Effect of intravenous infusion of dexmedetomidine on perioperative haemodynamic changes and postoperative recovery: A study with entropy analysis

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ABSTRACT

Background: Dexmedetomidine, an α2 agonist, when used as an adjuvant in general anaesthesia attenuates stress response to various noxious stimuli, maintains perioperative haemodynamic stability and provides sedation without significant respiratory depression postoperatively. Methods: Sixty patients were randomly divided into two groups of 30 each. In group A, fentanyl 2 μg/kg and in group B dexmedetomidine were given intravenously as loading dose of 1 μg/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 μg/kg. Sevoflurane was used as inhalation agent in both groups. Haemodynamic variables and entropy (response entropy and state entropy) were recorded continuously. Postoperative sedation and recovery were assessed by sedation score and modified Aldrete’s score, respectively. Results: Dexmedetomidine significantly attenuates stress response at intubation with lesser increase in heart rate (10% vs. 17%), systolic blood pressure (6% vs. 23%) and diastolic blood pressure (7% vs. 20%) as compared to the control group (P<0.05). Intraoperatively, an average of 8% fall in systolic blood pressure and 8.16% fall in diastolic pressure in the test group as compared to 3.6% rise in systolic and 3.3% in diastolic pressure of the control group was observed. Postoperatively, the test group showed significant sedation at 2 h as compared to the control group (P=0.00) and recovery was better in the control group for the first 2 h post extubation. Conclusion: Dexmedetomidine attenuates various stress responses during surgery and maintains the haemodynamic stability when used as an adjuvant in general anaesthesia. Also, the sedative action of dexmedetomidine delays recovery for the first few hours post extubation.

Key words: Dexmedetomidine, entropy, perioperative haemodynamics, recovery

INTRODUCTION

Dexmedetomidine, the pharmacologically active d-isomer of medetomidine, is a highly selective and specific α2-adrenoceptor agonist.[1] Dexmedetomidine, by its central sympatholytic action, promotes haemodynamic stability when used as an adjuvant during general anaesthesia. It has analgesic and anaesthetic sparing property.[2] Dexmedetomidine has potent sedative properties.[3,4] However, because of its sedative property, it is unknown if the recovery from anaesthesia would be delayed when used as continuous infusion. The aim of this study was to assess the effect of intravenous dexmedetomidine on perioperative haemodynamics and also postoperative recovery in elective surgical procedures with continuous monitoring of depth of anaesthesia by entropy analysis.

METHODS

After obtaining the approval from institutional ethical committee and written informed consent from patients, 60 patients with ASA status I and II, aged 18–55 years,
and undergoing elective surgical procedures were randomly allocated into two groups: group A (control group): sevoflurane–fentanyl and group B (test group): sevoflurane–dexmedetomidine. Patients older than 55 years, those with a history of psychiatric/neurological illness, hypertensive patients, morbidly obese patients, pregnant and nursing women, patients with known allergic reaction to any of the study medications, patients on recent use of sedatives or analgesics, and patients with significant laboratory abnormalities were excluded.

On arrival in the operating room, patient’s heart rate, blood pressure and oxygen saturation were monitored by continuous electrocardiogram (ECG), noninvasive blood pressure (NIBP) monitor and pulse oximetry (SpO₂) monitor, respectively. Depth of anaesthesia was evaluated by entropy (state entropy, response entropy) analysis (Datex-Ohmeda S/5 Avance workstation™, GE Healthcare, Helsinki, Finland).

Inj. glycopyrrolate 4 μg/kg and ondansetron 0.15 mg/kg intravenous were given as premedication in both the groups. After a 5-min monitoring period, patients in the test group received inj. dexmedetomidine (2 ml diluted in 48 ml of saline) in a dose of 1 μg/kg over 10 min through infusion pump. Two minutes prior to induction, patients in the control group received inj. fentanyl 2 μg/kg intravenous slowly.

