RESEARCH ARTICLE

The effects of different doses of dexmedetomidine on the requirements for propofol for loss of consciousness in patients monitored via the bispectral index: a double-blind, placebo-controlled trial

Yang Gu[1,2†], Fan Yang[3†], Yonghai Zhang[3], Junwei Zheng[1], Jie Wang[1], Bin Li[1], Tao Ma[1], Xiang Cui[3], Kaimei Lu[1] and Hanxiang Ma[3*]

Abstract

Background: The α_2-adrenergic agonist dexmedetomidine (DEX) is a sedative and can be used as an adjunct to hypnotics. The study sought to evaluate the effects of different doses of DEX on the requirements for propofol for loss of consciousness (LOC) in patients monitored via the bispectral index (BIS).

Methods: In this randomized, double-blind, three arm parallel group design and placebo-controlled trial, 73 patients aged between 18 and ~ 65 years with a BMI range of 18.0–24.5 kg·m^{-2} and an American Society of Anesthesiologists (ASA) grade I or II who were scheduled for general anesthesia at the General Hospital of Ningxia Medical University were included in this study. Anesthesiologists and patients were blinded to the syringe contents. All patients were randomly assigned in a 1:1:1 ratio to receive a 0.5 μg·kg^{-1} DEX infusion (0.5 μg·kg^{-1} DEX group; $n = 24$), a 1.0 μg·kg^{-1} DEX infusion (1.0 μg·kg^{-1} DEX group; $n = 25$) or a saline infusion (control group; $n = 24$) for 10 min. Propofol at a concentration of 20 mg·kg^{-1}·h^{-1} was then infused at the end of the DEX or saline infusion. The propofol infusion was stopped when the patient being infused lost consciousness. The primary endpoint were propofol requirements for LOC and BIS value at LOC.

(Continued on next page)

* Correspondence: mahanxiang@hotmail.com
[†]Yang Gu and Fan Yang contributed equally to this work.
[3]Department of Anesthesiology, General Hospital of Ningxia Medical University, Yinchuan 750004, China
Full list of author information is available at the end of the article

(Continued from previous page)

Results: The data from 73 patients were analyzed. The propofol requirements for LOC was reduced in the DEX groups compared with the control group (1.12 ± 0.33 mg·kg^{-1} for the 0.5 µg·kg^{-1} DEX group vs. 1.79 ± 0.39 mg·kg^{-1} for the control group; difference, 0.68 mg·kg^{-1} [95% CI, 0.49 to 0.87]; $P = 0.0001$) (0.77 ± 0.27 mg·kg^{-1} for the 1.0 µg·kg^{-1} DEX group vs. 1.79 ± 0.39 mg·kg^{-1} for the control group; difference, 1.02 mg·kg^{-1} [95% CI, 0.84 to 1.21]; $P = 0.0001$). The propofol requirements for LOC was lower in the 1.0 µg·kg^{-1} DEX group than the 0.5 µg·kg^{-1} DEX group (0.77 ± 0.27 mg·kg^{-1} vs. 1.12 ± 0.33 mg·kg^{-1}, respectively; difference, 0.34 mg·kg^{-1} [95% CI, 0.16 to 0.54]; $P = 0.003$). At the time of LOC, the BIS value was higher in the DEX groups than in the control group (67.5 ± 3.5 for group 0.5 µg·kg^{-1} DEX vs. 60.5 ± 3.8 for the control group; difference, 7.04 [95% CI, 4.85 to 9.23]; $P = 0.0001$) (68.4 ± 4.1 for group 1.0 µg·kg^{-1} DEX vs. 60.5 ± 3.8 for the control group; difference, 7.58 [95% CI, 5.41 to 9.75]; $P = 0.0001$).

Conclusion: The study showed that DEX (both 0.5 and 1.0 µg·kg^{-1} DEX) reduced the propofol requirements for LOC. DEX pre-administration increased the BIS value for LOC induced by propofol.

Clinical trial registration: The study was registered at ClinicalTrials.gov (trial ID: NCT02783846 on May 26, 2016).

