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Effect of Dexmedetomidine Premedication on Sevoflurane Requirement using BIS during General Anaesthesia in Laparoscopic Cholecystectomy

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Abstract

Background: Dexmedetomidine is a highly selective α_2-adrenoreceptor agonist with sedative, anxiolytic and analgesic properties without any respiratory depression. It decreases the requirement of volatile anaesthetics with better hemodynamic stability in surgical patients. We avoided the risk of awareness under anaesthesia by using Bispectral index.

Aims: To evaluate the efficacy of Dexmedetomidine pre-medication on Sevoflurane requirement and to assess the haemodynamic stability during elective laparoscopic cholecystectomy surgeries.

Methods: Randomized double-blind control study.

Design: Forty eight patients were randomly allocated into two groups. Group A received saline infusion and Group 2 received Dexmedetomidine infusion in a dose of 1µg/kg over 15 min before induction. Vital parameters and bispectral index were noted throughout the surgery. Patients were induced and intubated as per the standard protocol and maintained with Oxygen & Nitrous oxide (1 litre Oxygen + 2 litre Nitrous oxide) with Sevoflurane concentration adjusted to achieve BIS values of 45–55. Demographic profile, hemodynamic parameters total Sevoflurane consumption were noted.

Statistical Analysis: Statistical analysis was performed using SPSS software version 22.0. Percentage analysis was done for qualitative data. Parametric data were compared using an unpaired t-test. Nonparametric data were compared with Fisher's exact test or Chi-square test.

Results: Mean Sevoflurane consumption in Group A and Group B were 0.379 ± 0.10, 0.169 ± 0.05 ml/min respectively with P<0.001 which was statistically significant. A 55.4% reduction in Sevoflurane consumption was found in patients receiving Dexmedetomidine premedication.

Conclusions: Dexmedetomidine premedication is useful to reducing Sevoflurane consumption during general anesthesia and it provides better haemodynamic stability.

Keywords: Bispectral index; Dexmedetomidine; General anesthesia; Sevoflurane; Laparoscopic Cholecystectomy.

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INTRODUCTION

Dexmedetomidine is a highly selective α2-adrenoreceptor agonist with sedative, anxiolytic and analgesic properties without any respiratory depression.[1] Volatile anaesthetics like Sevoflurane has been used since decades for the maintenance of general anaesthesia, and various adjuvants like Benzodiazepines and α2 adrenergic agonists, have been introduced to reduce the dose of inhalational agents and also to produce better sedation and hypnosis.[2] Laparoscopic cholecystectomy requires pneumoperitoneum and carbon dioxide insufflations, leading to increase in plasma nor-epinephrine, epinephrine levels and plasma renin activity.[3] All these changes lead to increase in heart rate, blood pressure, increased systemic and pulmonary vascular resistance, and reduced cardiac output. Moreover, the reverse Trendelenburg position required for the surgery leads to diminished venous return and thereby reduces cardiac output.[4] Dexmedetomidine stabilizes the changes in arterial pressure, heart rate and cardiac output during laparoscopic surgeries, thereby improving intra-operative and post-operative hemodynamic stability.[5] Several electroencephalogram dependent indices such as Bispectral index (BIS) and entropy have been used to measure the depth of anesthesia. Bispectral index for general anaesthesia corresponds with values of 40-60 and values above 60 highly correlate with the ability of subjects to respond to verbal commands.[1]

This study was conducted to assess the effect of dexmedetomidine premedication on sevoflurane requirement and to assess its effect on hemodynamic stability, while maintaining adequate BIS values to prevent awareness under anesthesia.

METHODS

After obtaining institutional ethics committee clearance and informed written consent from patients, a randomized double blind control study was formulated. The study population comprised 48 patients with ASA physical status I and II, aged 18–70 years, scheduled for elective laparoscopic cholecystectomyof duration up to 2 hours. Pregnant women, patients with morbid obesity, psychiatric illness, heart block, and patients on beta blockers were excluded from the study. The patients were divided into 2 groups randomly – Group A (Control group) and Group B (Study group), 24 patients in each group. Randomisation was done by using a computer generated randomisation table in blocks of four and a ratio of 1:1, that placed patients into two groups (A and B) equally. An anaesthesiologist who was not involved in the study or management of the patients opened the sealed envelope and set up either an infusion dose of dexmedetomidine in 100ml normal saline or normal saline alone based on the code mentioned in the envelope.

