

# The effect of dexmedetomidine continuous infusion as an adjuvant to general anesthesia on sevoflurane requirements: A study based on entropy analysis

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## Abstract

**Background:** Dexmedetomidine, a  $\alpha_2$  agonist as an adjuvant in general anesthesia, has anesthetic and analgesic-sparing property.

**Aims:** To evaluate the effect of continuous infusion of dexmedetomidine alone, without use of opioids, on requirement of sevoflurane during general anesthesia with continuous monitoring of depth of anesthesia by entropy analysis.

**Materials and Methods:** Sixty patients were randomly divided into 2 groups of 30 each. In group A, fentanyl 2 mcg/kg was given while in group B, dexmedetomidine was given intravenously as loading dose of 1 mcg/kg over 10 min prior to induction. After induction with thiopentone in group B, dexmedetomidine was given as infusion at a dose of 0.2-0.8 mcg/kg. Sevoflurane was used as inhalation agent in both groups. Hemodynamic variables, sevoflurane inspired fraction ( $FI_{sevo}$ ), sevoflurane expired fraction ( $ET_{sevo}$ ), and entropy (Response entropy and state entropy) were continuously recorded. Statistical analysis was done by unpaired student's *t*-test and Chi-square test for continuous and categorical variables, respectively. A *P*-value < 0.05 was considered significant.

**Results:** The use of dexmedetomidine with sevoflurane was associated with a statistical significant decrease in  $ET_{sevo}$  at 5 minutes post-intubation ( $1.49 \pm 0.11$ ) and 60 minutes post-intubation ( $1.11 \pm 0.28$ ) as compared to the group A [ $1.73 \pm 0.30$  (5 minutes);  $1.68 \pm 0.50$  (60 minutes)]. There was an average 21.5% decrease in  $ET_{sevo}$  in group B as compared to group A.

**Conclusions:** Dexmedetomidine, as an adjuvant in general anesthesia, decreases requirement of sevoflurane for maintaining adequate depth of anesthesia.

**Key words:** Depth of anesthesia, dexmedetomidine, entropy, fentanyl, sevoflurane

## Introduction

Alpha ( $\alpha_2$ )-adrenoceptor agonists have been used as adjuvant to anesthetic agents in peri-operative period for its several beneficial actions. These drugs improve hemodynamic stability during endotracheal intubation and surgical stress by its central sympatholytic action, and thus reduce anesthetic and opioids requirements.<sup>[1]</sup>

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Access this article online	
Quick Response Code: 	Website: www.joacp.org
	DOI: 10.4103/0970-9185.117066

Dexmedetomidine, the pharmacologically active d-isomer of medetomidine, is highly selective and specific  $\alpha_2$ -adrenoceptor agonist.<sup>[2,3]</sup> The analgesic effect of dexmedetomidine is qualitatively different as compared to opioids and can be used as an alternative to opioids in general anesthesia.<sup>[4-6]</sup> The anesthetic sparing effect of dexmedetomidine demonstrated in earlier studies is confounded by the use of opioids.<sup>[7-13]</sup> Opioids, when used as analgesic in general anesthesia, are known to decrease MAC value of sevoflurane.<sup>[14]</sup> Inhalation agents were titrated based on either hemodynamic criteria and/or bispectral index values in studies done earlier, and none of them demonstrated the effect of dexmedetomidine alone on requirement of sevoflurane with the use of entropy as a measure of depth of anesthesia.<sup>[8-13]</sup> The primary objective of our study was to evaluate the effect of continuous infusion of dexmedetomidine alone, without use of opioids, on sevoflurane requirement during general anesthesia with continuous monitoring of depth of anesthesia by entropy analysis.

## Materials and Methods

The study protocol was approved by ethical committee of the institute, and written informed consent was obtained from all patients included in the study. The study population comprised of 60 patients, aged 18-55 years, with American Society of Anesthesiologists (ASA) status of 1 and 2, undergoing major elective surgical procedures. We excluded patients older than 55 years, those with a history of psychiatric/neurological illness, cardiovascular disease, hypertensive patients, morbid obese patients, pregnant and nursing women, with known allergic reaction to any of the study medication, recent use of sedatives or analgesics, and with significant laboratory abnormalities. The consenting patients were randomly allocated into one of the two anesthetic groups based on the simple randomization table generated: Group A (control group): Sevoflurane-fentanyl and group B (test group): Sevoflurane-dexmedetomidine.

