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SHORT COMMUNICATION

Pentazocine increases bispectral index without surgical stimulation during nitrous oxide–sevoflurane anesthesia

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Abstract Although there have been a large number of reports on the effects of opioids on the bispectral index (BIS) during anesthesia, the effects of pentazocine on the BIS have not been reported. In this study, 60 patients scheduled for elective oral surgery [30 females, 30 males; all American Society of Anesthesiologists Physical Status (ASA PS) category 1] were enrolled in the trials. Maintaining gender parity, we randomly assigned the patients to one of three groups: pentazocine group (0.3 mg/kg; $n = 20$), fentanyl group (1 μg/kg; $n = 20$), or saline group ($n = 20$); these opioids were administered intravenously 15 min after the intubation. Anesthesia was induced with thiopental and vecuronium bromide and maintained with nitrous oxide (4 l/min)–oxygen (2 l/min)–sevoflurane (1%). At 15 min after the intubation, mean arterial blood pressure (MAP), heart rate (HR), and BIS index were recorded as baseline values. MAP, HR, and BIS values were measured at 2.5-min after the intubation up to 30 min. All data were expressed as the mean ± standard deviation. Differences in BIS values, MAP, and HR among the three groups throughout the experiment were analyzed using two-way repeated-measures analysis of variance (ANOVA), and demographic data among the three groups were analyzed using one-way ANOVA. Post hoc comparisons were performed using Fisher's protected least significant difference test. A P value of <0.05 was considered to indicate statistically significance. MAP and HR showed no significant differences among the three groups during the study. BIS values significantly increased between 5 and 15 min after the intubation relative to the baseline value in the pentazocine group ($P < 0.001$), and BIS values in this group were significantly during this time period than those in the fentanyl and saline group ($P < 0.001$). BIS values were not significantly different between the fentanyl group and saline group. These results indicated that pentazocine, but not fentanyl, under nitrous oxide–sevoflurane anesthesia caused a statistically significant increase in BIS in our patients.

Keywords Pentazocine · Fentanyl · Bispectral index

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Many investigators have reported that opioids produce minimal changes in bispectral index (BIS) values in the absence of painful stimulation [1, 2] but that the addition of opioids to anesthetics does affect BIS values when a painful stimulus is applied. However, despite the large number of published reports on the effects of mu opioids, such as fentanyl and remifentanil, on the BIS during general anesthesia [1, 2], no comparative studies on pentazocine, a kappa agonist, versus fentanyl, a mu agonist, on the BIS values have been reported. Consequently, we have compared the effect of pentazocine and fentanyl on BIS values during nitrous oxide–sevoflurane anesthesia without surgical stimulation.

The study was designed and performed as a prospective, randomized, double-blinded, controlled clinical trial.

Table 1 Patient demographics

Demographics	Saline group ($n = 20$)	Pentazocine group ($n = 20$)	Fentanyl group ($n = 20$)	P values
Gender (female/male)	10/10	10/10	10/10	1.000
Age (year)	38.0 ± 17.4	38.3 ± 13.7	41.1 ± 17.3	0.847
Weight (kg)	58.6 ± 9.8	56.5 ± 9.2	53.6 ± 8.8	0.389
Height (cm)	166.6 ± 8.0	164.9 ± 9.5	160.0 ± 9.1	0.079
Body mass index	20.8 ± 2.7	20.6 ± 2.7	21.0 ± 3.3	0.874
Rectal temperature (°C)	36.7 ± 0.4	36.9 ± 0.4	36.7 ± 0.4	0.300
Expired CO_2 pressure (mmHg)	29.6 ± 2.8	29.9 ± 1.9	29.5 ± 2.8	0.467
Expired sevoflurane (%)	0.90 ± 0.05	0.92 ± 0.04	0.93 ± 0.04	0.171
Expired nitrous oxide (%)	63.4 ± 1.6	62.7 ± 2.3	63.0 ± 2.0	0.482

Data are presented as the mean ± standard deviation, or as actual numbers, where appropriate

P values are derived from analysis variance for continuous variable and chi-square for dichotomous variables after the comparison of all three groups

Approval was obtained from the ethics committee of our institution, and written informed consent was obtained from all patients. Patients with known disorders were excluded from the study. Thirty female and 30 male patients, all American Society of Anesthesiologists Physical Status (ASA PS) category 1, scheduled for elective oral surgery were enrolled in the trials. These 60 patients were randomly assigned to one of three groups, namely, the pentazocine group (0.3 mg/kg; Sosegon, Astellas Pharma, Tokyo, Japan; $n = 20$), fentanyl group (1 μg/kg; Fentanyl Inj. Janssen, Janssen Pharma K.K. Beerse, Belgium; $n = 20$), or saline group ($n = 20$); these opioids were administered intravenously (i.v.) 15 min after the intubation. Saline was used as the placebo and given at the same time (15 min after the intubation). Fifteen minutes after the intubation, mean arterial blood pressure (MAP), heart rate (HR), and BIS index were recorded as the respective baseline values.

