A study on intraoperative and postoperative effects of dexmedetomidine on haemodynamic stress response and anaesthetic requirements

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ABSTRACT

Background: Dexmedetomidine(Dex), an α2 adrenoreceptor agonist, is widely used in various clinical settings for its sympatholytic, sedative, anaesthetic sparing and haemodynamic stabilising properties without significant respiratory depression.

Objectives: The objective of this study is to evaluate the efficacy of dexmedetomidine in attenuating the sympathoadrenal response to tracheal intubation and reduction in requirements of propofol and fentanyl intra-operatively.

Materials and methods: Hundred patients scheduled for elective surgeries like thyroidectomy and abdominal surgeries for more than 3 hours duration were randomly divided into group C and group D with 50 patients in each group. The control group received isoflurane–opioid and study group received isoflurane–opioid-dexmedetomidine anaesthesia. Dexmedetomidine infusion in a dose of 1 μg/kg was given over 10 min before the induction of anaesthesia and was continued at a dose of 0.2–0.7 μg/kg/hour until skin closure. All patients were induced with propofol, fentanyl and vecuronium. Haemodynamic variables were continuously recorded.

Results: It was observed that dexmedetomidine effectively controlled the increase in heart rate following intubation compared to the control group 68.56 vs. 77.30 ($p<0.0001$). Reduction of mean arterial pressure was significant in dexmedetomidine group compared to control group ($p< 0.0001$). Dexmedetomidine reduced the intra-operative use of propofol compared to control group 92.04 (2.84) mg vs. 112.20 (7.90) ($p<0.0001$) and fentanyl compared to control group 81.5 (2.31) vs.105.40 (9.08) ($p<0.0001$). Dexmedetomidine also reduced postoperative analgesic requirement significantly compared to control group.

Conclusion: Perioperative infusion of dexmedetomidine is effective in attenuating sympathoadrenal response to tracheal intubation. It has significant anaesthetic and opioid sparing effect.

Keywords: Dexmedetomidine, Stress response, Analgesia, Tracheal intubation, Anaesthetic requirement

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INTRODUCTION

Stress response is the term given to the hormonal and metabolic changes, which follows an injury or a trauma.[1] Stress response to surgery is characterized by an increase in secretion of the endocrine system and activation of immunological and sympathetic nervous system. Strenuous efforts have been done to attenuate the cardiovascular, neuroendocrine and inflammatory response to surgery to improve the outcome and the effect on organ function.[2]

Clonidine, α2 agonist, has been introduced to clinical anaesthesia for its sympatholytic, sedative,

anaesthetic sparing effects and haemodynamic stabilising properties.[3-6] Dexmedetomidine, the pharmacologically active d-isomer of medetomidine (4,[5]-[1-(2,3-dimethylphenyl)-ethyl] imidazole is a highly specific and selective α2 adrenoreceptor agonist.[7,8] The α2: α1 binding selectivity ratio of dexmedetomidine is 1620:1 compared to 220:1 for clonidine.[8] Studies in human volunteers have demonstrated that dexmedetomidine is also having clonidine like analgesic, sedative, sympatholytic and cardiovascular effects.[9-11] In recent studies, dexmedetomidine has been shown to reduce anaesthetic requirements, haemodynamic responses induced by anaesthesia and surgery in patients.[12] It has also been observed that an intraoperative infusion of dexmedetomidine combined with inhalation anaesthetics provided satisfactory intraoperative conditions without adverse haemodynamic effects and decreases emergence of agitation in children.[13] Dexmedetomidine is increasingly being used as a sedative for monitored anaesthesia care (MAC) because of its analgesic properties, "cooperative sedation", and lack of respiratory depression.[14,15] It has also been explored as a noninvasive premedication through intranasal route.[16]

The study was undertaken to assess the efficacy of dexmedetomidine in attenuating heart rate and mean arterial pressure to tracheal intubation and to analyse reduction in intraoperative anaesthetic requirement of propofol and fentanyl.

MATERIALS AND METHODS

After obtaining approval from the institutional ethical committee, a randomised open- label study was formulated. The study population comprised 100 patients with ASA physical status I and II, aged 18-65 years, scheduled for elective surgery, planned to be done under general anaesthesia were included in the study, after obtaining written consent from them. Pregnant and nursing women, patients with morbid obesity, heart block, and hypertensive patients on beta blockers were excluded from the study. Patients with diabetes and renal disease were not included in the study. None of the patients were on any significant drug therapy preoperatively like antihypertensive which may influence the study.

