

# Dexmedetomidine attenuates sympathoadrenal response to tracheal intubation and reduces perioperative anaesthetic requirement

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## ABSTRACT

**Background:** Dexmedetomidine, an  $\alpha$ -2 adrenoreceptor agonist, is gaining popularity for its sympatholytic, sedative, anaesthetic sparing and haemodynamic stabilising properties without significant respiratory depression. **Methods:** We assessed the efficacy of dexmedetomidine in attenuating sympathoadrenal response to tracheal intubation and analysed reduction in intraoperative anaesthetic requirement. Sixty patients scheduled for elective surgery of more than 3 hours were randomly selected. Control group received isoflurane–opioid and study group received isoflurane–opioid–dexmedetomidine anaesthesia. Dexmedetomidine infusion in a dose of 1  $\mu$ g/kg was given over 10 min before the induction of anaesthesia and was continued in a dose of 0.2–0.7  $\mu$ g/kg/Hr until skin closure. All patients were induced with thiopentone, fentanyl and vecuronium. Haemodynamic variables were continuously recorded. **Results:** The need for thiopentone and isoflurane was decreased by 30% and 32%, respectively, in the dexmedetomidine group as compared to the control group. After tracheal intubation, maximal average increase was 8% in systolic and 11% in diastolic blood pressure in dexmedetomidine group, as compared to 40% and 25%, respectively, in the control group. Similarly, average increase in heart rate was 7% and 21% in the dexmedetomidine and control groups, respectively. Fentanyl requirement during the operation was 100 $\pm$ 10  $\mu$ g in the control group and 60 $\pm$ 10  $\mu$ g in the dexmedetomidine group. **Conclusion:** Perioperative infusion of dexmedetomidine is effective in attenuating sympathoadrenal response to tracheal intubation. It has significant anaesthetic and opioid sparing effect.

**Key words:**  $\alpha$ -2 adrenoreceptor, dexmedetomidine, sympathoadrenal response, tracheal intubation

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## INTRODUCTION

Clonidine,  $\alpha$ 2 agonist, has been introduced to clinical anaesthesia for its sympatholytic, sedative, anaesthetic sparing effects and haemodynamic stabilising properties.<sup>[1-4]</sup> Dexmedetomidine, the pharmacologically active d-isomer of medetomidine (4,[5]-[1-(2,3-dimethylphenyl)-ethyl] imidazole is a highly specific and selective  $\alpha$ 2 adrenoreceptor agonist.<sup>[5,6]</sup> The  $\alpha$ 2: $\alpha$ 1 binding selectivity ratio of dexmedetomidine is 1620:1 compared to 220:1 for clonidine.<sup>[6]</sup> Animal experiments have indicated that it has prominent anaesthetic effect.<sup>[7]</sup> Studies in human volunteers have demonstrated clonidine like analgesic, sedative, sympatholytic and cardiovascular

effects.<sup>[8-10]</sup> In recent studies, dexmedetomidine has been shown to have clinically significant effects on anaesthetic requirements, haemodynamic responses induced by anaesthesia and surgery in patients.<sup>[11]</sup> 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 agitation in children.<sup>[12]</sup> 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.<sup>[13,14]</sup> It has also been explored as a noninvasive premedicament through intranasal route.<sup>[15]</sup>

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The study was undertaken to assess the efficacy and safety of dexmedetomidine in attenuating sympathoadrenal response to tracheal intubation and to analyse reduction in intraoperative anaesthetic requirement.

## METHODS

After obtaining approval from the institutional ethical committee, a randomised controlled study was formulated. The study population comprised 60 patients with ASA physical status I and II, aged 18–65 years, scheduled for elective surgery of duration 3 hours or more. Written informed consent was taken from each patient. 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. The patients were randomly assigned to one of the two groups, each containing 30 patients, using a “slips of paper in a box” technique. None of the patients were on any significant drug therapy preoperatively.

The grouping is as follows:

Group C: Control group: Isoflurane–opioid–saline anaesthesia

Group D: Dexmedetomidine group: Isoflurane–opioid–dexmedetomidine anaesthesia

All the patients were premedicated with inj. glycopyrrolate 0.2 mg intramuscularly, 30 min prior to induction of anaesthesia. On arrival in the operating room, the patients’ baseline heart rate, blood pressure, oxygen saturation ( $\text{SpO}_2$ ), and respiratory rate were recorded after 5 min settling in the operative room. A large bore intravenous canula was inserted for drug and continuous fluid administration. All the patients in group D received inj. dexmedetomidine in a dose of 1  $\mu\text{g}/\text{kg}$  over a period of 10 min 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 min intervals and at 10 min (end of infusion). All the patients in group C received saline through an infusion pump.

