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Addition of epinephrine to intrathecal tetracaine augments depression of the bispectral index during intraoperative propofol sedation

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Abstract
Purpose. Epinephrine added to local anesthetic agents for spinal anesthesia is frequently used to prolong the duration of anesthesia. Epinephrine stimulates the α-adrenoceptor, and it is known that the α2-adrenoceptor agonists have a central inhibitory effect. We investigated the effect of intrathecal epinephrine during propofol sedation with spinal anesthesia, using a bispectral index (BIS) monitor.
Methods. Twenty adult patients, scheduled for spinal anesthesia, were allocated to the control group (n = 10) or epinephrine group (n = 10). Patients in the control group received 14 mg of tetracaine, whereas the epinephrine group received 14 mg of tetracaine and 0.2 mg of epinephrine. Immediately after the pinprick test, propofol was administered at 0.5 mg·kg^{-1} by infusion for the initial dose, then continuously at 2 mg·kg^{-1}·h^{-1} in both groups. BIS scores were recorded before subarachnoid block, and then every 5 min for 90 min after subarachnoid block.
Results. There were significant differences in the BIS score between the two groups at 45–55 min and at 60–70 min after subarachnoid block.
Conclusion. Intrathecal epinephrine augments the sedative effect of propofol during spinal anesthesia.

Key words Epinephrine · Bispectral index · Spinal anesthesia · Propofol

Introduction

Central neuraxial anesthesia has been reported to decrease the dose of anesthetics needed to reach a defined level of sedation, while having a sedative effect of its own [1–3]. Tverskoy et al. [2] reported that subarachnoid blockade decreased the hypnotic requirements of sedative drugs. Epinephrine has been added to local anesthetic agents used for spinal anesthesia to prolong the duration of anesthesia [4–7]. Epinephrine stimulates α-adrenoceptors in the decending pathways of the spinal cord, which then inhibit the transmission of pain signals [8,9], and it is known that α2-adrenoceptor agonists have a central inhibitory effect [10–12]. Although spinal anesthesia with epinephrine has been employed for many years, few clinical studies have been conducted to investigate its effect on sedation.

In the present study, we investigated the effect of epinephrine during propofol sedation with spinal anesthesia. The bispectral index (BIS) has been shown to be simple and sensitive for assessing the level of consciousness during propofol sedation [13–15]. It was reported that spinal anesthesia was accompanied by sedation at 60–80 min [3]. Therefore, we tested the hypotheses that levels of sedation, quantified with the BIS, during spinal anesthesia and propofol infusion would be lower when epinephrine was added to the intrathecally administered solution, and that this effect would be time-dependent.

Subjects and methods

Following local Ethics Committee approval and informed consent, 20 adults, American Society of Anesthesiologists (ASA) class 1 or 2 scheduled for spinal anesthesia, were enrolled in this study. Patients were undergoing urological, orthopedic, or vascular surgery. Patients were allocated randomly to the control group (n = 10) or epinephrine group (n = 10), and no premedication was given. All patients were monitored with an electrocardiograph, non-invasive blood pressure monitor, pulse oximetry, bladder temperature, and a bispectral index (BIS) monitor (A-1050) ver. 3.4; (Aspect Medical Systems, Natick, MA, USA). All patients

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received 14 mg of tetracaine in 2.8 ml of 10% glucose solution. Patients in the control group received the hyperbaric tetracaine solution. For patients in the epinephrine group, 0.2 ml of 0.1% epinephrine was carefully drawn up into a 1-ml tuberculine syringe, added to the hyperbaric tetracaine solution and mixed thoroughly before injection. Subarachnoid block was performed with the patient in the lateral decubitus position, with the use of a 25-G Quincke needle (SPINOCAN, B. Braun, Melsungen AG, Melsungen, Germany) at the L 2–3 or L 3–4 intervertebral space. A total of 0.2 ml cerebrospinal fluid was aspirated into the syringe containing the local anesthetic before the solution was injected. The hyperbaric tetracaine solution with or without epinephrine was then injected at a rate of 0.5 ml·s^{-1}. The patient was immediately turned to the supine position. The operating table was sloped to extend the blocking height to Th 5 level. Sensory level was assessed by pin-prick, using an 18-G needle, 10 min after injection and at the end of operation. Immediately after the pinprick test, propofol was administered at 0.5 mg·kg^{-1} by infusion for the initial dose, then continuously at 2 mg·kg^{-1}·h^{-1} in both groups. BIS measurement was begun before administration of the hyperbaric tetracaine solution with or without epinephrine, and was recorded every 5 min for 90 min during maintenance. The anesthetist who recorded the BIS monitor details was blinded regarding the presence or absence of epinephrine.