Premedication was not used. After arriving at the operating room, electrocardiogram (ECG) and oxygen saturation (SpO_2) monitoring readings were made for each patient. An automated system to measure MAP (noninvasive: BP608EV; Nippon Colin, Aichi, Japan) was placed on the patient's right arm, set to cycle, and recorded at 2.5-min intervals for the duration of the study. The system also monitored the heart rate (HR), the concentrations of inhaled anesthetic agents, expired CO_2 tension, and rectal temperature. The BIS was monitored using an XP monitor (model A-XP; Aspect Medical Systems, Natick, MA) equipped with an electrode BIS Quatro (Aspect Medical Systems, Newton, MA) that was placed on the forehead of the patient. During part of our study, the raw EEG signal was recorded on a personal computer using the Bispectrum Analyzer BIS A2000 version (BSA Ver3.22B2) [2].

All 60 patients were anesthetized with sodium thiopental 6 mg/kg (Ravonal Inj.; Mitsubishi Tanabe Pharma Corp, Osaka, Japan) and vecuronium bromide 0.1 mg/kg for tracheal intubation and then anesthetized with sevoflurane at 1.0% plus nitrous oxide (4 l/min) and oxygen (2 l/min). Lactated Ringer's solution was infused at the rate of 10 ml/kg/h. BIS values, HR, MAP, SpO_2, the concentrations of inhaled anesthetic agents, expired CO_2 tension, and rectal temperature were recorded before and at approximately 2.5-min intervals after the intubation up to 30 min after induction. No surgical procedure was performed during the study.

All data were expressed as the mean ± standard deviation (SD). Differences in BIS index, MAP, and HR among the three groups throughout the experiment were analyzed using two-way repeated-measures analysis of variance (ANOVA); other parameters, such as age, weight, height, body mass index, expired CO_2 tension, and body temperature, among the three groups were analyzed using one-way ANOVA. Post hoc comparisons were done by performing Fisher's protected least significant difference test. A P value of <0.05 was considered to indicate statistical significance.

There were no significant differences among the three groups in terms of demographics (Table 1). The baseline BIS index values were similar among the three groups ($P = 0.692$) (Fig. 1). In the saline group, the BIS index was approximately 40 between 2.5 and 30 min after the intubation, which is not a significant statistical change from the baseline value ($P = 0.995$) (Fig. 1). In the pentazocine group, the BIS index increased significantly from the baseline values between 5 and 15 min after the intubation ($P < 0.001$). The BIS index in the pentazocine group was significantly larger during this time period than those for the fentanyl and saline groups ($P < 0.001$). The BIS values in the fentanyl group and saline group were not statistically significantly different ($P = 0.218$) (Fig. 1). MAP and HR showed no significant differences among the three groups during the study ($P = 0.446$ and 0.093, respectively)