Patients were randomly divided into two groups by drawing chits, group C (the control or placebo group) and group D (dexmedetomidine group) with 50 patients in each group. All the patients received oral alprazolam 0.5 mg, the night before the operation. Patients were premedicated with injection glycopyrrolate 0.2 mg intramuscularly, 30 minutes prior to induction of anaesthesia. On arrival in the operating room, patient's baseline heart rate, blood pressure, oxygen saturation (SpO2), and respiratory rate were recorded after 5 minutes settling in the operative room. A large bore intravenous cannula was inserted for drug and continuous fluid administration. All the patients in group D received injection dexmedetomidine in a dose of 1 μg/kg over a period of 10 minutes prior to induction of anaesthesia through an infusion pump. During the infusion, heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, oxygen saturation and sedation score were recorded at 5 minute intervals and at 10 minutes (end of infusion). All the patients in group C received saline through an infusion pump.

All the patients received injection ondansetron 4 mg, injection fentanyl 1 μg/kg and injection midazolam 1 mg intravenously (IV), before the induction of anaesthesia. Then a dose of injection propofol sufficient to abolish eyelash reflex was injected followed by injection vecuronium 0.1 mg/kg to facilitate laryngoscopy and tracheal intubation. The lungs were ventilated by mask for at least 3 minutes using 100% oxygen. Laryngoscopy was performed with a Macintosh laryngoscope and trachea was intubated with appropriate size endotracheal tube. Anaesthesia was maintained with N_2O in O2 (60:40), isoflurane, injection fentanyl and injection vecuronium. The isoflurane was used in lowest possible concentration necessary to keep the blood pressure and heart rate within the 20 % limit of patient's preoperative baseline values. The inspiratory concentration of isoflurane was adjusted in steps of 0.2% when needed to keep the haemodynamic parameters to acceptable values. Injection fentanyl in increments of 0.4 μg/kg was given when inspiratory isoflurane concentration exceeded by 1%. In both the groups, additional adjuvants were provided in the form of injection diclofenac sodium or injection propofol intravenously after injection fentanyl exceeded 2 μ g/kg. The dexmedetomidine infusion was continued after intubation in a dosage of 0.2–0.7 μg/kg/ hour in group D, till the start of skin closure. All the patients

in group D received isoflurane in minimum concentrations of 0.4%, which was further increased when requirement of injection dexmedetomidine exceeded 0.7 µg/kg/hr to keep the haemodynamic parameters within the acceptable range. Similarly, isoflurane was terminated at the start of skin closure and N_2O was discontinued after skin closure. At the end of anaesthesia, the neuromuscular blockade was antagonised with injection neostigmine 0.04 mg/kg and injection glycopyrrolate 0.02 mg/kg intravenously. Patients were extubated when respiration was deemed sufficient and patients were able to obey simple commands.

The mean arterial blood pressure (MAP) and heart rate (HR) monitoring started 30 minutes before induction of anaesthesia; the data were collected and recorded every 15 minutes, and continued after the end of the surgery by 6 hours.

The data collection was performed every 2 minutes during induction of anaesthesia and for 10 minutes after tracheal intubation.

The need for postoperative analgesia was decided according to the visual analogue scale (VAS). The Visual Analogue Scale (VAS) was used to measure the intensity of pain that a patient feels (fig. 4). It ranges from zero mm (at the left end) that indicates no pain at all, to 100 mm (at the right end) that indicates worst imaginable pain. It was explained to the patient at the time of pre anaesthetic check up, and they were taught how to mark on the line the point that they feel it represents their pain perception. It was explained to the patients that this instrument will be used after the end of surgery to assess their pain.

Tramadol (1-2 mg/kg) intermittent intravenous bolus doses was given and repeated in the first 6 hours when the VAS was 3 or more.

The level of sedation was assessed and recorded in the preoperative period immediately before induction by one minute and in the post- operative period once after 2 hours in the post-anaesthetic care unit (PACU) using Ramsay Sedation Score (RSS)[17] which was shown to the patients.

Statistical analysis: Data were collected and entered into the software STATA (version 11.0). Continuous variables were expressed as mean and standard deviations. Between group analysis was done using an unpaired t test. The results were expressed as Mean± (SD). *P* value less than 0.05 was considered significant.

