

Effect of different doses of dexmedetomidine on median effective concentration of propofol for anesthesia induction: a randomized controlled trial

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Abstract. – OBJECTIVE: Dexmedetomidine, a highly selective α_2 -adrenergic receptor agonist with sedative and analgesic properties, is used as an anesthetic adjunct. We determined the effects of different dexmedetomidine doses on the median effective concentration (EC50) of propofol and bispectral index (BIS) values during anesthesia induction.

PATIENTS AND METHODS: This randomized, prospective, case-control clinical trial involved 120 patients (56 women; physical status, American Society of Anesthesiologists grades I or II) scheduled to undergo surgery requiring general anesthesia from July 15th, 2014 to June 15th, 2015. The patients were divided into groups of 30 and received dexmedetomidine (0.5 $\mu\text{g}/\text{kg}$, group L; 0.75 $\mu\text{g}/\text{kg}$, group M; 1 $\mu\text{g}/\text{kg}$, group H) with propofol for loss of consciousness or propofol only (control group, group C). EC50, BIS, hemodynamics, and side effects were assessed.

RESULTS: The EC50 of propofol was significantly lower in the dexmedetomidine groups than in group C, and decreased with increasing dexmedetomidine dose ($p < 0.05$). BIS values significantly decreased after 2 min of dexmedetomidine infusion in all dexmedetomidine groups; the values at 8 and 10 min were lower in the dexmedetomidine groups than in group C. The heart rate was lower in the dexmedetomidine groups than in group C. The incidence of bradycardia at loss of consciousness increased with increasing dexmedetomidine dose.

CONCLUSIONS: Dexmedetomidine significantly and dose-dependently reduced the EC50 of propofol and BIS values during anesthesia induction. A loading dexmedetomidine dose of 0.5 $\mu\text{g}/\text{kg}$ significantly reduced the EC50 of propofol and BIS value, and was associated with a lower incidence of bradycardia than higher doses.

Key Words:

Dexmedetomidine, Propofol, Median effective concentration, Bispectral index.

Introduction

Propofol is one of the most commonly used intravenous drugs to induce anesthesia. Propofol alone can be used to induce general anesthesia. However, when administered singly, the drug produces minimal and brief analgesia¹, and large doses are required to induce general anesthesia. Moreover, depending on the dose used, propofol can result in an excessive depth of sedation, which may be associated with clinically significant cardiovascular and pulmonary depression, or in insufficiently deep sedation, which may be associated with intraoperative recall^{2,3}. To overcome these drawbacks, sedatives and analgesics have been co-administered with propofol for the purpose of anesthesia induction. The co-induction of anesthesia with multiple drugs is typically planned by studying the potential interactions, particularly synergism, between the drugs to be used, mostly benzodiazepines, opioids, and propofol.

Dexmedetomidine⁴, a highly selective α_2 -adrenergic receptor agonist with sedative and analgesic properties, was approved by the US Food and Drug Administration in December 1999 for use as a short-term medication to provide less than 24 h of analgesia and sedation in the intensive care unit setting. The drug's unique

properties render it a useful adjunct for general and regional anesthesia and postoperative sedation and analgesia. Patients receiving dexmedetomidine can be effectively sedated but can also be easily aroused, a characteristic not observed with other drugs belonging to this class, e.g., clonidine. Premedication with dexmedetomidine can significantly reduce the propofol requirement for anesthesia induction^{5,6}. However, at high doses, dexmedetomidine can severely decrease heart rate, causing bradycardia⁷⁻¹¹. Its other side effects include hypotension, hypertension, decreased renin, and decreased secretions. The present research aimed to determine whether lower loading doses of dexmedetomidine were associated with a lower occurrence of bradycardia while still being sufficient to decrease the propofol requirement for anesthesia induction. We therefore compared the median effective concentration (EC50; i.e., the concentration at which loss of consciousness occurred in 50% of the patients) of propofol and the incidence of bradycardia between groups of patients who had received different dexmedetomidine doses.

Patients and Methods

Patient Selection and Ethical Approval

This randomized, prospective, case-control clinical trial was conducted at the Department of Anesthesia of the First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, P.R. China after obtaining approval from the hospital authority from July 15th, 2014 to June 15th, 2015. We enrolled 120 patients who were scheduled to undergo spine surgery requiring general anesthesia and whose physical status was classified as American Society of Anesthesiologists (ASA) grade I or II from July 15th, 2014 to June 15th, 2015 (Figure 1). All patients were required to be between 20 and 60 years of age and have a body mass index (BMI) of 18-30 kg/m². The exclusion criteria were as follows: (1) patients who refused to give consent; (2) patients with a physical status of ASA grade III or more; (3) patients who were allergic to an α_2 -adrenergic receptor agonist or to one of the anesthetic agents used in the study (propofol or lidocaine); (4) patients taking beta blockers and/or other sedatives; (5) patients with hearing impairment; and (6) patients with a heart rate of < 60 beats/min.