All the patients received inj. ondansetron 4 mg, inj. fentanyl 1  $\mu\text{g}/\text{kg}$  and inj. midazolam 1 mg intravenously (IV), before the induction of anaesthesia. Then, a dose of inj. thiopentone sufficient to abolish eyelash reflex was injected followed by inj. vecuronium 0.1 mg/kg to facilitate laryngoscopy and tracheal intubation.

The lungs were ventilated by mask for at least 3 min using 100% oxygen. Laryngoscopy was performed with a Macintosh laryngoscope and trachea was intubated with appropriate size endotracheal tube. Anaesthesia was maintained with  $\text{N}_2\text{O}$  in  $\text{O}_2$  (60:40), isoflurane, inj. fentanyl and inj. vecuronium. The isoflurane was used in lowest possible concentration necessary to keep the blood pressure and heart rate within 20% limits 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. Inj. fentanyl in increments of 0.4  $\mu\text{g}/\text{kg}$  was given when inspiratory isoflurane concentration exceeded by 1%. In both the groups, additional adjuvants were provided in the form of inj. diclofenac sodium or inj. propofol intravenously after inj. fentanyl exceeded 2  $\mu\text{g}/\text{kg}$ . The dexmedetomidine infusion was continued after intubation in a dosage of 0.2–0.7  $\mu\text{g}/\text{kg}/\text{hour}$  in group D, till the start of skin closure. All the patients in group D received isoflurane in minimum concentration of 0.4%, which was further increased when requirement of inj. Dexmedetomidine exceeded 0.7  $\mu\text{g}/\text{kg}/\text{Hr}$  to keep the haemodynamic parameters within acceptable range. Similarly, isoflurane was terminated at the start of skin closure and  $\text{N}_2\text{O}$  was discontinued after skin closure.

At the end of anaesthesia, the neuromuscular blockade was antagonised with inj. neostigmine 0.04 mg/kg and inj. glycopyrrolate 0.02 mg/kg intravenously. Patients were extubated when respiration was deemed sufficient and patients were able to obey simple commands.

## Parameters studied

All the parameters and the results from the two groups (group C and group D) were entered in the predesigned study proforma sheet.

- (1) Sedation score at 5 min and 10 min after administration of loading dose of dexmedetomidine in group D according to Ramsay sedation score.
- (2) Heart rate, systolic and diastolic blood pressure,  $\text{SpO}_2$  at 5 min and 10 min after dexmedetomidine administration, preinduction, induction, 0 min, 1 min, 5 min after intubation.
- (3) The dose of the inj. thiopentone for induction of anaesthesia.
- (4) Total fentanyl requirement throughout the operative procedure.
- (5) The average inspiratory isoflurane concentrations

was calculated as the sum of the products of inspiratory concentrations and times divided by total anaesthesia time.

- (6) The intraoperative need for adjuvants such as inj. diclofenac sodium and propofol.

### Statistical analysis

Statistical analysis was conducted with SPSS (version 10, 2010) for Windows statistical package using paired and unpaired student's *t* test. The results were expressed as Mean  $\pm$  SD.  $P < 0.05$  was regarded as statistically significant,  $P < 0.001$  was taken as highly significant, and  $P > 0.05$  was regarded as nonsignificant. A sample size of 20 patients per group was needed to detect an intergroup difference of at least 20% with two-sample *t*-test.

## RESULTS

The two groups were comparable in patient characteristics [Table 1]. Dexmedetomidine was well tolerated and no drug-related adverse events were observed. About 10 min after receiving dexmedetomidine, patients were drowsy but arousable (sedation score 2).

The mean sleep dose of inj. thiopentone required in group C was 6 mg/kg, while it was 4.4 mg/kg in group D [Table 2]. The decrease in the dose requirement was by 30% in dexmedetomidine group as compared to control group ( $P = 0.00$ ).

The average inspiratory concentration of isoflurane required during anaesthetic maintenance was 0.8% in group C and 0.54% in group D. A decrease of 32% was observed in group D compared to group C ( $P = 0.00$ ).

Also, the requirement of inj. fentanyl was 1.8  $\mu$ g/kg in group C as opposed to 1.1  $\mu$ g/kg in group D. Group C patients required 33% more fentanyl as compared to group D patients ( $P = 0.00$ ) [Table 2].

