THE EFFECT OF DEXMEDETOMIDINE ON BISPECTRAL INDEX MONITORING IN CHILDREN*

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Abstract

The primary aim of this study was to test whether dexmedetomidine administration based on the bispectral index (BIS) monitoring caused a reduction in consumption of sevoflurane.

Following Institutional Ethic Committee approval and written informed consent from all parents, fifty-four children undergoing sevoflurane anaesthesia randomly allocated to receive either dexmedetomidine (Group D) or saline (Group S). The anaesthesia was induced with 8% sevoflurane in nitrous oxide/oxygen in all children.

Following anaesthesia induction, Group D (n=27) children received a loading dose of dexmedetomidine 1 μgkg^{-1} IV over ten minutes, followed by a continuous infusion at a rate of 0.5 $\mu gkg^{-1} hr^{-1}$ throughout the surgery. Group S (n=27) children received same volume of saline infusion due to obtained blindness. Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), body temperature and peripheral oxygen saturation (SpO_2), end-tidal concentrations of oxygen, carbon dioxide ($ETCO_2$), and sevoflurane (ETsevo) were monitorized. Bispectral index numbers and ETsevo concentrations were recorded at 2 min before incision, 2 min after incision, at the end of surgery and before the termination of anaesthesia, and finally immediately after wake-up from anaesthesia (Final BIS number).

BIS number was found significantly lower in group D at before incision, after incision and at the end of surgery than in group S (p=0.000, 0.001, 0.007). End tidal sevoflurane concentrations were significantly higher in group S at before incision, after incision and at the end of surgery than in group D ($p < 0.000$ to $p < 0.001$). Final BIS number and sevoflurane concentrations were similar and there were no significant difference between the groups.

It was concluded that intravenous (IV) dexmedetomidine infusion at a rate of 0.5 $\mu gkg^{-1} hr^{-1}$ during sevoflurane anaesthesia significantly reduces end-tidal sevoflurane concentration and BIS number in children undergoing minor surgical interventions.

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Introduction

Dexmedetomidine is a selective and potent α2-adrenoceptor agonist, with hypnotic, analgesic and sympatholytic properties[1]. In contrast with many anaesthetic agents, dexmedetomidine preserves spontaneous ventilation. This property makes it a useful adjuvant to general anaesthesia during procedures requiring spontaneous ventilation, such as upper airway surgery and manipulation[2,3].

In the paediatric population, dexmedetomidine has been reported to have effective agent for various clinical scenarios, including the provision of sedation during mechanical ventilation, prevention of emergence delirium after general anaesthesia, procedural sedation during non-invasive radiologic procedures and in the control of withdrawal after the prolonged use of opioids and benzodiazepines[3-6]. In surgical patients, it has been reported that dexmedetomidine reduces the use of other anaesthetics, minimizes sympathetic response to nociceptive stimuli and improves intraoperative haemodynamic stability[1]. In a study, dexmedetomidine given before induction of anaesthesia has shown to diminish isoflurane requirements during abdominal surgery in adults[7].

This prospective, randomized, double-blind, controlled study was designed to see if a similar reduction in sevoflurane requirements can be achieved by giving intravenous (IV) dexmedetomidine administration during sevoflurane anaesthesia. Thus, the primary aim of this study was to test whether dexmedetomidine administration based on bispectral index (BIS) monitoring caused a reduction in consumption of sevoflurane.

Methods

After approval by the Institutional Ethics Committee, and written informed consent of all parents, 54 children, between 3 and 10 years old, ASA class I and II, undergoing minor surgery were enrolled. Patients were excluded if they had neurological disability, impaired hearing, epilepsy, chronic renal or hepatic illness, metabolic disorders were taking sedative or stimulant medication, or if they had any contraindication to the planned anaesthesia technique. No premedication was administered preoperatively.

Anaesthesia was induced with 8 % sevoflurane in nitrous oxide/oxygen (70%/30%) and maintained with sevoflurane in the same N_2O/O_2 concentrations. Following sevoflurane induction, intravenous access was obtained. A dose of fentanyl 1 μgkg^{-1} was administered before the initiation of dexmedetomidine or saline infusions. No neuromuscular blocker has been used for endotracheal intubation. Trachea was intubated easily with suitable tracheal tube. After intubation of trachea, lungs were ventilated with volume-controlled ventilation to maintain end-tidal carbondioxide concentration ($ETCO_2$) at 32 to 35 mmHg. (Dräger Primus). Peripheral oxygen saturation and body temperature were maintained at least 97 % and in the range of 36.0–36.5°C, respectively.