The study was approved by the Ethical Committee of the First Affiliated Hospital of

Zhengzhou University, Zhengzhou, Henan, P.R. China. Patient records/information was anonymized and de-identified prior to analysis.

Study Protocol

Patients were randomly divided into four groups of 30 patients each: control group (group C), low-dose group (group L), middle-dose group (group M), and high-dose group (group H). Patients in group C received only propofol for the loss of consciousness, while those in groups L, M, and H received dexmedetomidine at doses of 0.5, 0.75, and 1 μ g/kg, respectively, in addition to propofol for the loss of consciousness. Dexmedetomidine (100 μ g/mL) and propofol (10 mg/mL) were supplied by Jiangsu Hengrui Medicine Co. Ltd. (Jiangsu, China) in identical 2-mL ampules and AstraZeneca Corporation (London, England) in identical 50-mL ampules respectively.

The randomization was accomplished by using a computer-generated randomization table. Group allocation was concealed in sealed opaque envelopes that were numbered. A nurse who was not involved in any other sections of the study opened the envelopes sequentially after patient consent had been obtained and prepared the medications according to the orders.

In all patients, an intravenous line was placed in the upper arm upon the patients' arrival in the operating room, and an infusion of Ringer's lactate solution was started. The patients then underwent noninvasive monitoring of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), oxygen saturation and pulse rate (with a pulse oximeter), heart rate, electrocardiographic parameters, and the depth of sedation (with a bispectral index [BIS] monitor). Each patient's forehead was cleaned with 75% alcohol and allowed to dry. Then, BIS sensors were carefully placed over the forehead as follows: sensor #1, at the center of the forehead, approximately 5 cm above the bridge of the nose; sensor #4, directly above the eyebrows; sensor #2, at the midpoint between sensor #1 and sensor #4 and sensor #3, on the temple, between the corner of the eye and the hairline. Once placed, the sensors were connected to the BIS machine. The sensors were gently pressed against the forehead till all the leads were shown "pass" signal in the monitor. All patients were given supplementary oxygen at a rate of 4-5 l/min via a close-fitting mask. Propofol can cause severe pain at the site of injection, so all patients were premedicated with lidocaine