All patients were pre-medicated with tab. Alprazolam 0.5 mg oral, the night before surgery and tab. Ranitidine 150 mg 4 hours before surgery and a minimum fasting state of 6 h before anesthesia was ensured in all patients.

Patients were wheeled into the operating room, and standard monitoring like electrocardiogram (ECG), non-invasive blood pressure (NIBP), pulse oximeter (for SPO_2) and BIS monitor were connected and base line values were recorded. Patients received 15 minutes infusion of either 100 ml NS (control group – Group A) or Dexmedetomidine 1μg/kg in 100 ml NS (study group – Group B) before induction.

All patients were preoxygenated with 100% O_2 for 3 minutes. Anesthesia was induced with 2μg/kg IV Fentanyl and 2 mg/kg IV Propofol. Muscle relaxation was achieved with IV Vecuronium 0.1mg/kg. After 3 minutes of assisted ventilation with 100% oxygen at 8L/min, trachea was intubated with appropriate size endotracheal tube. Correct placement of ET Tube was confirmed by end-tidal carbon dioxide ($EtCO_2$) and auscultation. In addition to the pre-induction monitors, post intubation $EtCO_2$ was also monitored and maintained between 30-40 mmHg using circle system and CO_2 absorber. All patients received IV Ondansetron (0.1mg/kg), Dexamethasone (8mg), Paracetamol (15mg/kg), Ketorolac (0.5mg/kg) and maintenance dose of Vecuronium (0.05mg/kg) as standard protocol for general anesthesia. Anesthesia was maintained on Oxygen & Nitrous oxide (1 litre Oxygen + 2 litre Nitrous oxide) with Sevoflurane.

Depth of anaesthesia was monitored using the BIS monitor to maintain a target value of 45-55 by manipulating Sevoflurane vaporizer setting. At the end of surgery, neuromuscular blockade was reversed with intravenous Glycopyrrolate (10 μg/kg) and Neostigmine (0.05mg/kg), and 100% O_2. Patients were extubated after adequate spontaneous ventilation, a BIS ≥ 80 and after patient's response to verbal commands were established.

Intraoperative monitoring of heart rate, mean arterial pressure, ECG and SPO_2 were done during pre-induction, post induction, 1 minute after

intubation and then at intervals of 5, 10, 15 minutes, then every 15 minutes till the end of surgery, at extubation and 10 minutes after extubation. $EtCO_2$ and BIS values were also documented.

Sevoflurane consumption was assessed by weighing the Sevoflurane vaporizer before and after the surgery (by subtracting the two values), and the amount of drug consumed in millilitre per minute was calculated.

In our present study, an approximate 2 hours of operating time was similar to that of elimination half-life of Dexmedetomidine; so it was possible for proper recovery to occur without sedation in the study group, so as to result in a similar recovery profiles between the two groups.

Statistical analysis was performed using SPSS software version 22.0. Data was represented in graphical and tabular format. Percentage analysis was done for qualitative data. Parametric data were compared using an unpaired t-test. Nonparametric data were compared with Fisher's exact test or Chi-square test. Data were presented as mean (SD) with $P< 0.05$ considered statistically significant.

Sample size was calculated using the statistical formula for difference between two means

$$n = \frac{2\sigma^2(Z_{1-\beta} + Z_{1-\alpha/2})^2}{(\text{Difference})^2}$$

Where,

n – Sample size in each group (assumes equal sized groups)

σ – Standard deviation of outcome variable = 3.01

$Z_{1-\beta}$ - desired power (typically 1.28 for 90% power)

α – significance = 5%

$Z_{1-\alpha/2}$ = 1.96 (for 95% confidence interval)

$2x\ (3.01)^2\ _x\ (1.28 +1.96)^2 / (13.76 -10.69)^2 = 21$

Therefore, total number of patients in both groups = 42

Considering a drop-out rate of 10%, (e.g. Conversion into open technique intra-operatively) a total of 48 patients were enrolled in the study.

Mean values and standard deviation were taken from study named 'Effect of bolus dose of Dexmedetomidine on Isoflurane consumption in surgical patients under general anaesthesia' by Muniyappa *et al*.[6]

RESULTS

Among 48 patients enrolled in the present study 2 patients were excluded, one in each group because of the intra operative conversion to open surgery. Analysis of the study was done with 46 patients, 23 in each group.

