 1 hour prior to shifting patient to respective O.T suite. After taking the patient to operation suite, a multiparameter monitor (Drager Infinity Delta) was applied and baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) , oxygen saturation (SpO_2) were noted down. This monitor had inbuilt facility for end tidal carbon dioxide ($ETCO_2$) concentration. BIS strip was attached and Bispectral index (BIS) monitor was connected to it. The infusion of ringer lactate (RL) was continued at the rate of 10ml/kg/hr. Patients were blinded and randomized to receive a 10 minute infusion of either normal saline 20 ml (control group) or dexmedetomidine 1µg/kg in normal saline 20 ml (study group) before anaesthetic induction.

After completion of the test drug infusion, patients were given Inj. midazolam 0.05mg/kg i.v. and Inj. fentanyl 0.001mg/kg i.v. After preoxygenation with 100% O2 at 8 L/min for 5 mins, all patients received Inj. thiopentone sodium 5 mg/kg intravenously and Inj. vecuronium 0.12 mg/kg intravenously for tracheal intubation. Anaesthesia was maintained with sevoflurane with O2 (1.5 L/min) and N_2O (1.5 L/min) ventilated to maintain end-tidal CO2 ($EtCO_2$) between 35 and 40 mmHg. Anaesthetic depth was monitored using the Bispectral Index to reach a target value of around 40 by manipulating sevoflurane vaporizer setting. For hemodynamic stability, Inj. fentanyl in a bolus dose of 10 mcg i.v. was administered if the patient's mean arterial pressure (MAP) was more than 20% above the baseline value (value before anaesthetic induction) while decreases in MAP of a similar magnitude were treated with ephedrine 4-8 mg i.v. and also atropine 0.5 mg i.v.if the patient's heart rate (HR) was less than 20% of baseline. Neuromuscular block was monitored during the operation and incremental doses of Inj. vecuronium bromide 0.02 mg/kg i.v. were given when a train of four (TOF) stimulus produced two twitches. After skin closure, all

anaesthetics (sevoflurane, N_2O) were turned off, and the ventilation was controlled with O2 (6 L/min) until extubation. Residual muscle paralysis was reversed with Inj. neostigmine 0.05mg/kg i.v. and Inj. glycopyrrolate 0.01mg/kg i.v. Patients were extubated after adequate return of muscle power and protective reflexes, aBIS of greater than 90, and after they respond to verbal commands. Visual analog scale (VAS) was assessed in the recovery room. Patients who showed VAS more than 4 were given Inj. diclofenac 75mg i.v. Ramsay sedation scale was assessed before drug infusion and after drug infusion. HR,SBP,DBP,MAP,SPO2,BIS were monitored before drug infusion, after drug infusion, at induction, at intubation, thereafter at 2,5,10,15,20,25,30,40,50,60, 80,100,120 mins. After turning off all anaesthetic agents, time to respond to suction catheter, to obey verbal commands and time taken for total extubation were recorded.

Total sevoflurane consumption during surgery was measured using Dion's formula.

$$\text{Agent consumed} = \frac{\text{Mean FGF (ml/min) x mean agent conc (vol\%) x anaesthesia duration (min)}}{\text{Saturated gas volume (ml) x 100 (vol \%)}}$$

For Sevoflurane, Saturated gas volume at 20ºC = 184 ml. Post operative analgesia was assessed by Visual Analog Scale at recovery room in 0, 1st and 3rd hours. Microsoft Excel 2010 and SPSS 14.0 version software packages were used for data entry and analysis. Results were expressed as mean and Standard Deviation unless otherwise stated. Statistics were performed using Students unpaired t test, Fisher's exact test and Analysis of Variance (ANOVA) to compare the characteristics and GLM for repeated measures.

RESULTS

Sixty patients were enrolled in the study and randomized into groups. No patients were excluded in analysis. Two groups did not differ significantly in demographic characteristics and baseline parameters (Table 1).

Table 1. Characteristics of patients scheduled for surgery

	GROUP N (Control group)	GROUP D (Study group)
Age (yrs)	34.53±9.09	35.66±8.07
Height (cms)	166.1±5.73	166.23±5.26
Gender (M:F)	16:14	15:15
Weight (in kgs)	58.83±5.36	57.9±5.74
Asa status (I : II)	16:14	15:15
Baseline HR (beats/min)	79.23±7.29	81.4±6.62
Baseline SBP (mm Hg)	125.1±10.42	127.2±5.97
Baseline DBP (mm Hg)	77.13±8.22	79.2±5.26
Baseline MAP (mm Hg)	93.12±8.48	95.20±8.38
Type of surgery		
Gynaecology	8	7
Orthopaedics	5	6
General surgery	7	6
ENT	3	4
Plastic surgery	4	4
Urosurgery	3	3

Values are mean ± SD or number of patients (n).