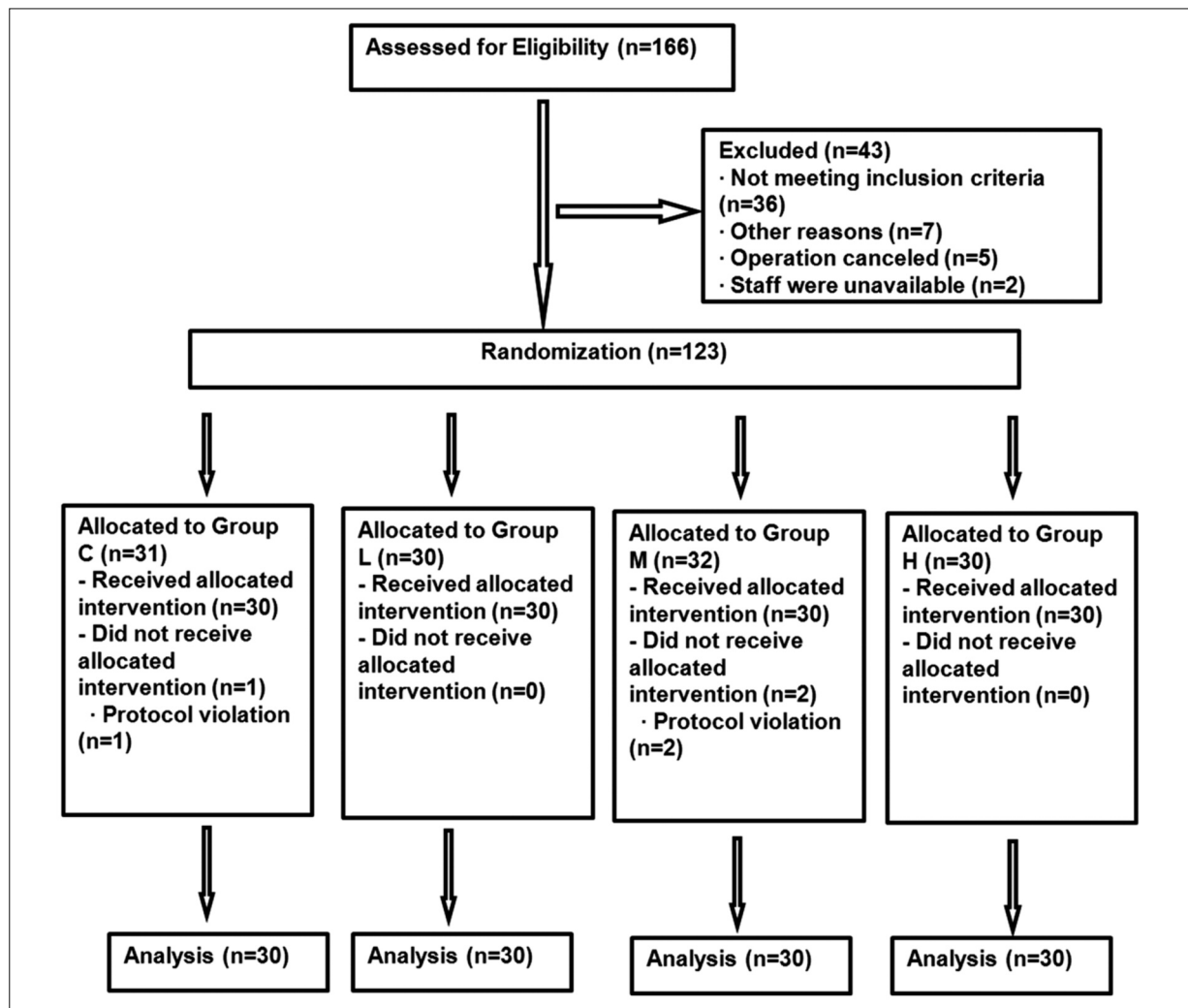


Figure 1. Participant flow diagram.

(0.6 mg/kg) with a tourniquet with arm down (venous engorgement)¹². Lidocaine is readily available in the operating room, and it has no effect on the sedative property of propofol¹³.

In group C, normal saline was loaded in a 50-ml syringe and infused for 10 min; then, propofol was administered to achieve the loss of consciousness. In all dexmedetomidine groups, dexmedetomidine was infused before the infusion of propofol. A single vial of dexmedetomidine contains 2 ml of a 100 $\mu\text{g/ml}$ solution. Dexmedetomidine was diluted in 0.9% sodium chloride solution prior to administration. To prepare the infusion, 48 ml of 0.9% sodium chloride injection was withdrawn into a 50-ml syringe. Then, 2 ml of dexmedetomidine was added, and the syringe was gently shaken to mix well. The final concentration of the 50 ml solution was 4 $\mu\text{g/ml}$. Dexmedetomidine was

infused at doses of 0.5, 0.75, and 1 $\mu\text{g/kg}$ in groups L, M, and H respectively within a period of 10 min via a syringe pump before the administration of propofol. In all groups, propofol was infused using a Diprifusor (Graseby 3500, Beijing Slog medical technology Co. Ltd., Beijing, China) target-controlled infusion (TCI) pump. The TCI pump for propofol used the Marsh et al pharmacokinetic model¹⁴. The Marsh variable set was selected for its accuracy and reliability, and is widely used in most commercially available TCI systems¹⁵. The target concentration of propofol was set at 3 $\mu\text{g/ml}$ in the first patient in each group. In subsequent patients, the Dixon modified up and down method was used to select target concentrations, with a step size of 0.5 $\mu\text{g/ml}$, depending on the response of the previous patient in the same group¹⁶.

Table I. Modified Observer's Assessment of Alertness/Sedation Scale.

Responsiveness	Score
Agitated	6
Responds readily to name spoken in normal tone (alert)	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to deep stimulus	0

The depth of sedation/alertness was assessed using the BIS and the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S; Table I).

A patient with an MOAA/S score of 2 or more was considered "responsive," i.e., they had no loss of consciousness. The next patient in the same group received 0.5 $\mu\text{g/ml}$ more propofol than the previous patient. At scores of 1 or less, patients were considered non-responsive, i.e., they had loss of consciousness. In such patients, immediate induction of anesthesia was performed according to the type of surgery. The next patient in the same group received 0.5 $\mu\text{g/ml}$ less propofol. In the case of responsive patients, the TCI of propofol was increased until the patient lost consciousness, and anesthesia was induced immediately thereafter according to the type of surgery. The EC50 of propofol was calculated using the mean of the median doses of all independent pairs of patients who manifested a crossover from "no loss of consciousness" to "loss of consciousness."