Before administration of the study drugs in the operating room, heart rate and blood pressure values between the two groups did not differ.

In group D patients receiving dexmedetomidine loading infusion, a fall in the heart rate and blood pressure was observed, which was not more than 5% of the baseline. Patients were sedated but arousable with sedation score of 2.

In both the groups, the maximal increase in heart rate and blood pressure occurred immediately after tracheal intubation (0 min) when compared to the baseline arterial blood pressure. The increase in heart rate after intubation was 21% in group C as compared to 7% in group D ( $P = 0.00$ ). Similarly, significant increase in systolic pressure was observed in group C which was 40% as compared to 8% in group D ( $P = 0.00$ ), while increase in diastolic pressure was 25% and 11% in group C and group D, respectively ( $P = 0.001$ ) [Figure 1].

In order to avoid analgesics that have sedative effect like inj. tramadol, we preferred to use inj. diclofenac sodium. Twenty-four out of 30 patients in group C required inj. diclofenac sodium 75 mg intravenously, while 7 out of 30 patients in group D required inj. diclofenac sodium 75 mg. Seventeen patients out of 30 in group C were supplemented with inj. propofol in an average of 175 mg. None of the patients required inj. propofol in group D.

Bradycardia was observed in two patients in group D intraoperatively. The heart rate dropped up to 42/min, which promptly responded to inj. atropine 0.6 mg intravenously. No fall in blood pressure was observed in either of the patients. Inj. atropine was repeated in the postoperative period after extubation in one patient out of the two.

The duration of recovery was similar in both the

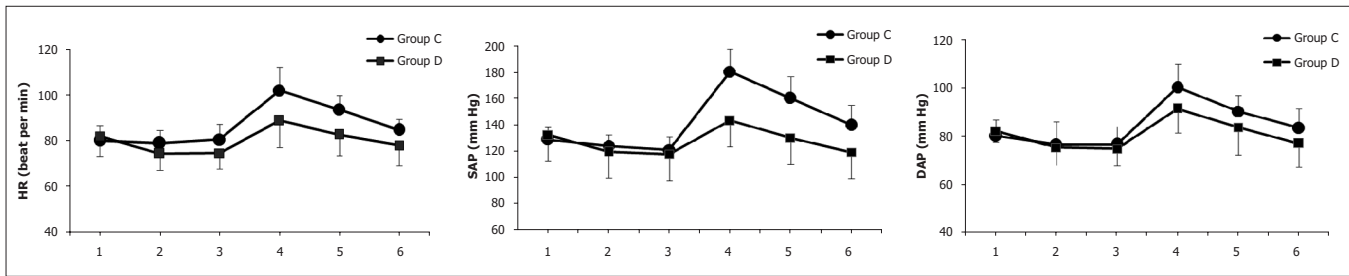
**Table 1: Patient characteristics [mean (SD)] and type of surgeries**

Patients characteristics	Group C	Group D
Age (years)	42 (12.4)	40 (11.9)
Sex (M/F)	17/13	16/14
Weight (kg)	55 (9.1)	53 (8.1)
Type of surgeries		
Laminectomy	11	9
Ca breast	4	3
Craniotomy	2	1
ENT surgery	4	4
Oro-maxillofacial	3	4
Thyroid	2	3
Miscellaneous	4	6

ENT: Ear, nose, throat

**Table 2: Anaesthesia characteristics [mean (SD)]**

Anaesthesia characteristics	Group C	Group D	P
Inj. thiopentone (mg/kg)	6 (0.76)	4.4 (0.90)	0.00
Inj. fentanyl ( $\mu$ g/kg)	1.8 (0.27)	1.1 (0.38)	0.00
Average isoflurane conc. (%)	0.8 (0.085)	0.54 (0.138)	0.00
Total duration (min)	270 (63)	288 (89)	NS



**Figure 1:** Cardiovascular response during tracheal intubation in group C (●) and group D (■). HR = heart rate; SAP = systolic arterial pressure; DAP = diastolic arterial pressure. Time points: 1 = baseline; 2 = preinduction; 3 = induction; 4 = 0 min after intubation; 5 = 1 min after intubation; 6 = 5 min after intubation

groups. All the patients were immediately able to obey commands upon arrival into recovery room.

In the recovery room, three patients in group D and two patients in group C experienced nausea. Transient headache was observed in one patient in group D in the recovery room. None of the patients had explicit recall of awareness or complained of any discomfort when interviewed after operation.