After infusion of the study drug was completed, BIS of study group was significantly lower than that of control group (57.36±3.88 vs 96.66±1.51, p<0.0001) (Fig. 1) without respiratory depression. After drug infusion for 10 mins, none of the patients in control group (Group N) reached Ramsay sedation scale (RSS) of 3 or more. While in study group (Group D), 9 patients reached RSS of 3, 19 patients reached RSS of 4 and 2 patients achieved RSS of 5. Applying Mann – Whitney U test it was found to be significant in Group D (Table 2).

Table 2. Comparison of Ramsay Sedation Scale

RSS	GROUP N	GROUP D
1	10	0
2	20	0
3	0	9
4	0	19
5	0	2

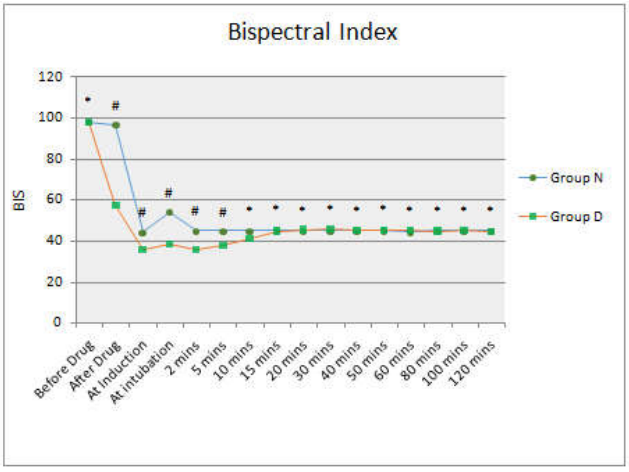
Table 3. Total sevoflurane consumption, Recovery profiles, VAS

	Group N (Control group)	Group D (Study group)
Total Sevoflurane used (in ml)	33.14±3.70	25.05±2.67*
Time to suction catheter response (sec)	423.86±22.79	484.43±27.70*
Time to obey verbal commands (sec)	622.46±23.62	642.7±26.41*
Time to tracheal extubation (sec)	727.16±20.65	741.96±26.73*
No. of patients with VAS >4		
At 0 Hrs	25	11*
At 1 Hrs	9	9
At 3 Hrs	20	19

Values are mean ± SD or number of patients (n). *P < 0.05 versus control group.

Table 4. Comparison of Side effects in Group N and Group D

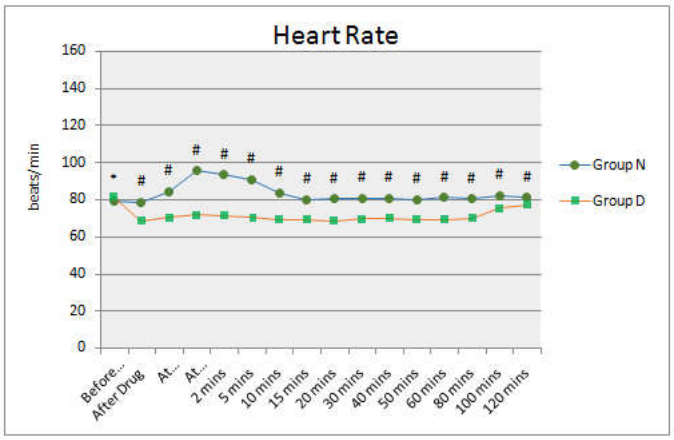
	Group N	Group D
Hypotension	0	5
Bradycardia	0	6
Vomiting	0	0
Shivering	0	0
Respiratory depression	0	0