To estimate the level of consciousness, the skin was cleaned with alcohol and got dried. The BIS sensor was placed on the forehead and temple using a frontal–temporal montage, pressed for 5 seconds, and skin-sensor connection was established. Sevoflurane concentrations were set to achieve BIS values between 40 to 60 therefore; we increased or decreased the sevoflurane vaporizer by 0.2 % step by step to reach predetermined values of BIS. An anaesthesiologist, who was unaware of the group, was responsible for recording the BIS values and adjusting the sevoflurane concentration. If there were other signs of inadequate anaesthesia (HR > 20% of baseline, movement or tears), sevoflurane concentration was increased by 0.5 % step by step to achieve deeper anaesthesia.

Immediately after anaesthesia induction and IV access, children were allocated randomly to one of two groups. Randomization was done by opening a sealed envelope. An anaesthetist, who was not one of the observers, prepared packages containing either dexmedetomidine (Abbott lab., N. Chicago, IL60064 USA) or 0.9 % saline. Both solutions were labelled 'study drug' and coded to maintain the double-blind nature of the study. Dexmedetomidine was supplied in 2-ml ampoules at a concentration of 100 μgml^{-1}, and diluted with 100 ml normal saline to a concentration of 2 μgml^{-1}. The placebo saline solution was prepared in a similar fashion.

Following anaesthesia induction, Group D (n=27) children received a loading dose of dexmedetomidine 1 μgkg^{-1} IV over ten minutes, followed by a continuous

infusion at a rate of 0.5 μgkg^{-1} hr^{-1} throughout the surgery. Group S (n=27) received same volume of saline infusion due to obtained blindness. Scores for haemodynamic parameters (systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), body temperature and peripheral oxygen saturation (SpO_2) were monitored throughout anaesthesia and recorded by an anaesthetist, who was blinded to the patient group, at before anaesthesia induction and every 5 min throughout the study period. End-tidal concentrations of oxygen, carbondioxide ($ETCO_2$), and sevoflurane (ETsevo) were also monitorized continuously. Bispectral index numbers and ETsevo concentrations were recorded 2 min before incision, 2 min after incision, at the end of surgery and before the termination of anaesthesia, and finally immediately after wake-up from anaesthesia (Final BIS number). The duration of wake-up was defined from discontinued the anaesthetic drugs to spontaneous eye opening. All data were recorded by an anaesthetist blind to the study groups.

It was planned that if the children' clinical condition would have necessitated any change during the infusion of study drugs; the infusion solution would have been stopped and children would have excluded from study. If hearth rate (HR) was lower than 80% of baseline, 20 μgkg^{-1} of atropine sulphate was administered intravenously. If bradycardia persists, then dexmedetomidine infusion was discontinued and children excluded from study.

A pilot study was performed to asses the number of children requiring sample size. Eight patients were accepted for pilot study. The end-tidal sevoflurane concentration was in group S (0.34±0.12) and in group D (0.19±0.17). Thus, this study required at two tails, α=0.05, (1-β) 95%, 54 patients, 27 in each group. All variables were tested for normal distribution by Kolmogorov–Smirnov test. Independent sample t-test was used for comparison of the means of continuous variables and normally distributed data. Data on side effects were analyzed with the chi-square test. A *p* value <0.05 was considered statistically significant.

Results

The two groups were similar with regard to age, sex, weight, duration of surgery and wake-up (table 1). BIS number was found significantly lower in group D at before incision, after incision and at the end of operation than in group S (p=0.000, 0.001, 0.007. table 2). End tidal sevoflurane concentrations were significantly higher in group S at before incision, after incision and at the end of operation than in group D ($p < 0.000$ to $p < 0.001$, table 3). Final BIS number and sevoflurane concentrations were similar and there were no significant difference between the groups. In group D, ten patients had bradycardia during the loading dose of dexmedetomidine, and these patients were treated with 20 μgkg^{-1} atropine sulphate. Heart rates, systolic and diastolic blood pressures were also similar between groups during the study periods.

Table 1
Demographic data of the groups

	Group S (n=27)	Group D (n=27)
Age (year)	6.1±2.2	5.7±2.1
Weight (kg)	24.9±6.1	24.3±5.9
Sex (girl/boy)	13/14	12/15
The duration of surgery (min)	58.0±9.5	57.5±8.6
The duration of wake-up (min)	5.1 ± 1.6	6.0 ± 1.2

Table 2
BIS number of the groups

BIS number	Group S (n=27)	Group D (n=27)	P
Before incision	50.1±8.4	42.5±6.5	,000
After incision	49.8±8.9	41.4±8.1	,001
End of operation	49.7±9.0	43.4±7.6	,007
Final	89.4±4.1	89.0±5.5	,268

Table 3
End tidal sevoflurane concentration of the groups

End Tidal Sevoflurane	Group S (n=27)	Group D (n=27)	P
Before incision	2.14±0.29	0.77±0.25	,000
After incision	2.01±0.25	0.63±0.19	,000
End of operation	1.87±0.20	0.56±0.12	,000
Final	0.29±0.19	0.20±0.18	0.81

Discussion

This is the first study evaluating the effect of dexmedetomidine on sevoflurane requirement and BIS numbers in children undergoing minor surgical interventions. The main finding of this study is that, in children undergoing minor surgical intervention, intravenous (IV) dexmedetomidine infusion at a rate of 0.5 $\mu gkg^{-1}\ hr^{-1}$ during sevoflurane anaesthesia significantly reduces sevoflurane requirements.