Ten minutes after the administration of the study drug, anaesthesia was induced with thiopentone sodium 5 mg/kg intravenous slowly. Succinylcholine 2 mg/kg was used to facilitate endotracheal intubation. Anaesthesia was maintained with O₂:N₂O (50:50) and sevoflurane. Inj. vecuronium bromide was used as muscle relaxant.

Anaesthesia was maintained with sevoflurane to a maximum of 2.5% end tidal to maintain the heart rate and blood pressure within 20% of the baseline value and entropy value between 40 and 60. Patients in the test group received dexmedetomidine continuous infusion between 0.2 and 0.8 μg/kg/h. The anaesthesiologist was permitted to treat haemodynamic events, defined as heart rate and/or blood pressure more than 20% of baseline, in spite of increasing sevoflurane concentration to 2.5% and dexmedetomidine infusion to 0.8 μg/kg, with incremental doses of metoprolol 2–5 mg, or fall in heart rate and blood pressure by more than 20% of baseline with ephedrine 5 mg intravenously.

In group B, dexmedetomidine was stopped approximately 15–20 min before the completion of surgery. Inj. diclofenac sodium 1 mg/kg (max dose of 75 mg) was given intravenously in both groups at the time of skin closure. N₂O and sevoflurane was discontinued after skin closure in both groups. Reversal of neuromuscular blockade was obtained with inj. neostigmine 0.05 mg/kg and glycopyrrolate 8 μg/kg intravenously.

Immediately after extubation, sedation was assessed with sedation score as follows: 1, awake; 2, sleepy but arousable; and 3, sleepy difficulty to awake. In the postoperative period, if Visual Analogue Score (VAS) was >6, inj. tramadol 50–100 mg was given as supplemental analgesia.

Heart rate, blood pressure, SpO₂ and entropy were recorded continuously at predetermined time intervals as per the protocol. Recovery was assessed by modified Aldrete’s and sedation score as follows: score 1, awake; score 2, sleepy but arousable; score 3, sleepy difficult to arouse.[5]

Statistical analysis was conducted with Epi Info software (version 3.5.3, 2011) for windows statistical package using unpaired t-test for continuous variables with normal distribution. The nonparametric Kruskal–Wallis test was used for variables not normally distributed. For categorical variables, chi-square test and Fisher’s exact test were used as applicable. The results were expressed as mean±SD. P<0.05 was considered as statistically significant. A sample size of 30 patients per group was needed to detect an intergroup difference of at least 10% in blood pressure and heart rate with a power of 0.80 and α of 0.05.

RESULTS

The two groups were comparable regarding age, sex, weight and ASA physical status. The type of surgery and duration of anaesthesia (P=0.27) were comparable between both groups. Pre-induction heart rate, systolic and diastolic blood pressure (SBP and DBP, respectively) were comparable between the two groups (P>0.05).

At intubation, there was 10% rise in pulse rate from baseline in the test group as compared to 17% rise in the control group (P=0.01). Intraoperatively, the test group showed significant fall in mean heart rate from baseline as compared to the control group at all time
points. The mean heart rate in the test group showed a 6% fall as compared to 3.7% rise in the control group from baseline. Post extubation, the test group showed significant fall in average pulse rate of 22.5% from baseline as compared to the control group which showed average 1% rise [Figure 1].

Ten minutes after administration of the test drug, significant fall in SBP and DBP of 6% and 9%, respectively, from baseline as compared to the control group was observed ($P<0.05$). At intubation, both the groups showed rise in SBP and DBP. The test group showed a rise of 6% versus 23% in SBP and 7% versus 20% in DBP as compared to the control group ($P<0.05$). Intraoperatively, a significant difference in the change of SBP and DBP from baseline was observed between the two groups at all time points till 60 min ($P<0.05$). The test group showed an average of 8% fall in SBP and DBP as compared to 3.6% rise in the control group [Figure 2]. Post extubation at 30 min, a 12% fall in SBP was seen in the test group as compared to 0% in the control group ($P<0.05$), while change in diastolic pressure was not significantly different between the two groups.