Measurements

Noninvasive evaluations of SBP, DBP, MAP, heart rate, BIS, blood oxygen saturation (SpO_2), and any side effects were performed at the baseline, after 2, 4, 6, 8, and 10 min (T_2 , T_4 , T_6 , T_8 , T_{10}) of dexmedetomidine infusion (normal saline infusion in the case of group C), and at loss of

consciousness (T_{LOC}). The effective concentration of propofol was recorded in all groups, and used to calculate the EC50. All episodes of pain, hypotension (SBP < 90 mmHg), hypertension (SBP > 140 mmHg), bradycardia (< 60 bpm), and respiratory depression were recorded.

Statistical Analysis

Data were recorded using Microsoft Excel 2007 and analyzed with various statistical tests using SPSS v20 (SPSS Inc., Chicago, IL, USA). Sex distribution and various side effects were analyzed using the chi-square (χ^2) test. Age distribution, BIS, EC50, and hemodynamic changes were analyzed using analysis of variance (ANOVA), a post hoc least significant difference test, and repeated-measures ANOVA, as appropriate. A p value of < 0.05 was considered to indicate significant differences.

Results

The study involved 120 patients (56 women and 64 men). The demographic characteristics of the patients have been shown in Table II. There were no statistically significant differences in age, BMI, or sex distribution among the four study groups.

There were no statistically significant differences in baseline BIS values among the groups (Table III). In the dexmedetomidine groups, the

Table II. Demographic data.

	Group C	Group L	Group M	Group H	p value
Age (yrs)*	40.43 \pm 10.75	44.73 \pm 8.67	40.83 \pm 10.72	41.16 \pm 10.48	0.36
Sex (M:F)	18:12	16:14	12:18	18:12	0.35
BMI (kg/m^2)*	23.31 \pm 2.62	24.69 \pm 2.96	23.92 \pm 2.82	24.59 \pm 1.99	0.15

Group C, propofol only; group L, 0.5 $\mu\text{g/ml}$ dexmedetomidine plus propofol; group M, 0.75 $\mu\text{g/ml}$ dexmedetomidine plus propofol; group H, 1 $\mu\text{g/ml}$ dexmedetomidine plus propofol. *Expressed as mean and SD.

Table III. BIS values.

	Group C	Group L	Group M	Group H
T0	97.06 ± 0.94	97.46 ± 0.50	97.20 ± 0.76	97.30 ± 0.70
T2	94.00 ± 3.63*	94.96 ± 3.74*	92.00 ± 6.05*	94.93 ± 2.91*
T4	93.03 ± 4.98*	93.43 ± 4.62*	91.90 ± 5.94*	93.40 ± 3.93*
T6	93.53 ± 3.60*	92.63 ± 4.81*	92.03 ± 5.20*	89.97 ± 6.58* ^{Δ□}
T8	94.13 ± 2.29*	90.83 ± 5.45* ^Δ	88.17 ± 6.88* ^Δ	87.80 ± 7.72* ^Δ
T10	94.40 ± 4.17*	88.03 ± 4.83* ^Δ	85.63 ± 6.81* ^Δ	85.10 ± 8.77* ^{Δ#}
TLOC	58.52 ± 4.80*	59.41 ± 3.50*	60.89 ± 5.16*	59.24 ± 3.95*

BIS, bispectral index; Tn, n minutes after dexmedetomidine infusion; TLOC, time point at loss of consciousness. * $p < 0.05$, compared to the baseline; ^Δ $p < 0.05$, compared to group C; [#] $p < 0.05$, compared to group L. Group C, propofol only; group L, 0.5 $\mu\text{g/ml}$ dexmedetomidine plus propofol; group M, 0.75 $\mu\text{g/ml}$ dexmedetomidine plus propofol; group H, 1 $\mu\text{g/ml}$ dexmedetomidine plus propofol.