Keywords: Propofol, Dexmedetomidine, Bispectral index, Loss of consciousness

Background

A variety of sedatives, such as propofol combined with midazolam, are commonly used in induction of anesthesia. Dexmedetomidine (DEX) is now commonly used in anesthesia induction because of its sympatholytic effect and it can attenuate the cardiovascular response during intubation [1, 2]. However, there is still a lack of clinical experience in the combined use of these two drugs in the induction of anesthesia, and sedative overdose may occur during induction of anesthesia.

Along with other drugs, propofol is frequently used as a sedative-hypnotic drug to induce anesthesia. Unfortunately, propofol at the recommended induction dose (2.0–2.5 mg·kg^{-1}) often causes cardiovascular depression during anesthesia induction [3]. Theoretically, decreasing propofol dose is associated with a low incidence of hypotension during anesthesia induction [4]. The techniques decreasing propofol dose for anesthesia induction as guided by bispectral index [5] may reduce the incidence of hypotension induced by recommended propofol dose.

DEX is a widely used drug in anesthesia for its sympatholytic, sedative and analgesic effects [6]. It has been reported that DEX decreased the propofol requirements by bispectral index-guided closed-loop anesthesia [7]. Many studies have observed the opioid-free effect of DEX when combined with other drugs during anesthesia [8, 9]. But few study has focused on the effect of DEX on propofol requirements for loss of consciousness (LOC) during anesthesia induction. Indeed, anesthesia induction is an important phase in the perioperative period; thus, it is urgent to separately evaluate the effect of DEX on the propofol requirements for LOC during this phase. Considering the anesthetic-free effect of DEX, we hypothesized that DEX can decrease the propofol requirements for LOC during anesthesia induction. Therefore, the first purpose of this study was to verify that DEX decreases the propofol requirements for LOC during anesthesia induction.

The bispectral index (BIS) is a common tool to determine the depth of the sedative state. The BIS value is constantly maintained ranged from 40 to 60 during general anesthesia through the titration of anesthetic agents [10]. It had been demonstrated that there was a good relationship between the BIS values and the blood concentration of propofol at LOC [11]. However, the BIS value at LOC varies when different sedatives are used [12]. It has been proven that the BIS value was different at the loss of response to voice commands when fentanyl, nitrous oxide, or alfentanil was added to the propofol anesthesia [13]. DEX produced resembling stage 2 NREM sleep in the EEG and characteristic arousal sedation [14, 15], and these makes it distinguishes from propofol. Therefore, we hypothesized that the BIS value at LOC was different between propofol alone and propofol combined with DEX administration. Thus, the second goal of this study was to evaluate the effect of DEX on the BIS value at LOC induced by propofol.

Methods

The study was approved by the ethics committee of the General Hospital of Ningxia Medical University (2016167). The study was registered at ClinicalTrials.gov (NCT02783846). The study was conducted in accordance with applicable CONSORT guidelines. This was a prospective, double blind, single center randomized study with a three arm parallel group design. No changes were made regarding important changes to methods after trial commencement. Written informed consent was obtained from 87 patients with an American Society of Anesthesiologists (ASA) score I or II, an age of 18–65 years, and a body mass index (BMI) of 18.0–24.5 kg·m^{-2} who were scheduled for elective surgeries under general anesthesia. Exclusion criteria

Gu *et al. BMC Anesthesiology*   (2020) 20:96

Page 3 of 7

included an allergy to α_2-adrenergic agonists, bradycardia, atrioventricular block, neurologic disorders and the recent use of psychoactive medications, hearing impairment, or alcohol abuse.

Sample size estimation was performed using NCSS-PASS software (version 11.0.7, Update time 2013-01-22). In a one-way ANOVA study, we estimated that the sample sizes of 0.5 µg·kg^{-1} DEX group, 1 µg·kg^{-1} DEX group and control group were 22, 23, and 22, which means were to be compared. The total sample of 67 subjects achieves 90% power to detect differences among the means versus the alternative of equal means using an F test with a 0.05 significance level. The data of the pilot study were not included in data analysis in the current study. Given an anticipated dropout rate of 10%, a total of 73 patients ($n = 73$) were incorporated in the study and distributed randomly with a 1:1:1 ratio into three groups: the 0.5 µg·kg^{-1} DEX group ($n = 24$), the 1.0 µg·kg^{-1} DEX group ($n = 25$) and the control group ($n = 24$), respectively. No interim analysis were made.