RESULTS

There were no statistically significant differences in the demographic characteristics in both groups regarding the age and gender (table1).

Table 1: Demographic characteristics of respondents

Variables	Group I (control)	Group II (Dexmedetomidine)
Age in years (Mean±SD)	35.5±10.7	33±10.32
Gender (F/M)	28/22	31/19

Heart rate: There was no significant difference between the two groups in baseline HR mean values. Before induction of anaesthesia, dexmedetomidine decreased heart rate significantly compared to control group (P<0.05) and baseline value (P<0.05).

The heart rate increased in both groups after intubation, the increase was significant in the control group (P<0.05) and is not significant in the dexmedetomidine group (P>0.05) compared to the baseline values, but the heart rate decreased significantly in the dexmedetomidine group compared to the control group (P<0.05).

During the course of surgery, dexmedetomidine reduced the heart rate significantly (P<0.05) in comparison to the baseline values at 15 and 30 minutes, and compared to the control group at 15, 30, 120 and 135 minutes, while in control group the heart rate increased significantly during surgery (P<0.05) in comparison to the baseline values at 120 and 135 minutes.

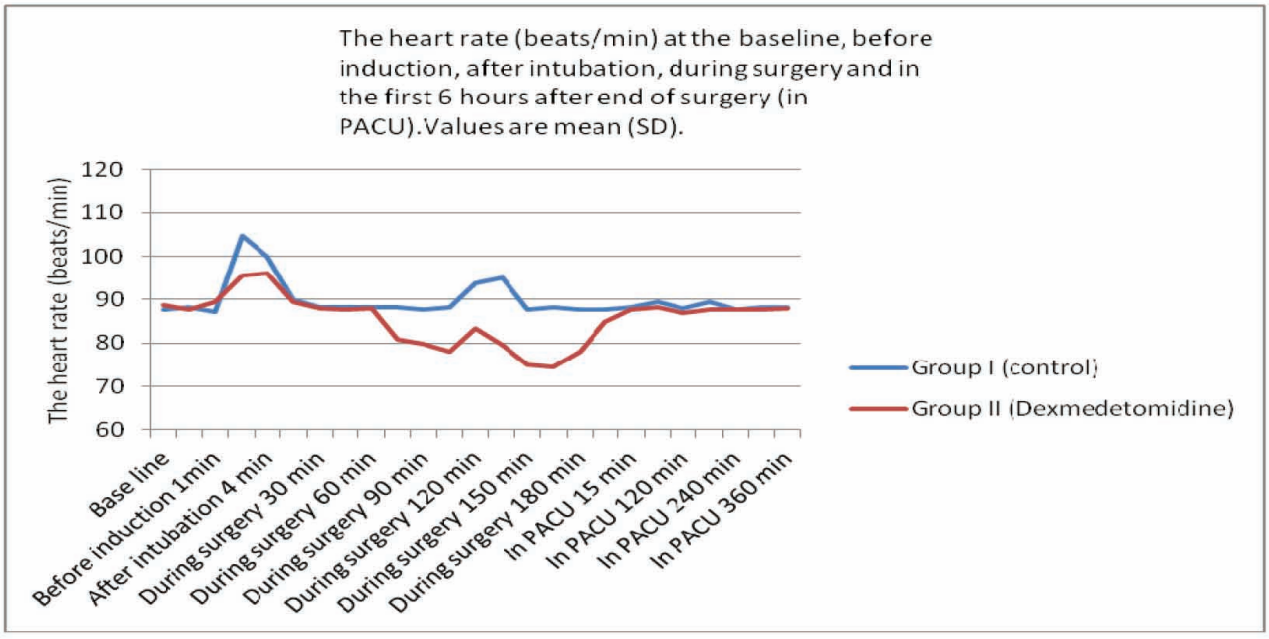
One minute after arrival of the patients to the post anaesthesia care unit (PACU) the values of heart rate recorded in the dexmedetomidine group were significantly lower than the values recorded in the control group (P<0.05) and baseline values. Rather, it was significantly higher than baseline values in the control group (P<0.05). The heart rate values recorded after 1,15, 60, 120 and 180 minutes in PACU were significantly less in dexmedetomidine group in comparison to control group (P<0.05) and to baseline values (P<0.05). After 240, 300, 360 minutes and in PACU there was no significant difference in the values of heart rate recorded in each group and its baseline values. No electrocardiographic changes were noticed among the study patients other than sinus bradycardia, and the response to atropine was adequate (Table 2), (fig 1).