## DISCUSSION

We conducted this prospective randomised 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 volatile anaesthetic and analgesic requirement.

Dexmedetomidine is a highly selective  $\alpha_2$  agonist that has been shown to have sedative, analgesic and anaesthetic sparing effects.<sup>[16,17]</sup> 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 dose of thiopentone needed for induction was reduced significantly (30%) in the patients receiving dexmedetomidine, as also found by Aantaa and coworkers, demonstrating the anaesthesia potentiating effects of the drug.<sup>[18]</sup>

It has also been shown that dexmedetomidine potentiates analgesia caused by fentanyl and reduces its dose requirements in humans during surgery.<sup>[19]</sup> The fentanyl dose in the control group was almost

twice that given in the dexmedetomidine group. The requirement of fentanyl was reduced by 33% in the dexmedetomidine group in our study. Analgesic property has been demonstrated earlier in a study with dexmedetomidine in experimental ischaemic pain in healthy volunteers<sup>[20]</sup> and as the sole analgesic after surgery.<sup>[20]</sup>

Dexmedetomidine has been widely studied as an anaesthetic adjuvant and its anaesthetic sparing effects are well known. In studies by Aho and colleagues and Aantaa and coworkers, it has been shown to reduce the isoflurane requirement dose dependently up to 90%.<sup>[21,22]</sup> In our study, isoflurane was used as the main anaesthetic agent, the requirement of which was decreased by 32% in group D, in accordance with earlier studies.

Tracheal intubation is associated with increases in arterial pressure, heart rate and plasma catecholamine concentrations.<sup>[23]</sup> Increases in arterial pressure and heart rate observed in the control group in the present study were similar to those reported in earlier studies.<sup>[23]</sup> In the present study, pretreatment with dexmedetomidine 1  $\mu\text{g}/\text{kg}$  attenuated, but not totally obtunded, the cardiovascular response to tracheal intubation after induction of anaesthesia. In patients undergoing general or gynaecological surgery, numerous studies have shown that dexmedetomidine blunts cardiovascular response to intubation<sup>[21,24,25]</sup> and our findings are in accordance with them. In addition to this beneficial property of  $\alpha_2$  agonists, they have also been reported to increase the risk of hypotension and bradycardia.<sup>[24]</sup> These effects have most often been seen in young healthy volunteers on rapid bolus administration.<sup>[24,26]</sup> In our study, bradycardia was observed in two patients receiving dexmedetomidine, with no fall in blood pressure, which responded promptly to IV atropine.

In our study, three patients were of craniotomies for supratentorial tumours. The perioperative haemodynamic stability is of utmost importance in such surgeries. Increase or decrease in blood pressure may cause bleeding or edema or predispose the patient to cerebral ischaemia. The haemodynamic responses to emergence from anaesthesia and extubation are blunted with dexmedetomidine and the centrally mediated sympatholytic effect is continued well in postoperative period, which was advantageous in these patients. Tanskanen and coworkers, in their study using dexmedetomidine as an anaesthetic adjuvant for intracranial tumour, concluded that there was an increased perioperative haemodynamic stability in patients undergoing brain tumour surgery without postoperative respiratory depression.<sup>[27]</sup> Also, dexmedetomidine has been studied as a supplement to isoflurane for vitreoretinal surgeries, without causing undue haemodynamic fluctuation, and has been shown to decrease the excitatory response during extubation with acceptable reduction in intraocular pressure.<sup>[28]</sup>

A possible limitation of our study may have been the use of subjective criteria to determine dose of thiopentone, isoflurane and fentanyl for each patient. Estimating anaesthesia depth by changes mediated by autonomic nervous system is difficult during dexmedetomidine infusion as it increases the haemodynamic stability. Intraoperative Bispectral index (BIS) monitoring would have been definitely more objective in deciding the depth of anaesthesia and the requirement of anaesthetic agent. Also, measurement of QT interval and plasma catecholamine levels, more objective means of haemodynamic response,<sup>[29]</sup> was not done because of practical difficulty. Measurement of the end-tidal isoflurane concentration would have been ideal to indicate the depth and for quantifying decrease in utilisation between groups than the inspired dial concentration. Postoperative requirement of analgesics was not taken into consideration as it was not part of our study. Measurement of time to recovery following extubation would have given an idea of recovery in both the groups.

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  $\alpha_2$  agonist, was counteracted by the use of atropine. There was no case of awareness suggesting adequate depth of anaesthesia.

## 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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