The demographic characteristics of patients and duration of surgery were comparable in both groups (Table 1).

Table 1: Demographic Characteristics

Parameters	Group-A n% Mean (SD)	Group-B n% Mean (SD)	P value
Age	39 (14)	37(14)	
Weight	54 (9)	54 (12)	
BMI	21.4 (1.7)	21.4 (2.4)	
ASA1	20 (87%)	17 (73.9%)	0.46
ASA2	3 (13%)	6 (26.1%)	
Duration of surgery (in minutes)	66.09 (28.10)	66.78 (23.23)	0.93

Sevoflurane consumption in Dexmedetomidine group was significantly lower than in control group (Table 2)

Table 2: Comparison of Sevoflurane consumption

Sevoflurane consumption in ml per minute (ml/min)	Group	Mean	P	t	95% confidence interva
	A	0.379±0.10	<0.001	9.10	0.16,0.26
	B	0.169±0.05			

The MAP in group B at pre-induction, post induction, at 1, 5, 10, 15, 30, 45, 60 and 75 minutes after intubation, at extubation and 10 minutes after extubation were lower compared to group A (P<0.001). MAP less than 60 was taken as hypotension. (Fig. 1) One patient in study group developed hypotension (MAP = 55) after loading dose of dexmedetomidine which was treated with Inj. Mephentermine 6 mg IV.

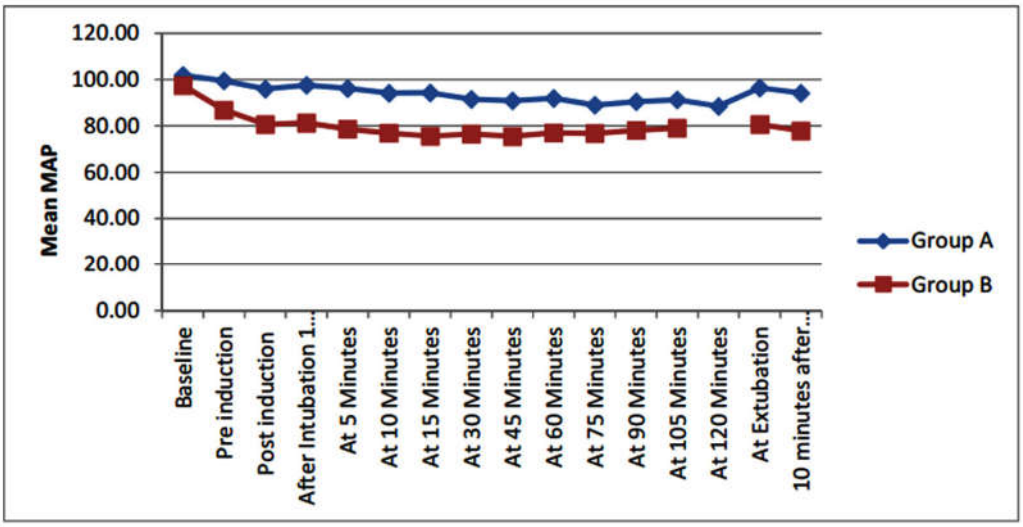

Fig. 1: Perioperative change in Mean arterial blood pressure

Heart rate in group B at pre-induction, post induction, at 1, 5, 10, 15, 30, 45, 60 and 75 minutes after intubation, at extubation and 10 minutes after extubation were lower compared to group A (P<0.001). (Fig. 2) One patient in control group and 2 patients in study group developed bradycardia after induction of anesthesia which were treated with 0.2 mg Glycopyrolate intravenously