BIS value was significantly lower after 2 min of dexmedetomidine infusion (T_2) than at the baseline. The BIS value at T_6 was significantly lower in group H than in group C ($p < 0.05$), and the BIS values at T_8 were significantly lower in all three dexmedetomidine groups than in group C ($p < 0.05$). At T_{10} , the BIS value was significantly lower in the dexmedetomidine groups than in group C, and was lower in group H than in group L. When the MOAA/S score was less than 2 (defined as loss of consciousness [T_{LOC}]), the BIS value was 58.52 ± 4.80 , 59.41 ± 3.50 , 60.89 ± 5.16 , and 59.24 ± 3.95 in groups C, L, M, and H, respectively.

The EC50 was determined by calculating the mean of the midpoint doses of all independent pairs of patients who manifested a crossover from “no loss of consciousness” to “loss of consciousness” in each group (Figure 2). The estimated EC50 of propofol was $2.47 \pm 0.51 \mu\text{g/ml}$ in group C, $1.7 \pm 0.25 \mu\text{g/ml}$ in group L, $1.36 \pm 0.29 \mu\text{g/ml}$ in group M, and $1.13 \pm 0.28 \mu\text{g/ml}$ in group H (mean \pm SD). The EC50 of propofol was significantly lower in the dexmedetomidine groups than in group C ($p < 0.05$). Moreover, there were significant differences in the EC50 of propofol among the dexmedetomidine groups (Figure 3).

There were no significant within-group differences in mean heart rate, SBP, DBP, and MAP at the baseline (Figure 4). In all four groups, the mean heart rate, SBP, DBP, and MAP were significantly lower at loss of consciousness than at the baseline ($p < 0.05$). In all three dexmedetomidine groups, the heart rate significantly decreased after 2 min of dexmedetomidine infusion. The heart rate at T_2 was significantly lower in group L than in group C ($p < 0.05$), and that at

T_4 was significantly lower in groups M and H than in group C ($p < 0.05$). In group L, mean SBP decreased from T_2 onward, mean DBP increased at T_2 and T_4 , and mean MAP increased at T_2 and then decreased, in comparison to the baseline. In group H, mean SBP, DBP, and MAP all increased at T_2 and T_4 and, then, decreased in comparison to the baseline. However, in group M, mean SBP, DBP, and MAP all decreased from T_2 onward.

Bradycardia occurred in 3 (10%), 9 (30%), 17 (56.66%), and 19 (63.33%) patients in groups C, L, M, and H, respectively. The occurrence of bradycardia significantly differed among the four groups (Figure 5). No other adverse effects were observed. Three patients in group C, 1 patient each in groups L and M, and none of the patients in group H complained of injection-related pain.

Discussion

This study was designed to compare the effects of different doses of dexmedetomidine on the EC50 of propofol during the induction of general anesthesia. Propofol has many of the properties of the ideal intravenous agent, namely, rapid onset of action, short duration of clinical effect, rapid clearance, minimal tendency for accumulation, and minimal side effects¹⁷. Although it is considered to have no analgesic property, Bandschapp et al¹ have reported that it shows short-lasting analgesic properties during its administration. They found that it significantly decreased pain scores and areas of hyperalgesia and allodynia compared with the combination of 10% intralipid solution and saline¹. However, the injection of propofol itself can cause pain, which is

