ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 11, Issue 6, 2018

Online - 2455-3891
Print - 0974-2441

Research Article

EFFECT OF DEXMEDETOMIDINE ON DOSE REQUIREMENT OF PROPOFOL AND THIOPENTONE INDUCTION IN PATIENTS UNDER GENERAL ENDOTRACHEAL ANESTHESIA

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Received: 08 February 2018, Revised and Accepted: 10 March 2018

ABSTRACT

Objectives: The present study was undertaken to assess the effect of dexmedetomidine as a premedicant on dose requirement of induction agents, thiopentone and propofol in patients undergoing various surgeries under general endotracheal anesthesia under the bispectral index (BIS) guidance.

Methods: A double-blinded randomized controlled study was conducted during the year 2014–2015 among 120 patients aged 18–55 years with American Society of Anesthesiologists' physical status Score I or II and Mallampati Grades I and II. After obtaining informed consent, all the eligible patients were randomly assigned to one of the four groups each containing 30 patients: Group SP (control group) - saline infusion before induction with propofol, group DP - dexmedetomidine infusion before induction with propofol, group ST (control group) - saline infusion before induction with thiopentone, and group DT - dexmedetomidine infusion before induction with thiopentone.

Results: The mean dose of propofol required was 95.0±6.15 mg and 55.0±7.0 mg in group SP and DP, respectively, whereas the requirement of thiopentone was 6.6±0.93 mg/kg in group ST as opposed to 4.8±0.58 mg/kg in group DT. The decrease in the dose requirement in dexmedetomidine groups than the control groups was statistically significant and also dose reduction in dexmedetomidine was more in DP group compared to that in DT group ($p<0.001$).

Conclusion: Dexmedetomidine as a preanesthetic medication significantly decreases intraoperative anesthetic requirement of thiopentone and propofol, and dose requirement is significantly less in case of propofol as compared to thiopentone.

Keywords: Dexmedetomidine, Thiopentone, Propofol, Bispectral index, Dose reduction.

 DOI: http://dx.doi.org/10.22159/ajpcr.2018.v11i6.25198

INTRODUCTION

The increase in sympathetic and sympathoadrenal activity results in pressor response [1,2], as substantiated by the fact that plasma catecholamines concentration increased in patients undergoing surgery under general anesthesia [3]. Dexmedetomidine, the pharmacologically active d-isomer of medetomidine imidazole is a highly specific and selective α2 adrenoreceptor agonist [4-6]. It has been shown to have significant analgesic, sedative, sympatholytic, anxiolytic, anesthetic-sparing effects, and hemodynamic stabilizing effects [7,8]; making it suitable for anesthesia and the perioperative period. Dexmedetomidine has α2:α1 binding selectivity ratio of 1620:1 compared to 220:1 for clonidine [5], and more predictable pharmacokinetic properties compared to clonidine [9,10]. It also possesses selective α2-adrenoceptor agonism, especially for the 2A subtype of this receptor, which causes it to be a much more effective sedative and analgesic agent than clonidine [11,12].

Dexmedetomidine attenuates sympathoadrenal response to painful stimulation during general anesthesia and surgery, thus providing improved hemodynamic, metabolic, and hormonal stability [13-19]. A reduction in the dose requirement for the intravenous induction agent thiopental, opioids, and volatile anesthetics has been shown in human and animal studies when pretreated with dexmedetomidine [7,14-19].

The bispectral index (BIS) is a derived multifactorial electroencephalographic (EEG) parameter in which the outcome of the EEG analysis is represented as a unitless value between 0 (isoelectric EEG) and 100 (alert and oriented). BIS monitoring is used by clinical anesthetists to titrate anesthetic agents to maintain loss of consciousness and prevent intraoperative awareness [20].

Various studies have shown the effect of pre-operative dexmedetomidine on induction dose requirement of propofol and thiopentone, but limited studies have been conducted under the guidance of BIS. The present study was undertaken to assess the effect of dexmedetomidine as a premedicant on dose requirement of induction agents, thiopentone and propofol in patients undergoing various surgeries under general endotracheal anesthesia under BIS guidance.