* -non-significant, # - significant

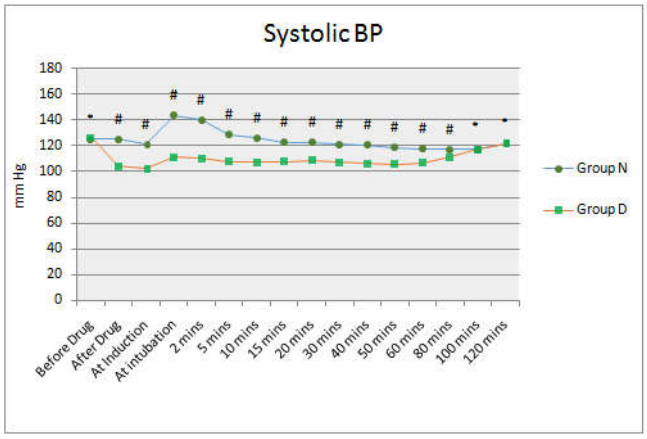
Figure 1. Graph showing comparison of BIS

After tracheal intubation, in the control group (Group N), HR (95.4±8.16 vs 71.66±4.61, p<0.0001), SBP (143.60±10.76vs 111.20±4.53, p<0.0001), DBP (86.8±8.47 vs 70.86±5.16, p<0.0001), MAP (105.73±8.49 vs 84.31±4.13, p<0.0001) is significantly higher than the study group (Group D). During maintenance, HR, SBP, DBP and MAP remained significantly lower (p < 0.05) in study group compared to control group (Figure 2-5). As shown in recovery profiles, patients in study group took significantly more time to respond to suction catheter, to obey verbal commands and for complete extubation than the control group (p<0.05, Table 3).



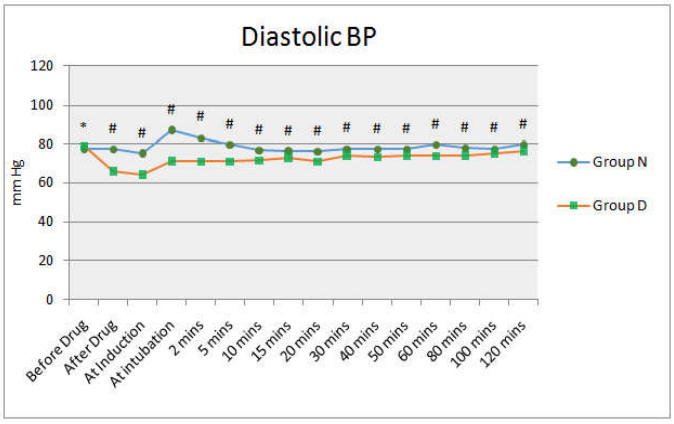
* -non-significant, # - significant

Figure 2. Graph showing change in Heart rate



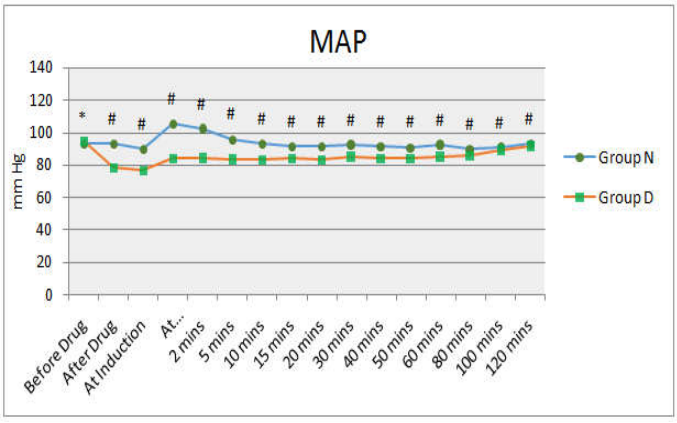
* -non-significant, # - significant

Figure 3. Graph showing comparison of Mean SBP



* -non-significant, # - significant

Figure 4. Graph showing comparision of mean DBP



* -non-significant, # - significant

Figure 5. Graph showing comparison of mean of MAP

Total sevoflurane consumption for 2 hours duration of surgery was significantly less in study group than control group ($p<0.0001$, Table 3). Post operatively, 25 patients in study group showed VAS >4 while in control group only 11 patients showed so which is significant ($p<0.05$). After 1st and 3rd hour, VAS in study group and control group was comparable and not significant ($p>0.05$, Table 3). Out of 30 patients in study group, 5 patients and 6 patients showed hypotension and bradycardia respectively and they responded well to Inj. ephedrine 4 mg i.v. and Inj. atropine 0.5 mg i.v. while in control group none of the patients showed so. None of the patients showed post-operative nausea or vomiting, shivering and respiratory depression (Table 4).