After arrival in the operating room, glycopyrrolate 0.004 mg/kg and ondansetron 0.15 mg/kg intravenous (IV) were given as pre-medication in both the groups. The patients in group B received dexmedetomidine (2 ml diluted in 48 ml of saline) IV in a dose of 1 mcg/kg over 10 minutes through infusion pump prior to induction. Monitoring consisted of continuous electrocardiogram (EKG), non-invasive blood pressure (NIBP), pulse oximetry (SpO<sub>2</sub>), CO<sub>2</sub> expired fraction (ETCO<sub>2</sub>), sevoflurane inspired fraction (FI<sub>sevo</sub>), sevoflurane expired fraction (ET<sub>sevo</sub>), and electroencephalograph (EEG) analysis by entropy (Response and State entropy). After the start of drug infusion, heart rate (HR), blood pressure (BP), respiratory rate (RR), SpO<sub>2</sub>, and entropy were measured at 5<sup>th</sup> and 10<sup>th</sup> minute. Patients in group A received fentanyl 2 µg/kg intravenous slowly, 2 minutes prior to induction.

After pre-oxygenation for 10 minutes, general anesthesia was induced with thiopentone sodium 5 mg/kg IV slowly. Endotracheal intubation was facilitated with succinylcholine 2 mg/kg IV. Anesthesia was maintained with oxygen: Nitrous-oxide (50:50) and sevoflurane. Vecuronium bromide was used as muscle relaxant.

In the group B, dexmedetomidine infusion was continued between 0.2 and 0.8 mcg/kg/h depending on HR, BP, and entropy value changes. Anesthesia was maintained with sevoflurane to a maximum of 2.5% end tidal to maintain heart rate and blood pressure within 20% of baseline value and entropy value between 40 and 60. The anesthesiologist was permitted to treat hemodynamic events, defined as heart rate and blood pressure more than 20% of baseline, in spite of increasing sevoflurane concentration to 2.5% and

dexmedetomidine infusion to 0.8 mg/kg with supplemental analgesia in the form of fentanyl 1 mcg/kg. If rise in heart rate and blood pressure persisted further after supplementation with fentanyl, anesthesiologist was permitted to administer incremental doses of metoprolol 2-5 mg. Ephedrine 5 mg IV was given for fall in heart rate and blood pressure more than 20% of baseline.

In the group B, dexmedetomidine was stopped approximately 15-20 minutes before completion of surgery, diclofenac sodium aqueous 1 mg/kg was given IV in both groups at the time of skin closure. Nitrous oxide and sevoflurane were discontinued after skin closure in both groups. Reversal of neuromuscular blockade was achieved with neostigmine 0.05 mg/kg and glycopyrrolate 0.008 mg/kg IV slowly. Tracheal extubation was done when respiration was satisfactory and adequate muscle tone was achieved.

### Parameters studied

- HR and BP were recorded before induction, at the time of induction, intubation, and then at 5, 10, 15, 30, 45, and 60 minute after intubation and at extubation.
- Depth of anesthesia was evaluated by entropy (State entropy, Response entropy) analysis (*Datex-Ohmeda S/5 Avance workstation*<sup>™</sup>, GE Healthcare, Helsinki, Finland) at 5, 10, 15, 30, 45, and 60 minute after intubation and at extubation.
- End tidal *concentration* of sevoflurane was assessed with anesthesia gas assessment module *E-CAiOVX*<sup>™</sup> at same interval as entropy analysis.

Statistical Analysis was conducted with *Epi Info* software (version 3.5.3, 2011, Centers for Disease Control and Prevention, Atlanta, GA, USA) for windows statistical package using unpaired *t*-test for continuous variables with normal distribution. The non-parametric Kruskal-Wallis test was used for variables not normally distributed. For categorical variables, Chi-square test was used. The results were expressed as mean ± SD. A *P*-value < 0.05 was considered as statistically significant.

## Results

A total of 60 patients enrolled in the study were included for statistical analysis. The two groups were similar regarding age, sex, weight, and ASA physical status [Table 1]. Laparoscopic cholecystectomy was the most frequent surgical procedure [Table 2]. The duration of anesthesia was comparable between both the groups. Pre-induction heart rate, systolic and diastolic blood pressures were similar between two groups (*P* > 0.05).

The depth of anesthesia as assessed by response entropy (RE) and state entropy (SE) was comparable between two groups at all time points during maintenance period ( $P > 0.05$ ). The RE and SE was maintained between 40 and 60 during the period of observation.

The  $FI_{sevo}$  concentration was significantly less in group B as compared to the group A at all time points ( $P < 0.05$ ) [Figure 1]. The average  $ET_{sevo}$  concentration during anesthetic maintenance was 1.35% and 1.72% in the group B and A, respectively. A significant decrease of 13% to 33% of  $ET_{sevo}$  concentration was seen with group B from 5 min to 60 minutes post-intubation ( $P < 0.05$ ) during surgery [Figure 2].