METHODS

After obtaining the approval from the Institutional Ethics Committee, a double-blinded randomized controlled study was conducted at S.C.B. Medical College, Cuttack, during the year 2014–2015. After explaining the detail procedures, informed consent was obtained from all the patients before their inclusion in the study. A total of 30 patients were randomly allocated to each control (saline) and test (dexmedetomidine) groups, satisfying the minimum criteria of sample size based on power and Cohen's *d* values. The study population comprised 120 patients aged 18–55 years with American Society of Anesthesiologists' physical status Score I or II and Mallampati Grades I and II, scheduled for different elective surgical procedures under general anesthesia (laparoscopic cholecystectomy, thyroidectomy, etc.). Pregnant and lactating patients, patients with morbid obesity, heart block, dysrhythmias, and hypertensive patients on β-blockers were excluded from the study. Patients with known suspected allergy to propofol, eggs, or soya products; patients with diseases such as hyperthyroidism, hypothyroidism, diabetes mellitus, and renal disease; and patients on long-term medications or any medication within 1 week before surgery were not included in the study.

Using block randomization technique, the patients were assigned to one of the four groups each containing 30 patients and received the drugs as follows:

Group assignment

- Group SP: Control group - saline infusion before induction with propofol
- Group ST: Control group - saline infusion before induction with thiopentone
- Group DP: Dexmedetomidine infusion before induction with propofol
- Group DT: Dexmedetomidine infusion before induction with thiopentone.

Previous studies showed that dexmedetomidine was effective at the dose of 1.0 μg/kg body weight in attenuating stress response to intubation [21,22], administered by a slow infusion over 10 min [15,17,18] and 10 min before induction [13-15,19] to blunt the hemodynamic response to laryngoscopy and intubation. In the present study, dexmedetomidine was diluted with 50 ml normal saline to make it 4 μg/ml solution and attached to the intravenous line with a 50 cm pressure extension line using a three-way stopcock. Calculated dose of the prepared drug was delivered using a syringe pump. All patients in group DP and DT received dexmedetomidine in a dose of 1 μg/kg in 10 min, 10 min before induction of anesthesia. Patients in group SP and ST received 50 ml of 0.9% NaCl solution in 10 min, 10 min before induction through an infusion pump. Syringe pumps were prepared and marked by a technician who was briefed about the study beforehand. Contents of syringe pump were not divulged till the completion of study.

The drugs used in our study included (a) dexmedetomidine: 200 μg in 2 ml ampoule, (b) propofol (1%): 200 mg in 20 ml, and (c) thiopentone (2.5%): 250 mg in 10 ml.

Anesthetic procedure

All these patients underwent detail preanesthetic checkups. Detail history of all cases was taken followed by thorough physical examination including examination of cardiovascular and respiratory system, airway assessment by Mallampati grading and rule 1-2-3, assessment of general condition, nutritional status, and body weight of patient. All patients were premedicated with glycopyrrolate 0.2 mg intravenously, midazolam 1 mg intravenously, fentanyl 1 μg/kg, and ondansetron 4 mg. In all cases, preoxygenation was done with 100% oxygen through face mask for at least 3 min before induction of anesthesia. As the patients were made calm and cooperative, easily arousable to verbal commands, they were induced with thiopentone/propofol sufficient to reach BIS value of 40–60. The dose of thiopentone or propofol needed to achieve BIS value 40–60 was considered as the induction dose. All the patients were intubated with appropriate size cuffed endotracheal tube, and intubation was facilitated with rocuronium 0.6 mg/kg. Dose required for induction with thiopental sodium and propofol was noted.

Anesthesia was maintained with N_2O 66% in O_2 33% and isoflurane. The lungs were ventilated maintaining a tidal volume of 7–10 ml/kg, respiratory rate of 12–15/min, and end-tidal CO_2 of 35–45 mm of Hg. Muscle relaxation was maintained with vecuronium bromide 0.1 mg/kg every 15 min. Isoflurane was terminated at the start of skin closure, and N_2O was discontinued after skin closure.

Hypotension (systolic blood pressure ≤20% of baseline value and/or <80 mm of Hg) was treated with IV fluids and supplemented with injection phenylephrine 50–100 μg intravenous bolus as and when required, and bradycardia (heart rate <55/min) was treated with atropine 0.6 mg intravenous and repeated if necessary. BIS score was recorded as 0/20/40/60/80/100 according to the clinical condition such as flat line EEG, burst suppression, deep hypnotic sleep, general anesthesia, light moderate sedation, and awake, respectively. At the end of the surgery, when patients' respiratory efforts were perceived slowly, residual neuromuscular block was reversed with injection neostigmine 0.04 mg/kg and injection glycopyrrolate 0.02 mg/kg. When the protective reflexes returned completely, the patients were extubated. When the patients were able to communicate with verbal commands, they were shifted to the recovery room.

Parameters studied

All the parameters and the results from the four groups were entered in the predesigned study pro forma sheet.