Table 2: Comparison of heart rate (beats/min) between Group-1 and Group II at baseline, before induction, after intubation, during surgery and in the first 6 hours after end of surgery (in PACU)

Timing in minutes		Group 1 (control)		Group II (Dexmedetomidine)		p value
		Mean	SD	Mean	SD	
Base line		76.14	3.70	77.22	2.06	0.0809
Before induction	15	77.30	4.03	68.56	3.19	0.0001*
After intubation	1	77.24	3.15	68.98	4.14	0.0001*
	2	85.50	4.60	78.04	2.29	0.0001*
	4	81.04	4.29	77.94	2.10	0.0001*
During Surgery	15	77	1.04	75.78	3.45	0.0335*
	30	77.24	3.54	75.90	3.31	0.0433*
	45	76.68	1.86	77.22	3.24	0.3091
	60	76.26	1.23	76.98	3.61	0.1843
	75	75.94	2.03	76.82	3.73	0.0733
	90	77.66	6.56	77.16	3.23	0.3150
	105	77.64	6.07	76.92	3.61	0.2364
	120	78.26	8.12	76.70	3.86	0.0412*
	135	78.68	7.24	76.46	4.18	0.0317*
	150	77.26	3.15	76.24	4.43	0.0939
	165	77.58	6.08	76.46	4.18	0.1429
	180	75.06	3.20	76.26	4.19	0.0554
In PACU	1	86.5	3.00	74.52	1.94	0.0001*
	15	77.52	6.10	69.92	1.31	0.0001*
	60	77.3	3.31	68.04	0.97	0.0001*
	120	77.12	2.34	66.64	1.03	0.0001*
	180	75.4	1.34	68.56	3.19	0.0001*
	240	77.6	5.96	76.32	4.24	0.1056
	300	75.16	2.41	76.28	4.23	0.0535
	360	76.82	2.80	76.34	4.29	0.4251

*significant difference compared to control group

Figure 1: Trends in heart rate



Mean arterial blood pressure (MAP): There was no significant difference between the baseline values in both groups. After administration of the study drug and before induction of anaesthesia the values of Mean Arterial Pressure(MAP) in the dexmedetomidine group were lower than the value in the control group (P>0.05) and the baseline mean value (P>0.05) which was not significant.

The mean arterial blood pressure increased after endotracheal intubation in both groups, this increase was significant in the control group (P<0.05) and in the dexmedetomidine group in comparison to the baseline values, however dexmedetomidine attenuated this response compared to saline (P<0.05).

During the course of surgery dexmedetomidine reduced the MAP significantly (P<0.05) compared to the baseline at 15, 90 ,105, 135 , 150 , 165 and 180 minutes and in comparison to control group (P<0.05) at 75 , 90 ,105, 120 , 135 , 150 , 165 and 180 minutes. However, in the control group the MAP increased significantly (P<0.05) during the course of surgery after 120 and 135 minutes in comparison to the baseline.

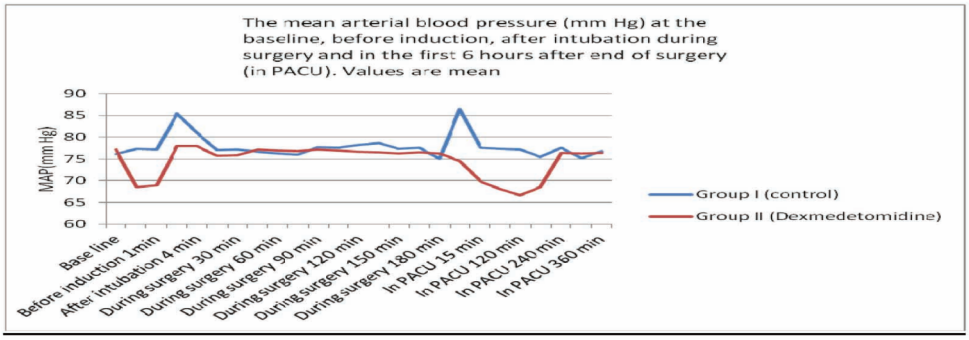
In PACU the MAP values recorded in dexmedetomidine were lower than the control group after 1,15,60,120,180 and 240 minutes (Table 3), (fig 2).