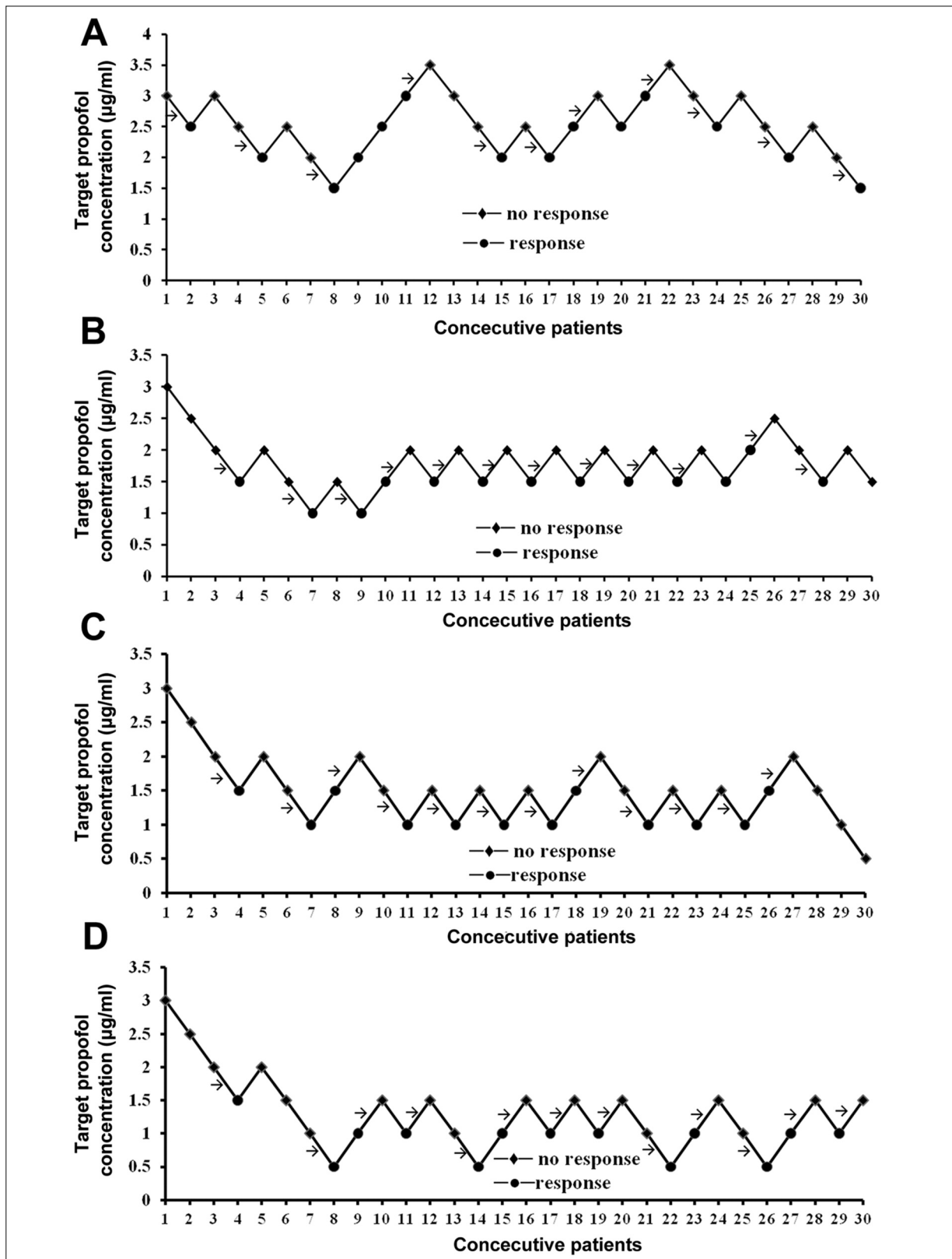


Figure 2. Target propofol concentration in group C (a), group L (b), group M (c), and group H (d). The responses shown were determined using the modified Dixon up and down method. Arrows indicate the midpoint doses of all independent pairs of patients who manifested a crossover from “no loss of consciousness” to “loss of consciousness”.

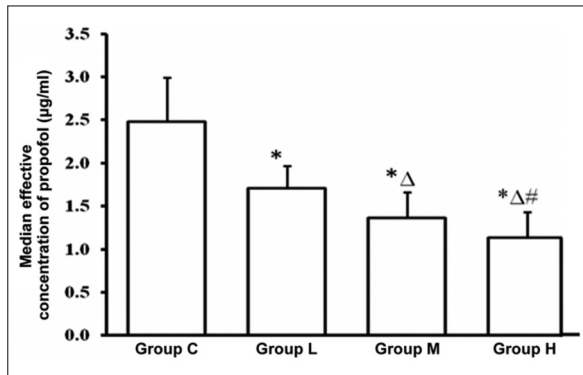


Figure 3. EC50 of propofol in groups C, L, M, and H * $p < 0.05$, compared with group C; $^{\Delta}p < 0.05$, compared with group L; $^{\#}p < 0.05$, compared with group M.

more severe when the injection is performed with a TCI system. In our study, we used lidocaine to reduce propofol injection-induced pain. Pretreatment with lidocaine in conjunction with venous occlusion is efficacious in reducing propofol injection-induced pain¹². In our study, 3 patients in group C, 1 patient each in groups L and M, and none of the patients in group H complained of injection-related pain. This result suggests that dexmedetomidine had some effect in reducing injection-related pain. Sarkilar et al¹⁸ studied the effect of dexmedetomidine on pain caused by the injection of propofol and found that compared to a placebo, dexmedetomidine decreased propofol injection-induced pain.