A computer-generated randomization table was used to assign each patient to one of the three groups. Study drugs (DEX or normal saline) in the identical 50-ml syringes were prepared by a pharmacist, and the syringes were consecutively numbered according to the randomization schedule. The details were as follows: the solution administered to the 1.0 µg·kg^{-1} DEX group was prepared by dissolving one ampoule of DEX (containing 200 µg in a concentration of 100 µg·ml^{-1}) in normal saline to make a 50 ml solution, yielding a final concentration of 4 µg·ml^{-1}; the solution administered to the 0.5 µg·kg^{-1} DEX group was prepared by dissolving one-half of an ampoule of DEX in normal saline to make a 50 ml solution, yielding a final concentration of 2 µg·ml^{-1}; for the solution administered to the patients of the control group, only 50 ml of 0.9% saline was prepared. Each patient was assigned an order number and received the different drugs, and the anesthesiologists were blinded to the syringe contents. No changes were made regarding blinding. DEX (100 µg·ml^{-1}) and propofol (10 mg·ml^{-1}) were supplied by Sichuan Guorui Medicine Co. Ltd. (Sichuan, China) in identical 2-ml ampules and AstraZeneca Corporation (London, England) in identical 50-ml ampules, respectively.

Patients were admitted to the operating room with no pre-medication. An 18G catheter was inserted into the large forearm vein for fluid and drug administration. Lactated Ringer's solution was infused at a rate of 15 ml·kg^{-1}·h^{-1} before the study. Non-invasive arterial pressure, electrocardiogram, and peripheral oxygen saturation (SpO$_2$) were continuously measured throughout the study period. The BIS was derived from the frontal electroencephalogram and calculated by an Aspect Vista monitor (version 3.2, Aspect Medical System, Inc.) using

BIS sensor electrodes. Four cutaneous electrodes (Zip-Prep; Aspect) were positioned: At$_1$ and At$_2$ (one each above the outer malar bones) with Fp (4 cm above the nasion) as the reference and Fp$_2$ (left forehead) as the ground. Impedance was kept at < 2000 Ω. The BIS (100 = awake, 0 = burse suppression) and its trend were displayed continuously. The time delay of the BIS should be addressed; therefore, the BIS data were recorded after the propofol infusion reached 61 s [16].

All groups were infused with a loading dose of DEX or normal saline via a Graseby syringe pump model 3500 at a speed of 1.5 ml·kg^{-1}·h^{-1} for 10 min. After the loading doses of DEX or normal saline, the propofol was not stopped with a continuous intravenous infusion by micro-pump at 20 mg·kg^{-1}·h^{-1} until the patient lost consciousness. The state of consciousness was evaluated once the propofol was initiated, with an interval of 10 s, until the patients lost consciousness. The endpoint of LOC was determined by loss of the eyelash reflex and not responded to their own name called loudly and repeatedly.

The primary outcomes were the propofol requirements for LOC and the BIS value at LOC. The secondary outcomes was the time to LOC. The mean arterial pressure (MAP), heart rate (HR) and the BIS value were recorded before infusion of the study drug, with an interval of 5 min throughout the study period. No changes were made regarding trial outcomes after the trial commenced.

If the systolic arterial blood pressure increased or decreased by 20% from the baseline or the systolic pressure was less than 90 mmHg, the urapidil or phenylephrine was administered immediately to adjust the blood pressure within a normal range. The atropine was used to maintain the HR above 50 beats·min^{-1}. Respiratory depression was treated with assisted ventilation via facemask.

The data were recorded using Microsoft Excel 2007 and analyzed with various statistical tests using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Sex distribution was analyzed using the chi-square (X^2) test. The propofol requirements for LOC, the BIS values at LOC, the time to LOC, and the patients' characteristics (age, height, and weight) were analyzed using analysis of variance (ANOVA) and LSD multiple comparisons. Statistical significance was defined as a *P* value of less than 0.05.