Five hundred ml of acetate Ringer's solution was infused intravenously before the spinal anesthesia injection. Intraoperatively, 5 ml·kg^{-1}·h^{-1} of acetate Ringer's solution was infused. Heart rate and blood pressure were recorded every 5 min. Atropine was administered in increments of 0.3–0.5 mg when the heart rate decreased below 60 beats·min^{-1} or decreased by greater than 25% from the baseline. Ephedrine was administered in increments of 5 mg when systolic blood pressure decreased below 90 mmHg or decreased by greater than 25% from the baseline. Blood pressure and heart rate were measured with the Sola 7000 (Marquet Electronics, Madison, WI, USA). BIS score was measured with the BIS monitor A-1050 ver. 3.4 (Aspect Medical Systems).

Statistical analysis was performed using Statview ver. 5.0 (Abacus Concepts, Berkeley, CA, USA). Values are shown as means ± SD. Demographic data of the patients were compared by unpaired *t*-tests. The BIS values from 15 to 85 min after subarachnoid block were analyzed by averaging the three successive values (i.e., divided into 5 blocks, 15–25 min, 30–40 min, 45–55 min, 60–70 min, and 75–85 min) for each group. Then, a two-factor (presence or absence of epinephrine × time after subarachnoid block) repeated measures analysis of variance was performed. The BIS values at the same time epoch were compared between the groups by unpaired *t*-tests. Because there were five epochs, the statistical significance for these post-hoc tests was judged at P values of less than 0.01 (= 0.05/5). For other tests, $P < 0.05$ indicated statistical significance.

Results

Patients in the two groups were similar with respect to sex, mean age , body weight, height, duration of surgery and anesthesia, blocking height, and the number of patients who needed atropine and ephedrine (Table 1). The type of surgical procedure, blood pressure, heart rate, and bladder temperature, and the total dose of propofol during the BIS monitoring were not different between the two groups.

There were significant differences between the two groups in the presence or absence of epinephrine ($P = 0.0356$; $F = 5.158$), in the time after subarachnoid block ($P < 0.0001$; $F = 10.786$), and in the presence or absence of epinephrine × time after subarachnoid block ($P = 0.0325$; $F = 2.402$).

There were significant differences in the BIS score between the two groups at 45–55 min and 60–70 min after subarachnoid block (Fig. 1; $P < 0.01$).

Table 1. Patient data

	Control group	Epinephrine group
No. of patients (male/female)	10 (5/5)	10 (5/5)
Age (years)	48.7 ± 11.6	50.7 ± 20.1
Weight (kg)	65.9 ± 17.8	58.3 ± 8.6
Height (cm)	165.2 ± 10.7	160.8 ± 8.2
Operation time (min)	83.2 ± 45.9	94.0 ± 54.7
Anesthesia time (min)	127.0 ± 51.6	117.7 ± 56.1
Blocking height (Th) at 10 min after injection	5.3 ± 1.8	4.9 ± 1.4
Blocking height (Th) at the end of operation	8.3 ± 2.8	8.1 ± 2.5
Total dose of propofol during the study (mg)	207 ± 17	182 ± 27
No. of patients who needed atropine, ephedrine	3, 3	2, 4

Values are shown as means ± SD
There were no significant differences between the two groups