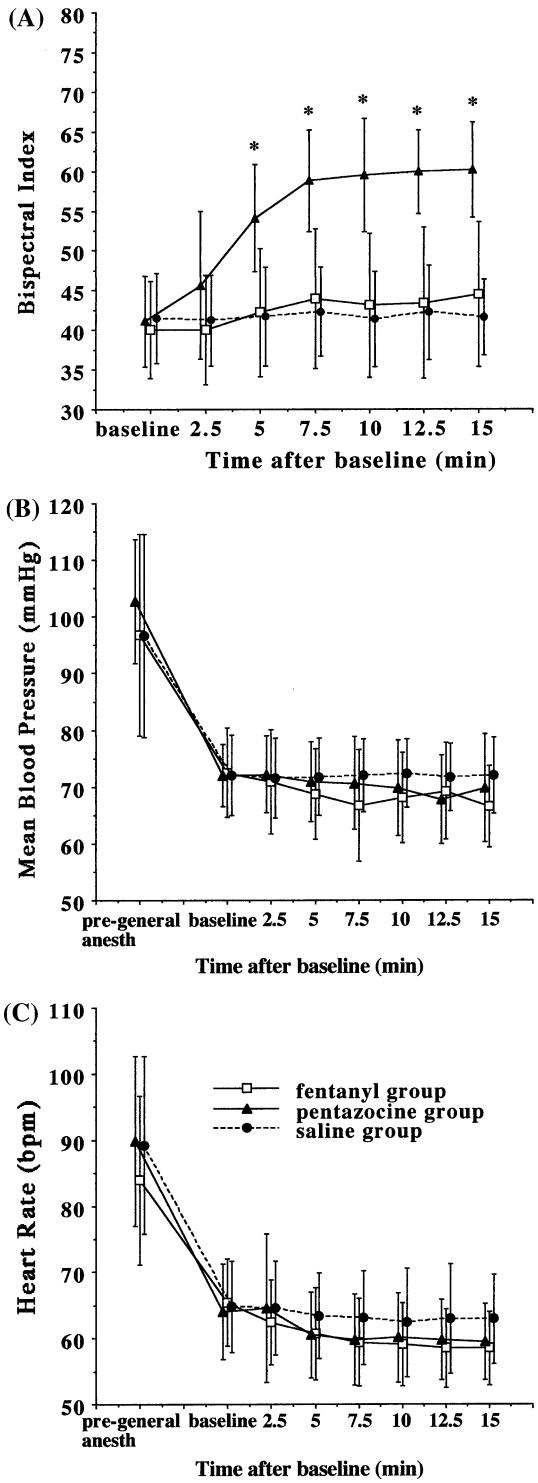


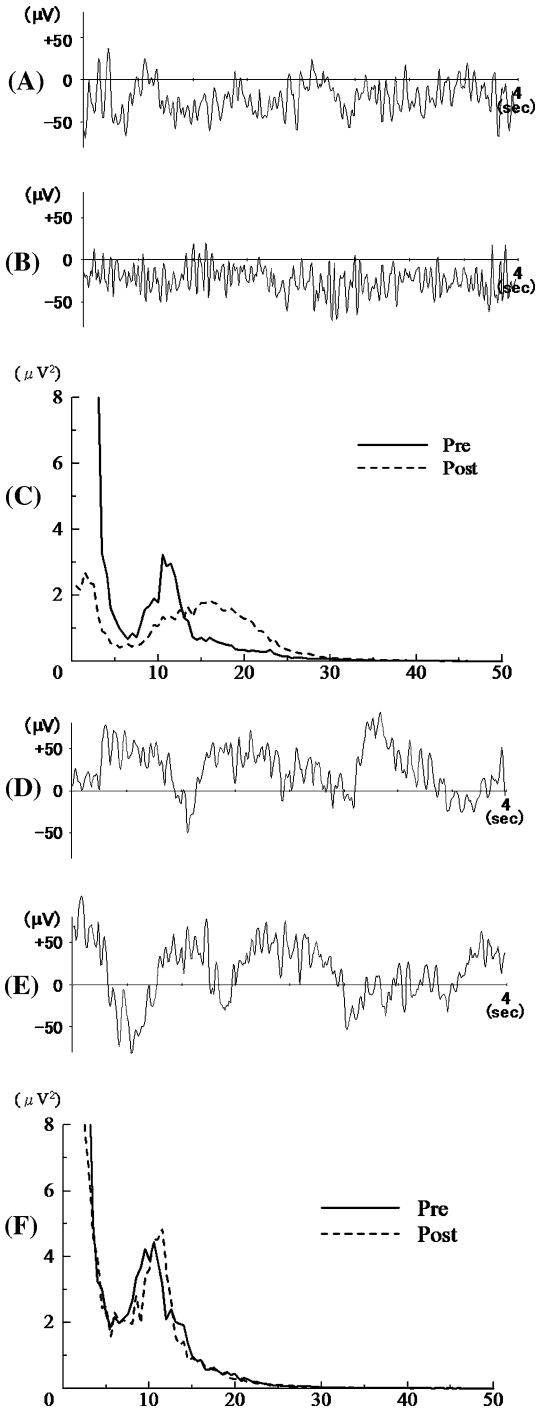
Fig. 1 Changes in the bispectral index (BIS; **a**), mean blood pressure (MAP; **b**), and heart rate (HR; **c**) after intravenously administered saline (saline group), pentazocine (pentazocine group), or fentanyl (fentanyl group) by injection in a patient anesthetized with sevoflurane and nitrous oxide. *Pre-general anesth* Before induction of general anesthesia, *bpm* beats per minutes. BIS, MAP, and HR were recorded as a baseline at 15 min after the intubation. Drug or placebo was administered at baseline on the scale. *$P < 0.001$ vs. the saline group and fentanyl group

(Fig. 1). In the saline group, MAP and HR remained unchanged compared with the baseline values ($P = 0.999$ and 0.937, respectively). In the pentazocine and fentanyl groups, MAP and HR values were not statistically significantly different from the baseline values (pentazocine group: $P = 0.614$ and 0.128; fentanyl group: $P = 0.249$ and 0.906, respectively).