Results

The trial was conducted from June 16, 2016 to August 17, 2016 at the General Hospital of Ningxia Medical University. A total of 73 patients were ultimately enrolled. Twenty-four patients were randomly assigned to the control group, 24 patients received 0.5 µg·kg^{-1} DEX, and 25 patients received 1.0 µg·kg^{-1} DEX (Fig. 1). The

Gu *et al. BMC Anesthesiology*   (2020) 20:96
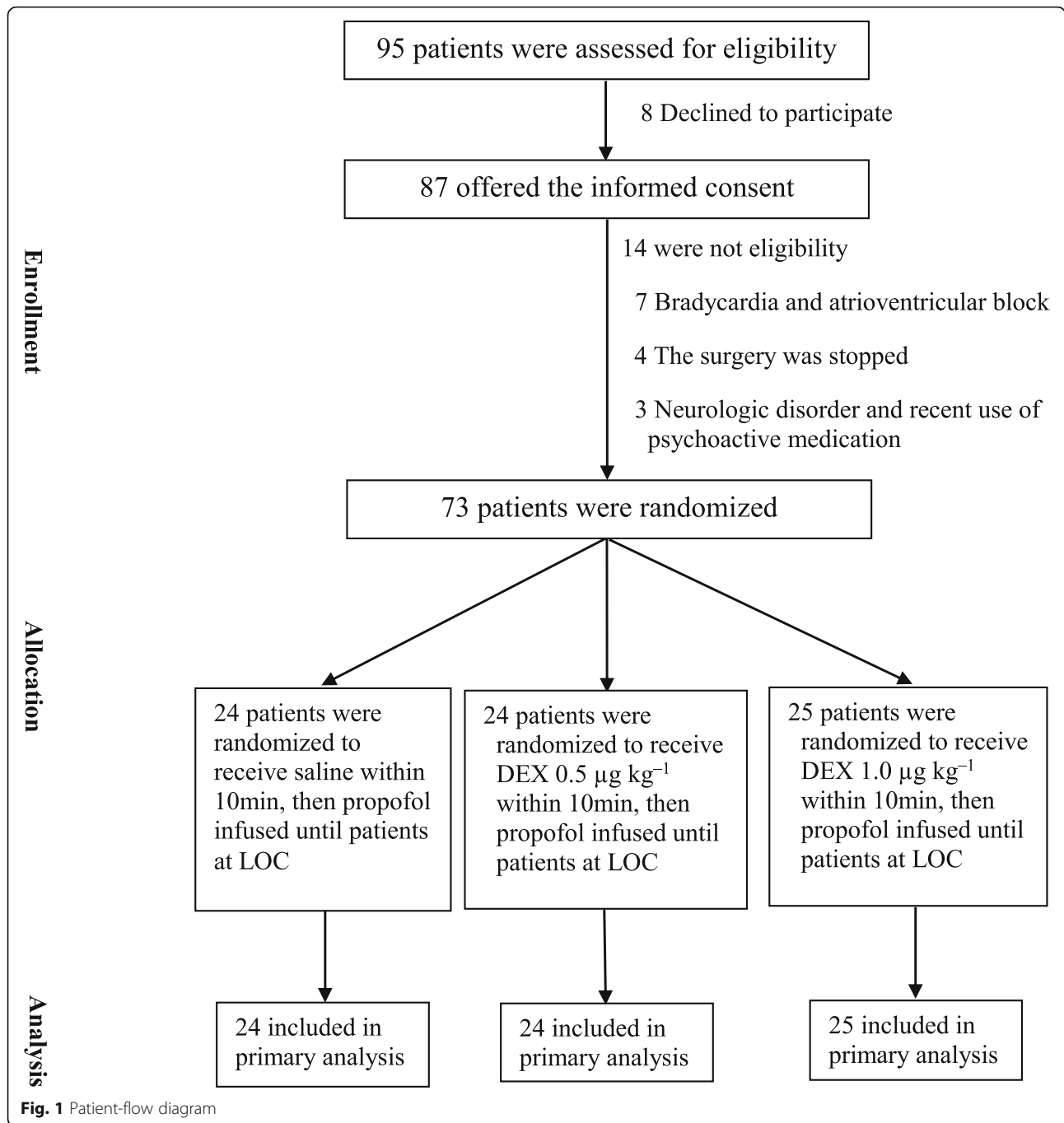
Page 4 of 7