DISCUSSION

This study shows that preanaesthetic dexmedetomidine 1µg/kg single infusion prevents hemodynamic changes by tracheal intubation and reduces the total cumulative consumption of sevoflurane. Dexmedetomidine is a highly selective α2 agonist that results in sedation and anxiolysis. It binds to transmembrane G protein-binding adrenoreceptors in the brain and spinal cord with a dose-dependent α2-selectivity that is approximately 7- to 8-fold greater than that of clonidine. Stimulation of α2- adrenoreceptor subtypes mediates sedative and antinociceptive actions (α2A) and a vasoconstrictive cardiovascular effect (α2B), and modulates dopaminergic neurotransmission, hypothermia and a variety of behavioral responses (α2C). The inhibition of norepinephrine release suppresses the level of excitation, especially in the locus coeruleus (α2A) which controls anxiety, arousal, sleep, and opioid withdrawal. When compared to other sedatives, dexmedetomidine has a favorable profile due to its ability to produce good sedative outcomes without respiratory depression, an important consideration in terms of emergence. Dexmedetomidine has not been routinely used in elective general anesthesia, especially day surgery, due to intraoperative hemodynamic instability such as hypotension, bradycardia, and delayed emergence. On the other hand, dexmedetomidine has been increasingly popularity as an adjuvant to general anesthesia since it features advantages such as anesthetic sparing, hemodynamic stability, and the reduction of emergence agitation. Aantaa, (1991), reported that dexmedetomidine 0.5-1.0 µg/kg induced sedation within 5 minutes and reached its maximum effects at 15 minutes. Patel ND *et al*. (2015) observed that Ramsay sedation scale was ≥ 4 in all patients in dexmedetomidine group and was ≤ 3 in fentanyl group. Song *et al*. (2013) concluded that intravenous injection of dexmedetomidine 1 µg/kg followed by continuous administration at infusion rates of 0.25, 0.50, or 0.75 µg/kg/hr produced adequate levels of sedation. Our results are in agreement with these studiesand we observed all patients who received dexmedetomidine to have sedation score ≥ 3.

Generally sedation induced by dexmedetomidine was similar to arousable sedation like normal sleep. Tracheal intubation and extubation evoke strong hemodynamic stress responses but most patients tolerate the stress well without serious sequelae. However, it can lead to myocardial ischemia in patients with pre-existing severe coronary artery disease. In these patients,

the use of dexmedetomidine maylower the risk of coronary ischemic events by lowering the rate pressure product (Muniyappa, 2016). Additionally, dexmedetomidine has been used to successfully facilitate the withdrawal of ventilation in intensive care unit patients who previously failed weaning attempts because of agitation (Muniyappa, 2016). Adverse reactions to dexmedetomidine include hypotension, bradycardia and even sinus arrest in healthy young volunteers with high vagal tone secondary to the attenuation of plasma catecholamine release (Ingersoll, 2004). In particular, large doses or rapid injection of dexmedetomidine have been associated with these adverse events (Khan, 1999). Dexmedetomidine (over 1.0 μg/kg) should be infused over 10 minutes and titrated to an adequate dosage on a case by case basis. We achieved stability in MAP by slowly infusing dexmedetomidine over 10 min at an adequate dosage for the patients.

The over-infusion or over dosage of anesthetics can be prevented by BIS monitoring. We maintained equal anesthetic depth in both groups at a BIS value of 40-60 by controlling sevoflurane vaporizer setting. Intraoperative co-administration of dexmedetomidine with other anesthetics could potentiate any hemodynamic instability by over-sedation or over-dosing. Therefore, use of an anesthetic depth monitor like BIS is essential when employing a dexmedetomidine adjuvant for general anesthesia. We observed BIS significantly lower in dexmedetomidine group during intubation compared to control group. The mean of BIS range in control group was 44 -55 while it was from 35-38 in dexmedetomidine group. Our results are in agreement with the studies by Shin *et al.* (2013), Dilek Özcengiz *et al*. (2012). Dexmedetomidine shows the biphasic hemodynamic effect that not only vasodilation by presynaptic effect on sympathetic and postsynaptic effect on central nervous system at high concentration but also vasoconstriction by postsynaptic effect on vascular system at low concentration (an initial increase in MAP followed by reduction in MAP and HR). We did not observe the biphasic e□ects of dexmedetomidine in this study, perhaps because the slow infusion of dexmedetomidine over 10 minutes may have caused low plasma concentrations and reduced MAP during induction period.