During anesthesia maintenance, group B showed a statistical significant decrease in heart rate, systolic and diastolic blood pressure from baseline at all time points as compared to the group A ( $P < 0.05$ ). An average 6.5% fall in heart rate from baseline in group B as compared to 3.7% rise in the group A, 8% fall in systolic blood pressure from baseline as compared

to 3.6% rise in the group A, and 8.16% fall in diastolic blood pressure from baseline as compared to 3.3% rise in the group A was observed [Figures 3 and 4].

In our study, none of the patients in either group required supplemental analgesia or anti-hypertensive drugs intra-operatively. Bradycardia was observed in 2 patients in group B within 10 mins post-extubation, which promptly responded to atropine 0.6 mg IV.

## Discussion

The major observation in our study was that dexmedetomidine infusion as an adjuvant in general anesthesia causes decreased requirement of sevoflurane without compromising adequate depth of anesthesia, thus it has anesthetic-sparing property.

Anesthetic-sparing effect of dexmedetomidine in our study is consistent with earlier studies. A study done on patients undergoing hysterectomy showed a 30% reduction of maintenance concentration of isoflurane.<sup>[10]</sup> Similarly, a reduction in 35% to 50% in isoflurane concentration with low or high dose of dexmedetomidine was found in a study on healthy human volunteers.<sup>[12]</sup> This larger reduction in isoflurane requirement seen as compared to our study might be due to difference in study population (healthy human volunteers vs. patients posted for elective surgery) and the type of stimulus (tetanus nerve stimulus vs. surgical stimulus). The results of our study are consistent with that of the study done by Fragen, *et al.*<sup>[13]</sup> in elderly patients, which showed a 17% reduction.

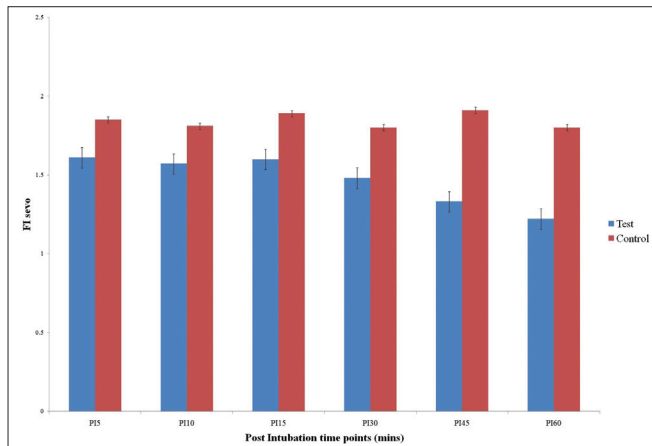
Dexmedetomidine by its sympatholytic action decreases heart rate and blood pressure, thus assessing the depth of anesthesia by hemodynamic parameters would be unreliable in evaluating its effect on requirement of inhalational agent.

**Table 1: Demographic data**

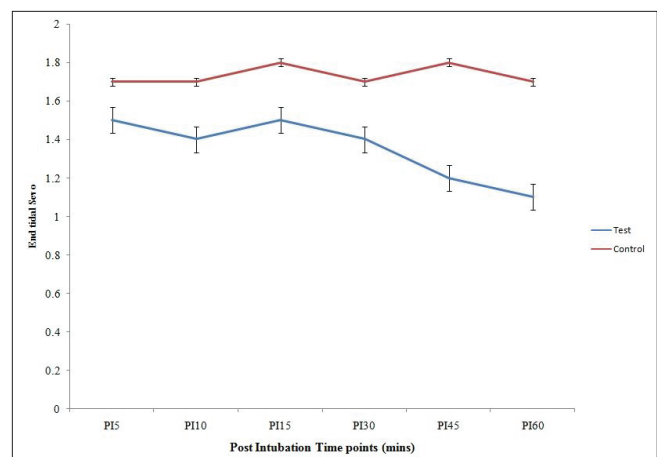
Variables	Group B (n=30)	Group A (n=30)	P value
Age	42.03±12.62	39.27±13.79	0.29
Sex (Male/Female)	8/22	13/17	0.27
Weight	57.53±10.53	54.46±10.01	0.24

**Table 2: Type of surgeries**

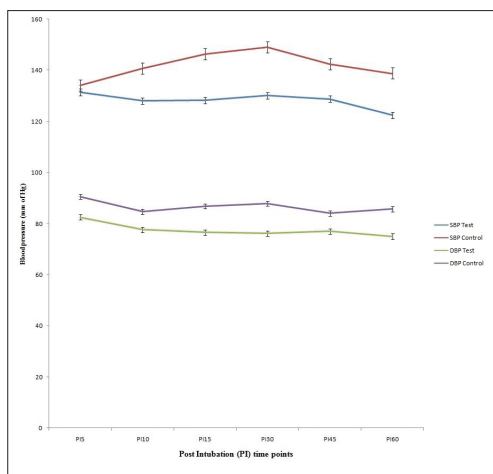
Type of surgeries	Group A (n=30)	Group B (n=30)
Laparoscopic cholecystectomy	19	17
Laparoscopic appendectomy	4	5
Open cholecystectomy	3	4
Modified radical mastectomy	2	2
Laparoscopic hernia repair	2	2