Fig. 1 Patient-flow diagram

Table 1 Patient characteristics and preoperative data before receiving drugs in the operating room

	Control group (n = 24)	0.5 µg·kg^{-1} DEX group (n = 24)	1.0 µg·kg^{-1} DEX group(n = 25)	P
Weight (kg)	62.5 ± 9.0	61.0 ± 9.8	62.2 ± 9.0	0.805
Height (cm)	166.9 ± 6.9	166.3 ± 7.4	166.9 ± 6.4	0.932
Age (yr)	40.9 ± 7.4	40.0 ± 11.4	42.9 ± 11.8	0.748
Sex (female)	13 (54.1%)	12 (50.0%)	12 (48.0%)	0.912
BIS	96.7 ± 1.4	96.3 ± 1.6	97.0 ± 1.7	0.095

Data are presented as the means ± SD or numbers (%). Statistical significance was defined as $P < 0.05$

Gu *et al. BMC Anesthesiology*   (2020) 20:96

Page 5 of 7

primary analysis was intention-to-treat (ITT) and in-volved all patients who were randomly assigned. The loading dose of DEX was not fully administered to one patient because bradycardia occurred in the $1.0\,\mu g \cdot kg^{-1}$ DEX group. There were no significant differences among the baseline and preoperative data (Table 1).

The propofol requirements for LOC decreased signifi-cantly in the DEX groups compared with the control group (ANOVA and LSD multiple comparisons, $1.12 \pm 0.33\,mg \cdot kg^{-1}$ for the $0.5\,\mu g \cdot kg^{-1}$ DEX group vs. $1.79 \pm 0.39\,mg \cdot kg^{-1}$ for the control group; difference, 0.68 $mg \cdot kg^{-1}$ [95% CI, 0.49 to 0.87]; $P = 0.0001$) (0.77 ± 0.27 $mg \cdot kg^{-1}$ for the $1.0\,\mu g \cdot kg^{-1}$ DEX group vs. 1.79 ± 0.39 $mg \cdot kg^{-1}$ for the control group; difference, $1.02\,mg \cdot kg^{-1}$ [95% CI, 0.84 to 1.21]; $P = 0.0001$), and the propofol re-quirements for LOC was lower in the $1.0\,\mu g \cdot kg^{-1}$ DEX group than that in the $0.5\,\mu g \cdot kg^{-1}$ DEX group (ANOVA and LSD multiple comparisons, $0.77 \pm 0.27\,mg \cdot kg^{-1}$ vs. $1.12 \pm 0.33\,mg \cdot kg^{-1}$; difference, $0.34\,mg \cdot kg^{-1}$ [95% CI, 0.16 to 0.54]; $P = 0.0001$). At the time of LOC, the BIS value was higher in the DEX groups compared with the control group (ANOVA and LSD multiple comparisons, 67.5 ± 3.5 for the DEX $0.5\,\mu g \cdot kg^{-1}$ group vs. 60.5 ± 3.8 for the control group; difference, 7.04 [95% CI, 4.85 to 9.23]; $P = 0.0001$) (68.0 ± 4.1 for the $1.0\,\mu g \cdot kg^{-1}$ DEX group vs. 60.5 ± 3.8 for the control group; difference, 7.58 [95% CI, 5.41 to 9.75]; $P = 0.0001$). However, there was no difference between the two DEX groups (ANOVA, LSD multiple comparisons, $P = 0.621$). The time to LOC induced by propofol in both the $0.5\,\mu g \cdot kg^{-1}$ and $1.0\,\mu g \cdot kg^{-1}$ DEX groups was significantly shorter than that in the control group (ANOVA and LSD mul-tiple comparisons, both $P = 0.0001$), and the time to LOC induced by propofol in the $1.0\,\mu g \cdot kg^{-1}$ DEX group was significantly shorter than that in the $0.5\,\mu g \cdot kg^{-1}$ DEX group (ANOVA and LSD multiple comparisons, $P = 0.0001$) (Tables 2 and 3). No patients in any of the groups developed hypoxia ($SpO_2 < 90\%$), hypotension or abnormal movements during the study period.