1. The dose of the injection thiopentone for induction of anesthesia in group ST and DT
2. The dose of the injection propofol for induction of anesthesia in group SP and DP
3. BIS score at 0 min, 5 min, and 10 min after administration of dexmedetomidine and at intubation.

Statistical analysis

Data were expressed as mean and standard deviation, percentage. The statistical analysis was performed using a standard GraphPad InStat software package. Student's t-test, ANOVA, and Chi-square test were used to compare the observations in various groups. $p<0.05$ was regarded as statistically significant, and $p<0.001$ highly statistically significant.

RESULTS

All the four groups were comparable in patients' characteristics as well as duration of anesthesia (Table 1). The mean dose of propofol required in group SP was 95.0±6.15 mg, while it was 55.0±7.0 mg in group DP. Furthermore, the requirement of thiopentone was 6.6±0.93 mg/kg in group ST as opposed to 4.8±0.58 mg/kg in group DT. The decrease in the dose requirement in dexmedetomidine groups than the control groups was statistically significant and also dose reduction in dexmedetomidine in DP group was more compared to that in DT group ($p<0.001$) (Table 2). Table 3 summarizes comparison of mean BIS scores between different groups at baseline, 5th min and 10th min after administration of drugs. In group DP, after 5 min of dexmedetomidine administration, BIS value went down to 92.26±5.12 from baseline value 97.56±2.84 and reduced further to 83.66±6.24, whereas in group DT, the baseline BIS score 98.3±2.10 changed to 91.60±5.56 after 5 min and 83.4±6.19 after 10 min. Compared to control groups, the BIS scores varied significantly after 5 and 10 min of drug administration indicating good sedation (sedated but not unconscious could be awakened by verbal commands).

Dexmedetomidine was well tolerated, and few dose-related adverse events were observed. Before administration of the study drugs in the operating room, heart rate and blood pressure values between the groups (SP vs. DP and ST vs. DT) did not differ. In group DP, eight patients had bradycardia and/or hypotension and only one needed treatment.

Table 1: Patient characteristics and duration of anesthesia

Variables	n=30				p
	Group SP	Group ST	Group DP	Group DT	
Age in years (Mean±SD)	42.0±10.49	43.73±8.17	40.13±8.90	41.86±9.20	0.518
Sex (M/F)	17/13	16/14	17/13	15/15	0.946
Weight in kg (Mean±SD)	53.50±6.27	52.47±6.14	54.02±6.14	55.16±6.20	0.404
ASA (I/II)	26/4	25/5	24/6	25/5	0.923
Duration of anesthesia (in min)	235.50±11.30	240.54±12.47	242.18±13.26	238.54±11.48	0.175

p>0.05 not statistically significant. SD: Standard deviation

Table 2: Effect of dexmedetomidine on dose of propofol and thiopentone sodium requirement

Induction agent	Mean±SD, n=30		
	Group SP	Group DP	Mean difference
Propofol dose (mg)	95.0±6.15	55.0±7.01*	40.0±1.70
	Mean±SD, n=30		
	Group ST	Group DT	
Thiopentone sodium (mg/kg)	6.60±0.93	4.80±0.58**	1.80±0.19***

*Statistically significant at p<0.0001 between group SP and group DP,
**statistically significant at p<0.0001 between group ST and group DT,
***statistically significant at p<0.0001 between group DP and group DT.
SD: Standard deviation

Table 3: Comparison of mean BIS scores

Time	Group SP	Group DP	p
Basal	98.23±2.48	97.56±2.84	0.334
5th min AD	97.70±3.03	92.26±5.12	<0.0001*
10th min AD	97.26v3.35	83.66±6.24	<0.0001*
Intubation	45.54±4.54	44.8±3.90	0.501
	Group ST	Group DT	
Basal	98.13±2.51	98.3±2.10	0.777
5th min AD	97.4±3.24	91.6±5.56	<0.0001*
10th min AD	96.8±3.98	83.4±6.19	<0.0001*
Intubation	48.33±3.46	47.06±4.10	0.199

*Statistically significant at p<0.0001. BIS: Bispectral index

In group DT, six patients had bradycardia and/or had hypotension and only one needed treatment.