The alpha 2-agonist dexmedetomidine is a new sedative, analgesic, and anxiolytic agent[8]. It has been demonstrated that intraoperative administration of dexmedetomidine significantly reduces anaesthetic requirements, speeds postoperative recovery, and blunts the sympathetic nervous system response to surgical stimulation[9,10]. The concomitant administration of dexmedetomidine has also been shown to reduce the anaesthetic requirements for propofol as well as the inhalation anaesthetic agents[1,11,12]. We expected that an alpha 2-agonist, dexmedetomidine, might also reduce the sevoflurane requirements, which exert an antinociceptive effect via stimulation of alpha-2 adrenoceptors in sympathetic nerve endings and the spinal cord. As expected, in the present study, dexmedetomidine significantly decreased sevoflurane consumption and BIS numbers during minor surgery in children. Ngwenyama et al. reported that dexmedetomidine decreases propofol requirements by approximately 25–30% during spine surgery[13]. A reduction of more than 95% of minimal alveolar concentration (MAC) of halothane is observed following intravenous administration of dexmedetomidine, which shows this drug may induce anaesthetic state if administered alone[14]. In our study, end tidal sevoflurane concentration was lower in dexmedetomidine group than in saline group during the study periods.

Recently, Kayusa et al reported that BIS values were lower with dexmedetomidine than with propofol at comparable Observer's Assessment of Alertness and Sedation (OAA/S) scores[15]. The authors noted that BIS values at OAA/S scores of 1, 2, 3, 4, and 5 during dexmedetomidine sedation were 95 (79 –98), 62 (53.5– 68.5), 45.5 (45.3–52), 39.5 (34.3– 41.8), and 24.5 (22.5–30.5), respectively. It was suggested that the combination of both BIS and sedative scales could provide different and complementary data to the clinician evaluating the patient's response to sedation than would either tool alone, especially when dexmedetomidine was used. In the present study, we found that BIS value and end tidal sevoflurane concentration reduced in a positive correlation. Also, haemodynamic parameters and other clinical data suggested the patients in deep anaesthesia. Our findings showed that dexmedetomidine reduced BIS number. However, Elias et al reported their experience with dexmedetomidine during microelectrode recording (MER) of subthalamic nucleus[16]. The bispectral index (BIS) was used to estimate the level of consciousness. The quality of microelectrode recording was evaluated as a function of BIS, clinical arousal, and dexmedetomidine dose. Microelectrode recording during wakefulness (BIS>80; 0.1 to 0.4 $\mu gkg^{-1}\ hr^{-1}$ dexmedetomidine) was similar to the unmedicated state. Subthalamic MER was reduced when the patient was asleep or unarousable (BIS < 80). In our study, BIS value was kept between 40 to 60. It is widely recognized among anaesthesiologists that BIS values between 40 and 60 generally indicate adequate general anaesthesia for surgery and improve recovery[17].

Hyperpolarization of noradrenergic locus ceruleus neurons seems to be an important factor for sedative activity of dexmedetomidine[18,19]. The transcriptional activator c-Fos expression pattern is similar to endogenous non-rapid eye movement sleep under sedation by dexmedetomidine, which is not the case when sedation is induced by GABAergic agonists[18-20]. Overall, dexmedetomidine enhances the non-rapid eye movement sleep promoting pathways, mainly at locus ceruleus.

Adverse cardiovascular effects are limited and include occasional episodes of bradycardia and hypotension that are mainly described with rapid administration of boluses[21,22]. In our study, ten patients had bradycardia however it was corrected after atropine sulphate injection. Possibly, intravenous atropine can prevent deep bradycardia before dexmedetomidine injection. Dexmedetomidine has been extensively used in adults and paediatrics for sedation and as an adjuvant to anaesthesia, although its use is off-label in patients under 18 yr of age[3,5-7,9,10,12,13,23,24].

Among paediatric patients, an inverse

correlation exists between BIS values and inhaled anaesthetic agents, and BIS values and age[25,26]. Kern et al. reported to confirm the good fit between BIS and end-tidal concentration of sevoflurane (PEsevo) concentration using an Emax model even during spontaneous ventilation in the non-steady state setting[27]. Present study confirm the inverse correlation between sevoflurane concentration an BIS number, as sevoflurane concentration increased, BIS number decreased.

It was concluded that intravenous (IV) dexmedetomidine infusion at a rate of 0.5 $\mu g kg^{-1} hr^{-1}$ during sevoflurane anaesthesia significantly reduces end-tidal sevoflurane concentration and BIS number in children undergoing minor surgical interventions.

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