Table 3: Comparison of mean arterial blood pressure (mm Hg) between Group-1 and Group-II at the baseline, before induction, after intubation, during surgery and in the first 6 hours after end of surgery (in PACU)

Timing in minutes		Group 1 (control)		Group 11 (Dexmedetomidine)		p value
		Mean	SD	Mean	SD	
Base line		87.62	1.783	88.78	3.903	0.059
Before induction	15	88.14	1.807	87.66	2.767	0.307
	1	87.26	1.759	89.38	4.218	0.0001*
After intubation	2	104.72	3.117	95.48	1.832	0.0001*
	4	99.82	2.067	95.96	1.009	0.0001*
During Surgery	15	89.96	2.194	89.34	4.173	0.0001*
	30	88.08	1.839	87.9	2.837	0.707
	45	88.14	1.807	87.66	2.767	0.307
	60	88.2	2.060	87.84	2.802	0.641
	75	88.16	2.502	80.84	1.448	0.0001*
	90	87.7	1.961	79.84	2.132	0.0001*
	105	88.24	2.520	77.88	2.125	0.0001*
	120	93.74	2.284	83.24	1.222	0.0001*
	135	95.12	1.172	79.56	1.343	0.0001*
	150	87.52	2.002	75	1.512	0.0001*
	165	88.08	1.861	74.48	1.147	0.0001*
	180	87.58	2.400	78	1.641	0.0001*
In PACU	1	87.52	2.002	84.88	1.081	0.0001*
	15	88.14	1.807	87.72	2.763	0.0001*
	60	88.06	1.695	89.3	4.032	0.0001*
	120	86.96	2.857	87.8	2.814	0.0001*
	180	87.6	2.020	89.34	4.173	0.0001*
	240	87.52	2.002	87.68	2.917	0.0001*
	300	88.08	1.839	87.72	2.763	0.445
	360	88.14	1.807	87.84	2.802	0.526

*significant difference compared to control group.

Figure 2: Trends in mean arterial blood pressure



Propofol and Fentanyl Requirements:

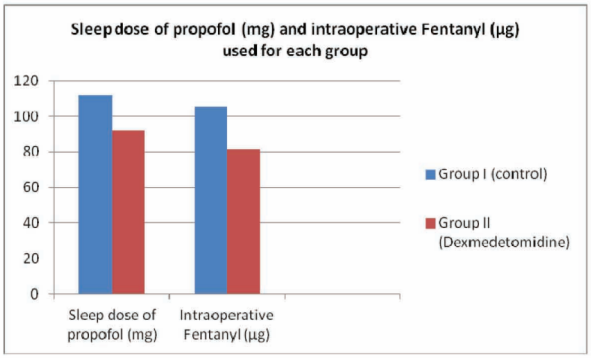
Dexmedetomidine reduced the sleep dose of propofol and intra-operative fentanyl significantly when compared to control group (P< 0.05) (Table 4), (fig 3).

Table 4: Sleep dose of Propofol (mg) and intraoperative Fentanyl (µg) used for each group

Timing	Group I (control) Mean ±SD	Group II (Dexmedetomidine) Mean ±SD	P value
Sleep dose of propofol (mg)	112.2(7.90)	92.04(2.84)	0.0001*
Intraoperative Fentanyl (µg)	105.4(9.08)	81.5(2.31)	0.0001*

*significant difference compared to control group.

Figure 3: Propofol and fentanyl requirements



Postoperative Analgesic Requirements: Dexmedetomidine reduced the hourly postoperative analgesia requirements in PACU to keep the VAS below 30 in the first 6 hours when compared to saline, this reduction was significant in 60, 120, 180 and 240 minutes (P<0.05) and it was not significant in the 300 and 360 minutes (P>0.05) (Table 5), (fig 4).

Preoperative Sedation Level: The preoperative sedative effect of Dexmedetomidine was remarkable. Dexmedetomidine reduced the number of patients with Ramsay Sedation Score (RSS) of 1 (anxious, agitated or restless) and increased the number of patients with Ramsay Sedation Score of 4 significantly in comparison to the control group (P<0.05), and it increased RSS of 2 and 3 which is not significant (P>0.05).