Discussion

In this study, we administered a loading dose of DEX be-fore the infusion of propofol for anesthesia induction. The propofol requirements for LOC and the BIS value at LOC were measured. Our study showed that DEX fa-cilitated LOC induced by propofol but increased the BIS value at LOC. The propofol requirements for LOC both decreased in the $0.5\,\mu g \cdot kg^{-1}$ and $1.0\,\mu g \cdot kg^{-1}$ DEX groups when compared with the control group. The result was similar to some early studies in which DEX was consid-ered to decrease the propofol dose during anesthesia [5, 17]. The results indicated that synergistic effect existed between propofol and DEX when they were co-used for sedation. Norepinephrine release in the preoptic area of hypothalamus decreased by DEX makes the disinhibition of the GABAergic and galanergic inhibitory projections to the major arousal nuclei in the midbrain and pons and decreased noradrenergic signaling by DEX acted at the thalamus and cortex both can induce sedation and LOC [18]. Propofol produces sedation by potentiating the activity of $GABA_A$ receptors and inhibiting the NMDA-mediated excitatory neurotransmission [19, 20]. Thus, LOC induced by DEX combined with propofol displays a synergistic effect.

In the study, both BIS and clinical evaluation were used to measure the sedative depth. BIS is generally con-sidered a reliable method to detect the level of sedation induced by some hypnotics, especially in propofol anesthesia. However, it had been reported that the BIS values can be influenced by different hypnotic drugs or their combinations [21, 22]. Our results showed the BIS value at LOC was higher when adding DEX to propofol than propofol administration alone. The former study demonstrated that the BIS values was less in DEX sed-ation than propofol sedation [22]. However, BIS values were higher at LOC when opioid combined with propo-fol [23]. One possible explanation is that the BIS value was dependent on the dose of propofol, and the BIS value is also larger when small dosage of propofol was administered. Other reasons may include that propofol mainly produces a delta to beta-frequency band in EEG [24], which was quite different from the delta, alpha, range activity induced by DEX [25]. What's more, the action site of DEX is different from that of propofol [18], which has been considered one factor that influences the BIS value. Furthermore, it should be noted that the BIS value has a time delay between 24 (7) and 122 (23) s [16, 26], which may influence the precision of the measure-ment of BIS values.

It is quite common that the circulatory and respiratory system were inhibited by propofol infusion. However, there were no episodes of hypotension or hypoxemia in

Table 2 ANOVA of the main results at LOC induced by propofol

	Control group(**n** = 24)	0.5 µg·kg^{-1} DEX group (**n** = 24)	1.0 µg·kg^{-1} DEX group (**n** = 25)	**P**
Propofol requirements (mg·kg^{-1})	1.79 ± 0.39	1.12 ± 0.33	0.77 ± 0.27	0.0001
BIS	60.5 ± 3.8	67.5 ± 3.5	68.0 ± 4.1	0.0001
Time to LOC (s)	309 ± 28	209 ± 53	131 ± 40	0.0001

Data are presented as the means ± SD. Statistical significance was defined as $P < 0.05$

Gu *et al. BMC Anesthesiology*　　　(2020) 20:96

Page 6 of 7

Table 3 LSD multiple comparison tests of the main results at LOC induced by propofol

	Propofol requirements (mg·kg^{-1})	BIS values	Time to LOC (s)
	Difference (95% CI) P	Difference (95% CI) P	Difference (95% CI) P
Control group vs. 0.5 µg· kg^{-1} DEX group	0.68 (0.49 to 0.87) 0.0001	−7.04 (− 9.23 to − 4.85) 0.0001	99.91 (76.20 to 123.63) 0.0001
Control group vs. 1.0 µg·kg^{-1} DEX group	1.02 (0.84 to 1.21) 0.0001	−7.58 (−9.75 to −5.41) 0.0001	177.56 (154.08 to 201.03) 0.0001
0.5 µg·kg^{-1} DEX group vs. 1.0 µg·kg^{-1} DEX group	0.34 (0.16 to 0.54) 0.0001	−0.54 (− 2.71 to1.63) 0.621	77.64 (54.17 to 101.12) 0.0001