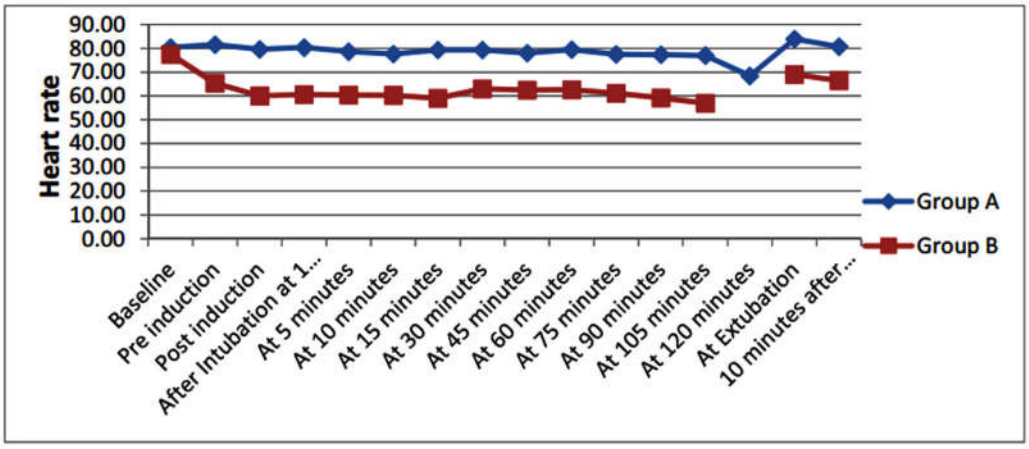

Fig. 2: Perioperative change in Heart rate

Bispectral Index between the two groups were comparable at all the intervals during the surgery (P= 0.07-0.95), except at post induction, 1 and 10 minutes after intubation. There was statistically significant reduction in BIS values during those intervals in group B (P= 0.01, 0.04, 0.001) (Fig. 3)

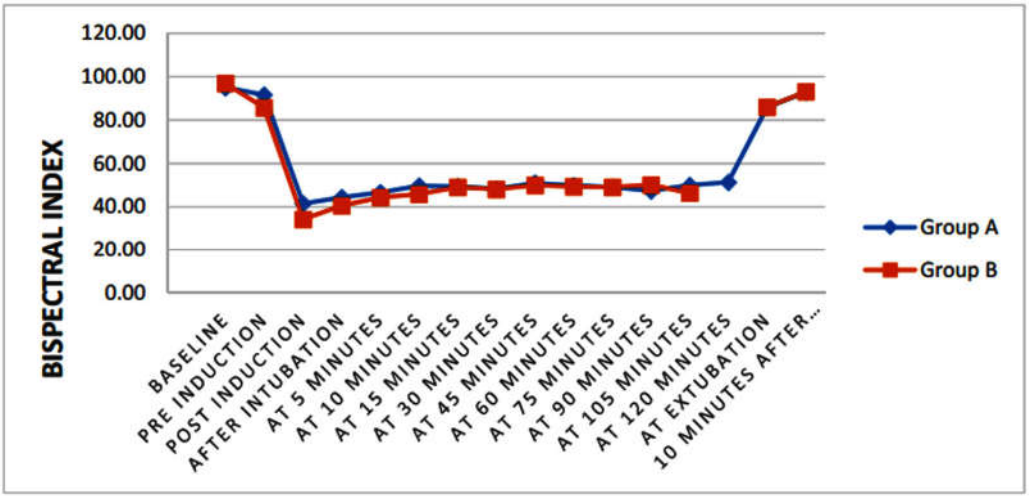

Fig. 3: Perioperative change in Bispectral Index

Respiratory rate, SPO_2, ECG and temperature were maintained normal throughout the study period in both control and study groups. There was no episode of respiratory depression, airway obstruction, apnea or dysrhythmia detected in any of the patients on drug infusion and all were easily arousable from sedation.

DISCUSSION

Dexmedetomidine is a α_2-adrenergic receptor agonist with sedative, anxiolytic, hypnotic, analgesic, and sympatholytic effects. During general anesthesia, it reduces the minimum alveolar concentration (MAC) of inhaled anaesthetics and decreases the consumption of volatile anaesthetics with better hemodynamic stability in surgical patients.[7] A 55.4% reduction of Sevoflurane consumption per hour was observed in dexmedetomidine group as compared to control group while maintaining adequate depth of anesthesia using BIS in patients undergoing elective laparoscopic cholecystectomy under GA. Patients in the dexmedetomidine group were more hemodynamically stable with significant reduction of MAP and heart rate compared to control group.