**Figure 1:** Fraction of inspired sevoflurane at different time interval (PI-post-intubation, FI-fraction of inspired)



**Figure 2:** End tidal sevoflurane at different time intervals (PI-post-intubation)

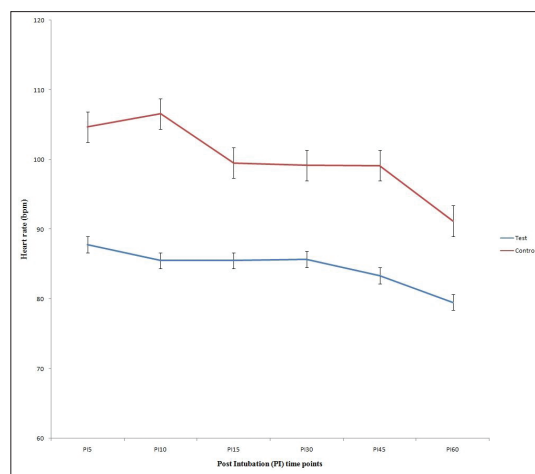


**Figure 3:** Changes in SBP and DBP at various time points post-intubation (PI-post-intubation, SBP-systolic blood pressure, DBP-diastolic blood pressure)

Several electroencephalogram-dependent indices such as bispectral index and entropy have been used to measure the depth of anesthesia.<sup>[15]</sup> Entropy is a useful monitor for measuring the electroencephalographic effects of increasing and decreasing sevoflurane concentration and assessing the depth of anesthesia.<sup>[15,16]</sup> Analogous to the bispectral index, entropy displays a high degree of specificity and sensitivity in assessing consciousness during anesthesia.<sup>[11,15]</sup> Using bispectral index to assess the depth of anesthesia, Magalhães *et al.* showed decreased requirement of sevoflurane with continuous infusion of dexmedetomidine during general anesthesia. In our study, we used entropy to measure the depth of anesthesia, thereby eliminating the bias of evaluation by hemodynamic parameters as in earlier studies.

Use of dexmedetomidine produces intra-operative and post-operative opioids-sparing effect. Dexmedetomidine by its sympatholytic action attenuates sympathoadrenal response to tracheal intubation.<sup>[17]</sup> In patients undergoing laparoscopic tubal ligation, a 33% decrease in morphine use post-operatively was observed when dexmedetomidine was used at a dose of 0.4 mcg/kg.<sup>[18]</sup> Dexmedetomidine when administered as infusion at a dose of 0.5 mcg/kg/h has specific analgesic effect and provides visceral pain relief.<sup>[4]</sup> In morbidly obese, dexmedetomidine produces a greater decrease in sympathovagal balance intra-operatively than fentanyl along with better post-operative analgesia.<sup>[19]</sup> Dexmedetomidine, when used as sole substitute for remifentanyl in ambulatory gynecologic laparoscopic surgery, provides better peri-operative hemodynamic stability and post-operative analgesia.<sup>[5]</sup> Dexmedetomidine provides similar intra-operative hemodynamic response and better post-operative analgesia compared to remifentanyl in patients undergoing supratentorial craniotomy.<sup>[20]</sup>

Use of fentanyl reduces minimum alveolar concentration



**Figure 4:** Changes in HR at various time points post-intubation (PI-post-intubation, HR-heart rate)

(MAC) of sevoflurane significantly.<sup>[14]</sup> Use of opioids along with dexmedetomidine would confound its effect on requirement of inhalation agent. Hence, in our study, fentanyl was not administered in dexmedetomidine group B, and we found a 21.5% decrease in the  $ET_{50}^{sev}$ , in contrast to 33.12% decrease in study done by Magalhães E *et al.*<sup>[11]</sup> where fentanyl was used.

One limitation of our study was that we included both laparoscopic as well as open surgeries. Requirement of inhalational agent can be different in laparoscopic and open surgeries.

To conclude, the continuous infusion of dexmedetomidine, as adjuvant in general anesthesia, significantly decreases the requirement of sevoflurane for maintaining adequate depth of anesthesia. Studies measuring plasma concentration of dexmedetomidine should be undertaken to establish the precise correlation between its dose and inhalational agent's requirements.

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**How to cite this article:** Patel CR, Engineer SR, Shah BJ, Madhu S. The effect of dexmedetomidine continuous infusion as an adjuvant to general anesthesia on sevoflurane requirements: A study based on entropy analysis. *J Anaesthesiol Clin Pharmacol* 2013;29:318-22.  
**Source of Support:** Nil, **Conflict of Interest:** None declared.