DISCUSSION

Dose of thiopentone required for induction

We studied the total dose of thiopentone required for induction in the control group ST and experimental group DT. The target dose for induction was up to the BIS score of 40–60. We observed that the mean dose of thiopentone required for induction was 6.60 mg/kg body weight and 4.80 mg/kg body weight in ST and DT group, respectively, showing a statistically significant reduction of 27.2% (p<0.0001). Various authors have studied the effect of dexmedetomidine on thiopentone requirements for induction of anesthesia. Scheinin *et al*. conducted a study on 24 ASA I patients undergoing elective surgery under general endotracheal anesthesia and observed that the mean sleep dose of thiopentone was significantly greater in control group (p<0.001) than in dexmedetomidine group [23]. In another study, Jaakola *et al*. showed 23% reduction in the dose requirement of thiopentone for induction in the dexmedetomidine group compared to control group [13]. Similar findings have been widely reported in various literatures [16,17,19,24]. The reduction in thiopental dose requirement in the dexmedetomidine group could be the expression of a direct dexmedetomidine effect on the central nervous system (pharmacodynamic effect) or on pharmacokinetics of thiopental or a combination of pharmacokinetic and pharmacodynamic drug interaction.

Dose of propofol required for induction

We also studied the total dose of propofol required for induction in the control group SP and experimental group DP. The target dose for induction was up to the BIS score of 40–60. In the control group, the mean dose of propofol required for induction was 95.0 mg, and in dexmedetomidine group, dose required was 55.0 mg showing a statistically significant reduction of 42.10% (p<0.0001). Turgut *et al*. in their prospective randomized double-blind study observed that propofol dose for induction and maintenance of anesthesia was significantly lower with dexmedetomidine [25]. Our study finding is consistent with the results of other studies [26-28]. The sedative effect of dexmedetomidine is mediated through the locus coeruleus in the brain stem, where it decreases sympathetic outflow and increases parasympathetic outflow. The different mechanisms of dexmedetomidine and propofol for producing a sedative effect suggest a possible synergism while administered combined. Furthermore, the dose reduction of dexmedetomidine in DP group (42.10%) is significantly more than that of DT group (27.17%) suggesting more synergistic action between dexmedetomidine and propofol.

BIS scoring

We have used an EEG-dependent index such as BIS to measure the depth of anesthesia as the use of hemodynamic endpoints for assessing the depth of anesthesia in a study would be unreliable as there may be a compromise in the depth of anesthesia. In our study, adequate depth of anesthesia was maintained with BIS value of 40–60. The mean BIS scores were similar between control group and dexmedetomidine group at baseline and at the time of intubation, whereas the scores after 5 and 10 min of drug administration were significantly less in dexmedetomidine groups. It was observed in a study that with loading dose of dexmedetomidine, entropy fell by 20% to reach BIS value of 60–80 [27].

Side effects

In group DP, four patients developed bradycardia after 30 min of the drug administration and three patients developed hypotension 20 min after intubation. Only one patient required atropine for bradycardia, and none required vasopressors for the correction of blood pressure. Hypotension was managed by decreasing volatile anesthetic concentration and infusing intravenous fluids. In group DT, three patients developed bradycardia after 36 min of the drug administration and hypotension occurred in two patients after 30 min of intubation. One patient required atropine for bradycardia and no patient required vasopressors for the correction of blood pressure. Previous studies reported that the undesirable effects of dexmedetomidine were dose related. Basar *et al*. reported that the incidence of bradycardia after a single dose of 0.5 μg/kg of dexmedetomidine was about 5% [17], while a study by Sulaiman *et al*. showed the development of hypotension or bradycardia with a similar dosage of dexmedetomidine [29].

In the present study, post-operative requirement of analgesics was not taken into consideration as it was not part of our study. Time to recovery following extubation was not measured which would have given an idea of recovery in the groups. However, the strength of our study lies on the use of intraoperative BIS monitoring which is definitely more appropriate in deciding the depth of anesthesia and the requirement of anesthetic agent.

CONCLUSION

Dexmedetomidine, as a preanesthetic medication, at a dose of 1.0 μg/kg body weight diluted in 50 ml saline given 10 min before induction significantly decreased intraoperative anesthetic requirement of thiopentone and propofol, and dose requirement is significantly less in case of propofol compared to thiopentone. It has significant opioid and anesthetic-sparing property [30]. It significantly attenuates sympathoadrenal response to tracheal intubation.

ACKNOWLEDGMENTS

We are very much thankful to the Head of Department of Anesthesia, S.C.B Medical College, Cuttack, Odisha, Dr. Ramesh Ch. Samantaray and Dr. Nibedita Pani, for their constant support and guidance.

AUTHOR'S CONTRIBUTIONS

Conceptualization of the study, data collection, and statistical analysis was done by Dr. Laxman Ku Senapati. Literature search and manuscript writing was done by Dr. Priyadarsini Samanta.

CONFLICTS OF INTEREST

None.

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