In study conducted by Sharma *et al*,[8] 41% reduction of Sevoflurane consumption per hour was observed in Dexmedetomidine group as compared to control group. The difference in Sevoflurane consumption is possibly due to lower loading dose of 0.5 µg /kg dexmedetomidine compared to our study. Harsoor *et al*[9] and Shin *et al*[7] reported a 28% and 23.4% reduction in Sevoflurane consumption respectively in various surgeries. This difference was possibly due to the non-standardization of the type and duration of surgery while, in our present study only laparoscopic cholecystectomy was included.

Study conducted by Ohtani *et al*[10] also demonstrated 27% reduction in Sevoflurane consumption in Dexmedetomidine group.

Laparoscopic cholecystectomy has been accepted worldwide as gold standard and safe treatment in most patients with gallbladder disease. Insufflation of CO_2 gas into the abdominal cavity, causes both mechanical (increased intra-abdominal pressure) and neurohormonal changes (secretion of catecholamines and vasopressin).[11] Due to associated stress response induced by surgery and anesthesia, adverse physiological effects of pneumoperitoneum and related positioning of the patient, general anesthesia is preferred for these patients.[8] Dexmedetomidine stabilizes the changes in arterial pressure, heart rate and cardiac output during laparoscopic surgeries, thereby improving intra-operative and post-operative hemodynamic stability.

In the present study, baseline heart rate and mean arterial blood pressure is comparable between the two groups. It is found that there is statistically significant decrease in heart rate and MAP in dexmedetomidine group at pre-induction, post induction, at 1, 5,10, 15, 30, 45, 60 and 75 minutes after intubation, at extubation and 10 minutes after extubation when compared to control group. In a study conducted by Harsoor *et al*[9] and Panchgar V *et al*[12] heart rate, systolic and diastolic blood pressures and MAP were significantly reduced in dexmedetomidine group during intraoperative period compared to control group. There was a significant rise in HR, SBP, DBP, and MAP following

laryngoscopy, intubation, pneumoperitoneum, and after extubation in control group. These results are in consistent with the study conducted by authors Bhattacharjee *et al*[13], Keniya *et al*[14] and Tufanogullari *et al.*[15] Study conducted by A.G. Yacout *et al*[16], VoraKS *et al*[17], Muniyappa *et al*[6], Nandal Bhagat *et al*[18] and Manne GR *et al*[19] showed similar reduction in MAP and HR in dexmedetomidine group compared to control group. In a study conducted by Sharma *et al*[8], patients in dexmedetomidine group had significantly lower HR and NIBP even before intubation as seen in our study, possibly due to a reduction in sympathetic outflow and sedative effects of dexmedetomidine. In studies conducted by Gulabani *et al*[20] and Vinit K. Srivastava *et al*[21] also reported decreased pressor response during intubation and extubation in patients who received dexmedetomidine in comparison to normal saline alone. This blunting effect of pressor response is particularly advantageous in known hypertensive patients in whom excessive rise in blood pressure can have deleterious effects.

In a study conducted by Harsoor *et al*[9], bradycardia was noticed in 3 out of 20 patients in dexmedetomidine group without any incidence of bradycardia in the control group. In study conducted by Sharma *et al*[8], 5 out of 50 patients who received dexmedetomidine developed bradycardia and was treated with Atropine 0.6 mg IV. Both the authors used dexmedetomidine 1 µg/kg followed by 0.5µg/kg/hr infusion Similarly, in the present study, two patients in dexmedetomidine group and one patient in control group developed bradycardia despite not using infusion of dexmedetomidine after loading dose. This bradycardia was treated with 0.2 mg Glycopyrolate IV. In the present study, one patient in study group developed hypotension immediately after loading dose of dexmedetomidine which was treated with Inj. Mephentermine 6 mg IV. No other patients in either groups developed hypotension during the study.

In the present study we kept BIS values between 45 to 55 for maintaining adequate depth of anesthesia. We noticed a reduction in BIS values in group B at post induction, 1 and 10 minutes after intubation. Similar reduction in BIS was noted in the study conducted by Shin *et al*[7] compared to control group.

CONCLUSION

A 55.4% reduction in Sevoflurane consumption was found in patients receiving IV dexmedetomidine as an adjuvant in patients scheduled for laparoscopic cholecystectomy under general anaesthesia. Dexmedetomidine premedication at 1mcg/kg was efficacious in providing attenuation of hemodynamic stress response due to laryngoscopy, intubation, pneumoperitoneum and extubation.

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