Our results were similar to the studies by Saraf *et al.* (2013) who observed that 0.6mcg/kg loading dose of dexmedetomidine decreased the mean of HR, SBP, DBP and MAP by 2.86 bpm, 15.86 mmHg, 9.54 mmHg and 1.98 mmHg respectively compared to basal values which wasstatistically significant. Our results also correspond to the studies by Gandhi *et al*. (2014) and Shin *et al* (2013). We observed dexmedetomidine efficiently attenuated the sympathoadrenal response to laryngoscopy and intubation (MAP =105.73mmHg vs 84.31mmHg, HR = 95.4 bpm vs 71.66 bpm). Our results showed that preanesthetic dexmedetomidine 1 μg/kg reduces the total consumption of sevoflurane by 24% (33.14 ml vs 25.05 ml) compared with control group. In previous studies of Aantaa *et al*. (1991) a 25% reduction of maintenance and concentration of isoflurane in patients who received dexmedetomidine was seen. Harsoor *et al*. (2014), observed 24% decrease in sevoflurane consumption after 2 hours of surgery duration in dexmedetomidine group compared to control group. Similar results were seen by Khan *et al*. (1999) and Muniyappa *et al.* (2016). Our results are in accordance with all the above studies. The pharmacoeconomic effect of dexmedetomidine may aid in reducing the concentration of anesthetics used and preventing adverse effects such as hepatic and renal toxicity, severe myocardial depression, and the greenhouse effect. In our study, although sevoflurane consumption was lesser in dexmedetomidine group, patients in dexmedetomidine group took longer time for recovery. A possible explanation is that the use of fentanyl along with dexmedetomidine might have prolonged the recovery time. Isik *et al.* (Isik, 2006) reported that in children undergoing magnetic resonance imaging, dexmedetomidine 1.0 μg/kg iv after anesthetic induction was effective in the reduction of agitation, but prolonged the removal of LMA and eye opening time. These findings can be attributed to the sustained therapeutic plasma concentrations of dexmedetomidine relative to the short procedure time (45-49 min). Our results are in accordance with Waindeskar *et al*. (2015), Shin *et al*. (2013). The prolongation of recovery in their studies may be because of the continuous infusion of dexmedetomedine till the end of the surgery. The duration of operation, drug infusion time, and context-sensitive half times must be considered when planning anaesthesia for patients. Some studies have reported that the postoperative analgesia due to dexmedetomidine is evident in the recovery room but did not continue after recovery room discharge (Feld, 2006). This may be related to the elimination half-life of dexmedetomidine. We observed significant analgesia in the dexmedetomidine group just after shifting patient to recovery room. Among the patients who received dexmedetomidine, 63% of them showed VAS less than 4 while in control group only 16% of patients showed so. At 1st and 3rd hours after surgery both the group showed similar VAS score.

The possible explanation of this may be administration of diclofenac post operatively. Using a single pre-induction infusion of dexmedetomidine 2 μg/kg, Lawrence and De Lange (1997), reported reduced analgesic use, antiemetic and a higher occurrence of hypotension and bradycardia despite similar findings of perioperative hemodynamic stability and lower isoflurane concentration. There was no incidence of nausea, vomiting or shivering. Tsai *et al*. (2010) observed 10% of patients showed bradycardia and needed atropine and 5% of patients required ephedrine to treat hypotension in dexmedetomidine group while none of the patients in propofol group showed so. Among the patients who received dexmedetomidine we observed 16% showed hypotension while 20 % of them showed bradycardia. This increased incidence of side effects can be because of fentanyl which was administered along with dexmedetomidine. Hypotension and bradycardia responded well to ephedrine and atropine. Many studies have been done on dexmedetomidine using loading and different maintenance dose while our study showed that even single loading dose of dexmedetomidine has clinical benefits for surgery of duration of 2 hours. It gives similar haemodynamic stability, provides anxiolysis, good analgesia, and also reduces anaesthetic agent consumption when compared to dexmedetomidine in maintenance dosage. We also observed that it can be safely used along with fentanyl as it provides better haemodynamic stability while maintaining good anaesthetic depth without much side effects. Our study proves that dexmedetomidine in single loading dose is an economical and useful adjuvant to general anaesthesia.

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