Figure 2 shows raw brain waves as revealed on an electroencephalogram (EEG) and the corresponding power spectra before and after the administration of pentazocine or fentanyl in patients anaesthetized with sevoflurane and nitrous oxide. Although fentanyl showed little effect on the raw EEG data, pentazocine increased the EEG frequency.

The main finding of our study is that i.v. pentazocine, given as a 0.3 mg/kg bolus before surgery under nitrous oxide–sevoflurane anesthesia, provoked a statistically significant increase in BIS values, in contrast previous reports on the effects of other opioids [1, 2]. In a preliminary study involving eight patients in which 1% sevoflurane alone was inhaled, we also observed a significant increase (from 49.3 ± 5.8 at baseline to 64.9 ± 2.8 at 15 min from baseline) in the BIS values following i.v. pentazocine (0.3 mg/kg) (unpublished observations). In the study reported here, we used the same protocol as in our preliminary study but included nitrous oxide in the protocol. Although the effect of co-administered opioids on BIS during general anesthesia is controversial [1, 2], it has been reported that BIS values are reduced by remifentanil in the absence of surgical stimulation under propofol anesthesia [3]. This change from the baseline BIS was suggested to indicate that remifentanil has some hypnotic properties or that it potentiates the hypnotic effect of propofol due to suppression of MAP and HR. However, the data from our study shows that BIS values were increased by pentazocine without changes in the MAP or HR in the absence of surgical stimulation during general anesthesia. In contrast to pentazocine, i.v. fentanyl (1 μg/kg), the analgesic dose of which was equivalent to that of pentazocine (0.3 mg/kg) [4], did not statistically significantly alter the BIS level under nitrous oxide–sevoflurane anesthesia. This result coincides with the findings of a previous report [1].

Our results shows that pentazocine increased both the 95% spectral edge frequency (SEF95) and BIS values and decreased MAP values. Previous studies found that, in contrast to small doses of fentanyl (200 μg), which produce minimal EEG changes [5], pentazocine (15 mg: almost equivalent to the dose used in our studies), when injected intravenously, produces low voltage fast activity in the EEG in awake patients [6]. This modification might be a reflection of an increase in BIS. Moreover, the characteristics of pentazocine on BIS values might resemble those of ketamine in terms of EEG activation, such as increases in β activity, BIS, and SEF95 [7, 8].



In conclusion, under nitrous oxide–sevoflurane anesthesia, bolus administration of pentazocine, but not fentanyl, increased BIS values during the subsequent 15 min. Practitioners must be aware that i.v. pentazocine impairs interpretation of the BIS index.

◀**Fig. 2** Representative raw brain waves, as revealed on an electroencephalogram (EEG) and the corresponding power spectra before and after the administration of pentazocine and fentanyl in patients anesthetized with sevoflurane and nitrous oxide. **a** Raw EEG wave before pentazocine (0.3 mg/kg) administration at baseline: BIS 43.1; amplitude 14.4 μV; 95% spectral edge frequency (SEF95) 15.2 Hz. **b** Raw EEG wave 5 min after the pentazocine administration: BIS 61.3; amplitude 12.5 μV; SEF95 22.2 Hz. **c** Superimposition of corresponding power spectra from pre-administration (*Pre*) and post-administration (*Post*). **d** Raw EEG wave before fentanyl (1 μg/kg) administration at baseline: BIS 37.9; amplitude 19.5 μV; SEF95 13.3 Hz. **e** Raw EEG wave 5 min after the fentanyl administration: BIS 35.4; amplitude 19.1 μV; SEF95 14.4 Hz. **f** Superimposition of corresponding power spectra from Pre and Post. Pentazocine can be seen to cause a prominent decrease in the lower frequency area of the power spectrum. This opioid also increases the β activity, BIS, and SEF95, but decreases the EEG amplitude. In contrast, fentanyl produces minimal changes in the power spectrum

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Conflict of interest The authors have no conflicts of interest.

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