Postoperatively, the test group showed significant sedation with a mean score of 1.43±0.50 at 2 h as compared to 1.0±0.0 of the control group ($P=0.00$). The recovery as assessed by modified Aldrete’s score was significantly better in the control group (10.00±0.0) as compared to the test group (8.06±0.64) at 30 min post extubation ($P=0.00$). However, modified Aldrete’s score significantly improved in the test group at the end of 2 h and was similar to that of control group. Postoperative analgesia as assessed by VAS, showed significant analgesic effect of dexmedetomidine with a mean score of 5.70±0.60 as compared to 8.13±0.70 of the control group ($P=0.00$) [Table 1].

Bradycardia was observed in two patients in the dexmedetomidine group within 10 min post extubation, which promptly responded to inj. atropine 0.6 mg intravenous. The duration of recovery was similar in both the groups. After operation, none of the patients in either of the groups complained of any discomfort or of intraoperative awareness.

**DISCUSSION**

This prospective randomised study demonstrated that intraoperative infusion of dexmedetomidine attenuates stress responses to various noxious stimuli
during surgery and maintains haemodynamic stability without the requirement of opioids with prolongation of recovery.

Dexmedetomidine, a highly selective \( \alpha_2 \) agonist, has significant sympatholytic and haemodynamic stability property.\(^6\) It causes dose-dependent decrease in heart rate and blood pressure.\(^7\) Earlier studies have shown that dexmedetomidine attenuates stress response to intubation by decreasing central sympathetic outflow, thereby decreasing serum epinephrine and norepinephrine levels.\(^8\) These findings are consistent with our study results which showed a significant decrease in change in heart rate, systolic blood pressure and diastolic blood pressure.\(^9,10\)

Tanskanen et al. in their study showed that intraoperative infusion of dexmedetomidine at a rate of 0.4 \( \mu g/kg/h \) maintains heart rate and blood pressure in acceptable range for a longer duration as compared to placebo group.\(^7\) The decrease in heart rate and blood pressure is similar to the findings by Feld et al. who compared dexmedetomidine with fentanyl in bariatric surgery.\(^11\) Thus, showing that dexmedetomidine by its sympatholytic activity attenuates various stress responses during surgery and maintains haemodynamic stability. Dexmedetomidine also blunts the haemodynamic response to emergence from anaesthesia and extubation.\(^8,10\) Our study showed a significant attenuation of heart rate at the time of extubation in dexmedetomidine group.

Use of haemodynamic end points for assessing the depth of anaesthesia in a study on sympatholytic drugs such as dexmedetomidine would be unreliable as there may be compromise in the depth of anaesthesia.\(^12\) Thus, use of electroencephalogram-dependent indices such as bispectral index and entropy to measure the depth of anaesthesia would be appropriate. In our study, adequate depth of anaesthesia was maintained throughout surgery with response and state entropy being maintained between 40 and 60.

One of the most commonly encountered problems in Postoperative Anaesthetic Care Unit (PACU) is delayed recovery and longer discharge time of patients receiving perioperative dexmedetomidine infusion.\(^13\) Similar findings were observed in our study. However, there was no difference between two groups at the end of 2 h. The delayed recovery might be due to the sedative property of dexmedetomidine.\(^6\) However, unlike opioids, sedation with dexmedetomidine is not associated with respiratory depression.

In our study, dexmedetomidine was discontinued 20 min prior to extubation, thus we could not establish the potential benefit of dexmedetomidine in attenuating haemodynamic response at the time of extubation and during postoperative period. Also, recording the time taken to extubate after the completion of surgery would have established objectively the effect of dexmedetomidine on immediate recovery.

**CONCLUSION**

Dexmedetomidine, when administered as a preanaesthetic medication and intraoperative infusion, attenuates stress response to various noxious stimuli and maintains haemodynamic stability. Dexmedetomidine’s sedative property delays postoperative recovery, thus continuous monitoring is essential during the first few hours of postoperative period.

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