Many drugs have been used as premedications to reduce the dose and side effects of propofol, such as midazolam, fentanyl, remifentanyl, and sufentanil. In this study, we used dexmedetomidine, a highly selective α_2 -adrenergic receptor agonist with sedative, analgesic, and sympatholytic properties^{7,19,20}. This drug has been widely studied as an anesthetic adjuvant, and its anesthetic-sparing effect is well known²¹⁻²⁴. It can lower blood pressure and heart rate, and has minimal effects on respiratory drive. It also has cardioprotective, neuroprotective, renoprotective, and anti-inflammatory properties. It is more hemodynamically stable and a more potent anesthetic adjuvant than midazolam in patients undergoing off-pump coronary artery bypass surgery²⁵.

In this work, the EC50 of propofol was significantly lower in the dexmedetomidine groups than in the control group (31.17%, 44.93%, and 54.25% less in groups L, M, and H, respectively, as compared to that in group C), which is consistent with the result reported

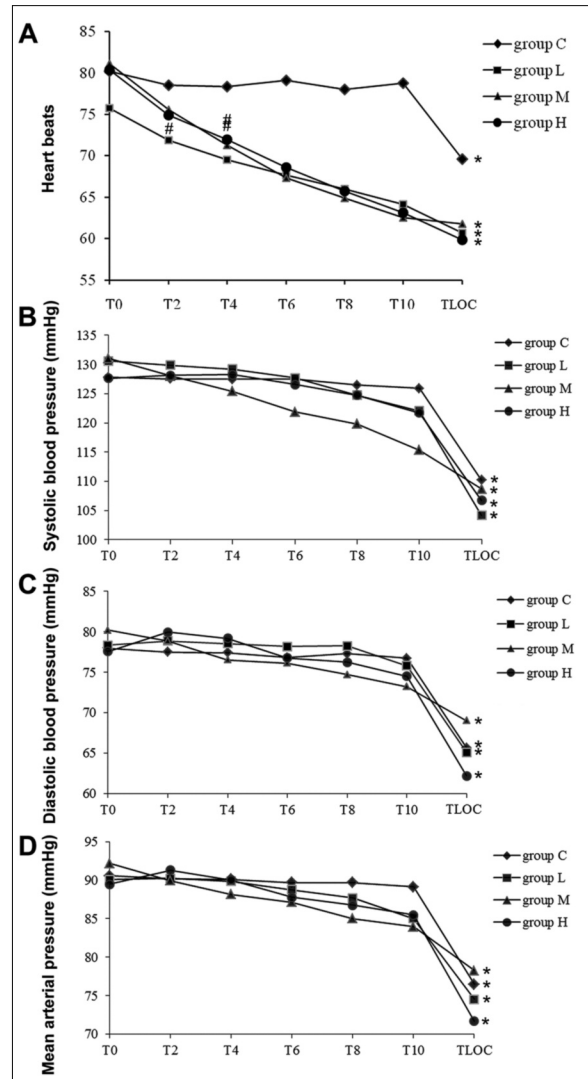


Figure 4. Changes in heart rate (a), systolic blood pressure (b), diastolic blood pressure (c), and mean arterial pressure (d) in the study groups from the baseline (T0) till loss of consciousness (TLOC). * $p < 0.05$, compared with baseline; $^{\#}p < 0.05$, compared with group C.

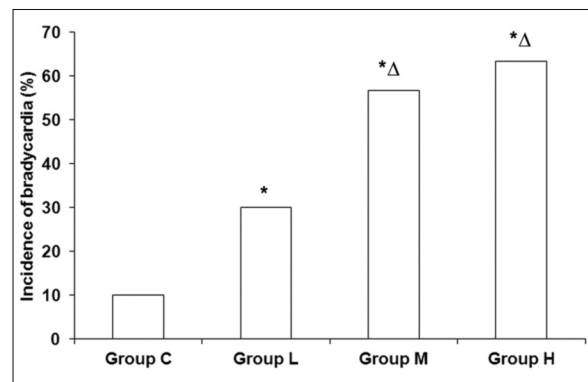


Figure 5. Prevalence of bradycardia of four groups. * $p < 0.05$, compared with group C; $^{\Delta}p < 0.05$, compared with group

in a similar study conducted by Dutta, S²⁶. In group C, only propofol was used for inducing loss of consciousness; the drug was injected with a TCI system, and the EC50 was found to be $2.47 \pm 0.51 \mu\text{g/ml}$. We enrolled only young and middle-aged patients in this study, as variations in age can affect the EC50 of propofol. In a similar study on elderly patients conducted by Qiu et al²⁷, the EC50 of propofol was $1.31 \mu\text{g/ml}$.