Statistical significance was defined as $P < 0.05$

the control group, which might have been due to either the small dosages of propofol than the recommended dosage used in this study or the small number of participants in our study. During the infusion of DEX, one patient exhibited adverse events of severe bradycardia with an HR of 43 beats·min^{-1}. The reason for these events was most likely due to the sympatholytic effect of DEX, a common side effect of α_2-adrenergic agonists, especially administered with the infusion of loading doses of DEX. However, it could be easily prevented and treated after the administration of receptor-M antagonists. The patient was treated by 0.01 mg·kg^{-1} atropine, and then the patient's heart rate rose to over 50 beats·min^{-1} in a minute. Although the number of participants was small, the sample size was calculated by a statistical tool.

Conclusions

In conclusion, the pre-administration of 0.5 µg·kg^{-1} or 1.0 µg·kg^{-1} DEX could reduce the requirements of propofol for LOC. DEX pre-administration increased the BIS value at LOC induced by propofol.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12871-020-01013-x.

Additional file 1. Raw data on oxygen saturation (SpO$_2$), mean arterial pressure (MAP) and heart rate (HR).

Abbreviations

DEX: Dexmedetomidine; LOC: Loss of consciousness; BIS: Bispectral index; ASA: American society of anesthesiologists; BMI: Body mass index; MAP: Mean arterial pressure; HR: Heart rate; SpO$_2$: Peripheral oxygen saturation; ITT: intention-to-treat

Authors' contributions

Conceived and designed the experiments: YG, FY, JWZ, XC and HXM. Performed the experiments: YG, FY, TM and YHZ. Analyzed the data: FY, JWZ, JW, BL, HXM, and KML. Wrote the paper: YG, FY and HXM. All authors have read and approval the final manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the ethics committee of the General Hospital of Ningxia Medical University (2016167). A written informed consent form was obtained from all patients agreed to participate in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details
[1]Department of Anesthesiology, Ningxia Medical University, Yinchuan 750004, China. [2]Department of Anesthesiology, People's Hospital of Ningxia Hui Autonomous Region, Yinchuan 750002, China. [3]Department of Anesthesiology, General Hospital of Ningxia Medical University, Yinchuan 750004, China.

References

1. Wei L, Deng X, Sui J, Wang L, Liu J. Dexmedetomidine improves intubating conditions without muscle relaxants in children after induction with Propofol and Remifentanil. Anesth Analg. 2015;121(3):785–90.
2. Kakkar A, Tyagi A, Nabi N, Sethi AK, Verma UC. Comparision of clonidine and dexmedetomidine for attenuation of laryngoscopy and intubation response - a randomized controlled trial. J Clin Anesth. 2016;33:283–8.
3. Win NN, Kohase H, Yoshikawa F, Wakita R, Takahashi M, Kondo N, et al. Haemodynamic changes and heart rate variability during midazolam-propofol co-induction. Anaesthesia. 2007;62(6):561–8.
4. Upton RN, Martinez AM, Grant C. Comparison of the sedative properties of CNS 7056, midazolam, and propofol in sheep. Br J Anaesth. 2009;103(6): 848–57.
5. El-Shmaa NS, El-Baradey GF. The efficacy of labetalol vs dexmedetomidine for attenuation of hemodynamic stress response to laryngoscopy and endotracheal intubation. J Clin Anesth. 2016;31:267–73.
6. Weerink MAS, Struys MMRF, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical pharmacokinetics and pharmacodynamics of Dexmedetomidine. Clin Pharmacokinet. 2017;56(8):893–913.
7. Dutta A, Sethi N, Sood J, Panday BC, Gupta M, Choudhary P, et al. The effect of Dexmedetomidine on Propofol requirements during anesthesia administered by Bispectral index-guided closed-loop anesthesia delivery system: a randomized controlled study. Anesth Analg. 2019;129(1):84–91.
8. Le Guen M, Liu N, Tounou F, Augé M, Tuil O, Chazot T, et al. Dexmedetomidine reduces propofol and remifentanil requirements during bispectral index-guided closed-loop anesthesia: a double-blind, placebo-controlled trial. Anesth Analg. 2014;118(5):946–55.
9. Feld JM, Hoffman WE, Stechert MM, Hoffman IW, Ananda RC. Fentanyl or dexmedetomidine combined with desflurane for bariatric surgery. J Clin Anesth. 2006;18(1):24–8.
10. Punjasawadwong Y, Phongchiewboon A, Bunchungmongkol N. Bispectral index for improving anaesthetic delivery and postoperative recovery. Cochrane Database Syst Rev. 2014;6:CD003843.

11. Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. Anesthesiology. 1997;86(4): 836–47.

12. Ibrahim AE, Taraday JK, Kharasch ED. Bispectral index monitoring during sedation with sevoflurane, midazolam, and propofol. Anesthesiology. 2001; 95(5):1151–9.

13. Lysakowski C, Dumont L, Pellegrini M, Clergue F, Tassonyi E. Effects of fentanyl, alfentanil, remifentanil and sufentanil on loss of consciousness and bispectral index during propofol induction of anaesthesia. Br J Anaesth. 2001;86(4):523–7.

14. Shehabi Y, Howe BD, Bellomo R, Arabi YM, Bailey M, Bass FE, et al. Early sedation with Dexmedetomidine in critically ill patients. N Engl J Med. 2019; 380(26):2506–17.

15. Yu X, Franks NP, Wisden W. Sleep and sedative states induced by targeting the histamine and noradrenergic systems. Front Neural Circuits. 2018;12:4.

16. Musizza B, Ribaric S. Monitoring the depth of anaesthesia. Sensors (Basel). 2010;10(12):10896–935.

17. Ali AR, El Ghoneimy MN. Dexmedetomidine versus fentanyl as adjuvant to propofol: comparative study in children undergoing extracorporeal shock wave lithotripsy. Eur J Anaesthesiol. 2010;27(12):1058–64.

18. Brown EN, Pavone KJ, Naranjo M. Multimodal general anesthesia: theory and practice. Anesth Analg. 2018;127(5):1246–58.

19. Brotherton AL, Hamilton EP, Kloss HG, Hammond DA. Propofol for treatment of refractory alcohol withdrawal syndrome: a review of the literature. Pharmacotherapy. 2016;36(4):433–42.

20. Orser BA, Bertlik M, Wang LY, MacDonald JF. Inhibition by propofol (2,6 di-isopropylphenol) of the N-methyl-D-aspartate subtype of glutamate receptor in cultured hippocampal neurones. Br J Pharmacol. 1995;116(2): 1761–8.

21. de Valence T, Elia N, Czarnetzki C, Dumont L, Tramèr MR, Lysakowski C. Effect of sufentanil on bispectral index in the elderly. Anaesthesia. 2018; 73(2):216–22.

22. Kasuya Y, Govinda R, Rauch S, Mascha EJ, Sessler DI, Turan A. The correlation between bispectral index and observational sedation scale in volunteers sedated with dexmedetomidine and propofol. Anesth Analg. 2009;109(6): 1811–5.

23. Lysakowski, C. Effects of fentanyl, alfentanil, remifentanil and sufentanil on loss of consciousness and bispectral index during propofol induction of anaesthesia. Br J Anaesth.86(4):523–7.

24. Verdonck O, Reed SJ, Hall J, Gotman J, Plourde G. The sensory thalamus and cerebral motor cortex are affected concurrently during induction of anesthesia with propofol: a case series with intracranial electroencephalogram recordings. Can J Anaesth. 2014;61(3):254–62.

25. Sleigh JW, Vacas S, Flexman AM, Talke PO. Electroencephalographic arousal patterns under Dexmedetomidine sedation. Anesth Analg. 2018;127(4):951–9.

26. Zanner R, Pilge S, Kochs EF, Kreuzer M, Schneider G. Time delay of electroencephalogram index calculation: analysis of cerebral state, bispectral, and Narcotrend indices using perioperatively recorded electroencephalographic signals. Br J Anaesth. 2009;103(3):394–9.

Publisher's Note