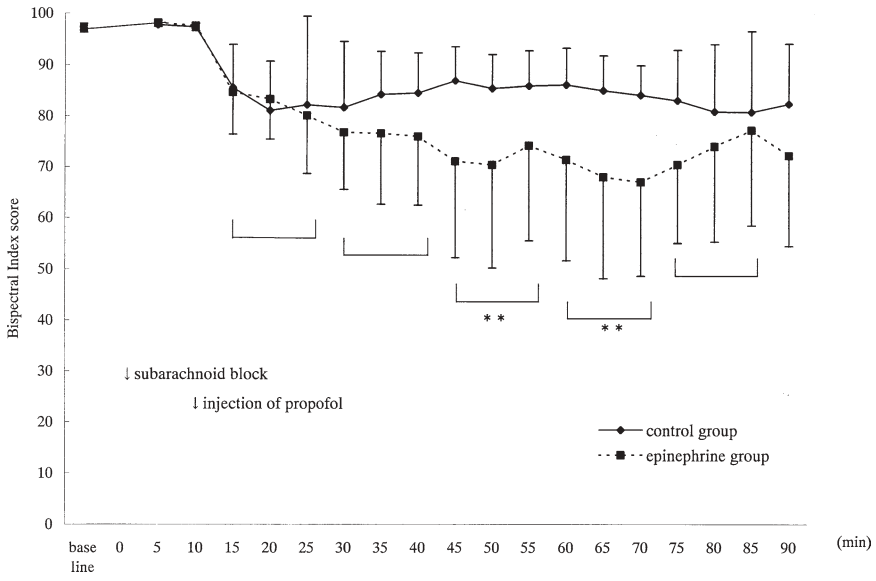

Fig. 1. Differences in the Bispectral Index score between the groups. ** $P < 0.01$ vs control group. Values are shown as means ± SD

Discussion

Subarachnoid block has a sedative effect of its own [3]. Pollock et al. [3] reported that spinal anesthesia was accompanied by sedation at 60–80 min. We also observed the lowest bispectral index (BIS) score near 60–70 min in the epinephrine group. There are several theories for the cause of the sedative effect of neuraxial anesthesia. These include the increased systemic level of local anesthetics, rostral spread of the local anesthetic with direct action on the brain, and interruption of spinal afferent input with a decrease in stimulation to the reticular activating system and a resultant hypnotic effect.

Although epinephrine has been employed for many years, few clinical studies have been conducted to investigate its effect on sedation. Epinephrine produces vasoconstriction, potentially decreasing vascular absorption of the local anesthetic and increasing the concentration of local anesthetic in the spinal cord, and epinephrine also stimulates the α2-adrenoceptor in the descending pathways of the spinal cord, which inhibits the transmission of pain signals [4–7]. Possibly through these mechanisms, epinephrine improves the quality of subarachnoid block. So far as sedation during spinal anesthesia is caused by the interruption of spinal afferents to the reticular activating system, it is conceivable that intrathecal epinephrine augments the sedative effects of spinal anesthesia by making the block "denser" [16,17]. Also, it is known that α2-adrenoceptor agonists have a central inhibitory effect and cause sedation [10–12].

Epinephrine is an α1, α2, and β agonist. α1 Stimulation has been shown to increase alertness, opposing the α2 effect. Actually, two investigations have reported an effect opposite to our fundings. Given intravenously [18] and epidurally [19], epinephrine reduced the incidence and level of sedation. But, epinephrine given intravenously causes a rise in blood pressure and may change the clearance of propofol. In the study by Armstrong et al. [19], an opioid was also given epidurally, so the systemic concentration of the opioid may have caused sedation.

Deep sedation may cause systemic side effects, e.g., airway obstruction, hypotension, etc. Propofol has often been used for sedation during surgery. We observed a significant depression of the BIS score with intrathecal epinephrine during spinal anesthesia and propofol sedation. BIS has been shown to be simple and sensitive for assessing the level of consciousness during propofol sedation [13–15]. We determined the amount of epinephrine and propofol from past studies [4–7].

The addition of epinephrine together with local anesthetics for spinal anesthesia may increase the sedative effect of propofol. The sedative drug should be used more carefully when epinephrine is used in spinal anesthesia. And, during that anesthesia, we should be especially careful at 45 min or more after the induction of the subarachnoid block.

In conclusion, addition of epinephrine to intrathecal tetracaine augments the depression of the bispectral index during intraoperative propofol sedation, and this effect is most evident 45 min or more after the placement of the subarachnoid block.

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