In addition to its beneficial α_2 -adrenergic receptor agonist property, dexmedetomidine has also been reported to increase the risk of hypotension and bradycardia. Many studies^{9-11,24,28} have assessed different maintenance doses of dexmedetomidine ($0.1-10 \mu\text{g/kg/h}$), but few have investigated variations in the loading dose. Most studies^{6,11,29-31} have used $1 \mu\text{g/kg}$ as a loading dose. Higher doses of dexmedetomidine are associated with bradycardia and hypotension. These effects have most often been seen in young volunteers on rapid bolus administration^{19,24}. Rapid bolus intravenous administration of dexmedetomidine results in a transient but significant increase in systemic and pulmonary pressure and a decrease in HR. Furthermore, the increase in diastolic pressure is greater than that in systolic pressure. These transient increases are more pronounced in the systemic system than in the pulmonary system³². In our study, the loading dose of dexmedetomidine was injected over a period of 10 min. In all groups, there was a significant decrease in heart rate and blood pressure at loss of consciousness as compared to the baseline. Heart rate significantly decreased after 2 min of dexmedetomidine infusion in all dexmedetomidine groups, and was lower than that in group C at the same time point. The occurrence of bradycardia increased with increasing dexmedetomidine dose. Also there was transient increase in DBP and MAP but not in SBP compared to baseline for dexmedetomidine group which is similar to study conducted by Lee et al³³. The initial increase in blood pressure after a large bolus dose can be caused by an immediate peripherally induced vasoconstriction due to high plasma dexmedetomidine concentrations that is soon reversed by the centrally mediated sympatholytic effect resulting in decreased blood pressure.

We used the BIS and the MOAA/S score to measure the depth of sedation. Sedation and analgesia include states of consciousness ranging from minimal sedation (anxiolysis) to gen-

eral anesthesia. Several sedation scales and scoring systems have been developed to describe the level of consciousness³⁴. The MOAA/S is currently the most commonly used observational sedation scale in clinical research. However, MOAA/S scores are not interchangeable with the ASA definitions of the levels of sedation, as the former do not take into account cardiorespiratory status and are subject to inter-rater variations as to which MOAA/S scores constitute moderate or deep sedation. The uniform assessment of sedation/alertness and subsequent assignment of a sedation scale score are crucial to ensure an accurate evaluation of the depth of sedation.

In 1994, the BIS was introduced by Aspect Medical Systems to objectively evaluate the depth of sedation. The BIS monitor assesses the level of consciousness by an algorithmic analysis of the patient's electroencephalographic data during general anesthesia³⁵. The BIS monitor has been used to titrate the doses of many anesthetic and sedative drugs, and its use is thought to reduce the prevalence of intraoperative awareness during surgery. Kasuya et al³⁶ assessed the correlation between BIS and observational sedation scale scores in volunteers sedated with dexmedetomidine and propofol, and found that the combination of BIS and sedation scale scores could provide different and complementary data than would either tool alone, especially when dexmedetomidine is used. Other studies^{37,38} have reported that BIS correlates well with MOAA/S scores. In this report, the mean BIS value at the end of the loading dose was 9.67%, 11.9%, and 12.53% less than the baseline value in groups L, M, and H, respectively. Thus, the BIS value decreased with increasing dexmedetomidine dose. From this, we concluded that dexmedetomidine produces a dose-dependent increase in the depth of sedation, as calculated using BIS. However, although the BIS value significantly decreased as compared to the baseline, the MOAA/S scores did not fall below 3 in all patients. The loading dose of dexmedetomidine caused sedation but could not induce loss of consciousness, even at a dose of $1 \mu\text{g/kg}$.

Our investigation has certain limitations. First, we did not calculate the plasma propofol concentration, and so it is possible that the values used in this study could be an underestimation of the actual plasma concentration. Wietasch et al³⁹ reported that the use of TCI pumps with the Marsh et al model underestimates plasma propofol con-

centrations during the induction and maintenance of anesthesia. Second, the study was carried out on young and middle-aged patients with ASA grades I and II. Patients with more severe systemic diseases may require smaller doses.

Conclusions

Dexmedetomidine was well tolerated, as no serious side effects or any adverse reaction occurred in the present study. Dexmedetomidine can significantly decrease the EC₅₀ of propofol and the BIS value in a dose-dependent manner during the induction of anesthesia. The prevalence of bradycardia is significantly lower with a loading dexmedetomidine dose of 0.5 µg/kg than with loading doses of 1 or 0.75 µg/kg.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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