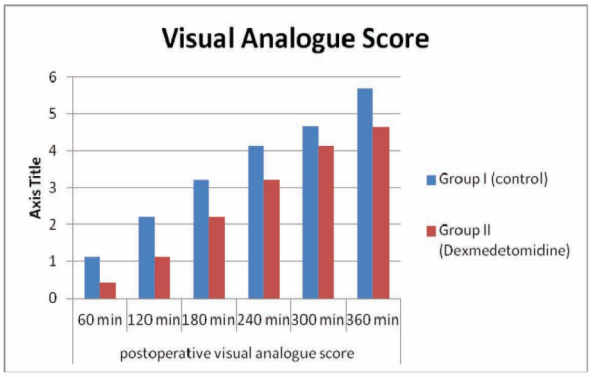
Postoperative Sedation Level: At the end of infusion of dexmedetomidine (after 2 hours in PACU) the number of patients with a Ramsay Sedation Score of 1 (anxious, agitated or restless) and score 5 were significantly lower in dexmedetomidine group (P<0.05) in comparison to control group. The number of patients with Ramsay Sedation Score of 2, 3, and 4 was higher in dexmedetomidine group than the control group but not significant (P>0.05).

The number of patients developed bradycardia that needed atropine was significantly higher in dexmedetomidine group in comparison to control group (P<0.05). The number of patients developed hypotension that needed ephedrine was higher in dexmedetomidine group than in control group (P>0.05) which is not significant.

Table 5: Postoperative visual analogue score
*significant difference compared to control group.

Timing in minutes	Group I (control)	Group II (Dexmedetomidine)	P value
60	1.14(0.35)	0.42(0.50)	0.0001*
120	2.22(0.46)	1.14(0.35)	0.032*
180	3.2(0.45)	2.22(0.46)	0.0001*
240	4.14(0.45)	3.2(0.45)	0.0001*
300	4.66(0.77)	4.14(0.45)	0.058
360	5.68(0.62)	4.64(0.78)	0.061

Figure 4: Postoperative visual analogue score



DISCUSSION

We conducted this prospective randomised open label study in an attempt to examine whether administration of dexmedetomidine to a commonly administered balanced anaesthetic regimen improves perioperative haemodynamic stability in patients undergoing major surgical procedure. It would also reduce perioperative anaesthetic and analgesic requirement.

Dexmedetomidine is a highly selective α2 agonist that has been shown to have sedative, analgesic and anaesthetic sparing effects.[18,19] It causes a dose-dependent decrease in arterial blood pressure and heart rate, associated with decrease in serum norepinephrine concentration. Dexmedetomidine was well tolerated, and no serious side effects or

adverse reactions occurred in the present study.

The results of this study showed that during the preanaesthetic period, dexmedetomidine caused a significant reduction in mean arterial blood pressure (MAP) without provoking any subjective symptoms. Laryngoscopy and endotracheal intubation induced significant increase in arterial blood pressure and heart rate in the control group, but dexmedetomidine blunted this increase, which was noted by lower values of heart rate and blood pressure in the dexmedetomidine group when compared to the control group after intubation. This might be beneficial in patients at risk of myocardial ischemia secondary to tachycardia.

During the course of surgery, there was variable degree of increase in heart rate and arterial blood pressure in the control group. Dexmedetomidine caused a variable degree of reduction in the heart rate and arterial blood pressure during surgery compared to the baseline values. The findings of the present study regarding surgery related haemodynamic stress response are in agreement with several studies about the effect of dexmedetomidine on heart rate and blood pressure in the perioperative period. Jalonen et al, compared the effect of dexmedeto midine with saline and concluded that dexmede-tomidine attenuated the increase of blood pressure during anaesthesia and surgery, decreased the incidence of intra and postoperative tachycardia and decreased plasma norepinephrine concentration by 90%.[20]

Similar results were observed by Aantaa and Colleagues, who noticed that dexmedetomidine attenuated the catecholamine response to anaesthesia and surgery and reduced the arterial blood pressure by 15-20% and heart rate by 10-15% during surgery.[17]

The present study findings corroborate with those of previous studies. No adverse cardiovascular effects from the drug were seen in the present study. Bradycardia, a possible consequence of administration of α2 agonist, was counteracted by the use of atropine.

CONCLUSION

Dexmedetomidine, as a pre-anaesthetic medication and intraoperative infusion, decreases intraoperative anaesthetic requirement. It has significant opioid and anaesthetic sparing property. It significantly attenuates sympathoadrenal response to tracheal intubation. In addition, continuous intraoperative administration of dexmedetomidine does not affect intraoperative cardiovascular stability.

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