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Respiratory and cardiovascular effects of fentanyl during propofol-induced sedation under spinal anesthesia

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Abstract

Purpose. To determine whether fentanyl augments respiratory and cardiovascular problems during propofol-induced sedation, we investigated the effects of propofol and fentanyl on respiratory and hemodynamic profiles in 30 female patients under spinal anesthesia, administering oxygen via face mask.

Methods. After spinal anesthesia, 20 patients were sedated with propofol ($0.5\,mg \cdot kg^{-1}$ bolus, $3\,mg \cdot kg^{-1} \cdot h^{-1}$), followed by administration of either $2\,\mu g \cdot kg^{-1}$ fentanyl in group PF or normal saline in group P, whereas another 10 patients (group F) received $2\,\mu g \cdot kg^{-1}$ fentanyl without propofol. We measured heart rate, mean arterial pressure, end-tidal carbon dioxide tension, and respiratory rate before and after treatment. We also evaluated apnea, arterial oxygen desaturation, and airway obstruction.

Results. Mean arterial pressure was significantly lower in group P and PF than in group F. However, there were comparable changes in heart rate in the three groups. The combination of fentanyl and propofol decreased respiratory rate and increased end-tidal carbon dioxide tension more than fentanyl or propofol alone. Although apnea occurred in groups F and PF, arterial oxygen desaturation did not occur in any of the groups.

Conclusion. The combination of fentanyl and propofol augmented the risks of respiratory depression and apnea compared with the use of fentanyl or propofol alone.

Key words: Fentanyl, Propofol, Sedation, Airway obstruction, Apnea

Introduction

Most patients prefer to be sedated during surgery because awareness makes them anxious and uncomfortable. To provide a satisfactory setting, sedative and analgesic medications are frequently administered as adjuvants during operations, even under spinal anesthesia. These medications have to provide rapid onset and recovery, good control of sedation, and no intraoperative side effects.

Propofol, a hypnotic agent, can have favorable effects for sedation when given either by intermittent bolus or continuous infusion [1,2]. Propofol-induced sedation, however, has some potential hazards, including pain at injection, respiratory and cardiovascular depression, prolonged apnea, and airway obstruction [3,4]. Moreover, propofol has little analgesic effect. To prevent pain from propofol injection and movement of the patient due to discomfort during surgery, opioids are frequently administered concomitantly with propofol. Opioids, however, can produce respiratory depression and increase the magnitude of hypotension when given with propofol during the induction of anesthesia [5]. Therefore, we hypothesized that the administration of opioids under propofol-induced sedation might augment respiratory and cardiovascular depression. We designed the current study to determine the effects of fentanyl on respiratory and hemodynamic profiles during propofol-induced sedation under spinal anesthesia.

Methods

After approval of our hospital ethics committee and informed consent from the patients, we studied 30 ASA class 1 and 2 patients, aged 30 to 60 years, who were scheduled for vaginal hysterectomy. All patients were unpremedicated. In the operating room, 500 ml hydroxyethyl starch was administered to prevent hypotension. All patients were monitored with intermittent noninvasive blood pressure measurement and continuous electrocardiogram. End-tidal carbon

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dioxide tension ($EtCO_2$), respiratory rate (RR), and hemoglobin oxygen saturation (SpO_2) were monitored throughout the procedure (Ohmeda RGM 5250, Louisville, CO, USA). Spinal anesthesia was provided with 3 ml of 0.5% tetracaine (containing phenylephrine) via a 25-gauge needle in the lumbar region. More than 15 min later, we measured baseline heart rate (HR), mean arterial pressure (mAP), $EtCO_2$, RR, and SpO_2 (pre-propofol control). Patients were then assigned to three groups of 10 each: groups P, F, and PF. In groups P and PF, 0.5 mg·kg^{-1} propofol was administered intravenously as a loading dose, followed by a continuous infusion of propofol at 3 mg·kg^{-1}·h^{-1}. The patients were checked to ensure that eyelash reflex and purposeful reaction to mild physical stimulation had been abolished. An additional bolus of propofol (10 mg) was administered if necessary. More than 20 min after achieving the objective level of sedation, group PF patients received a bolus dose of fentanyl 2 μg·kg^{-1}, whereas group P patients received the same amount of saline. Group F patients received a bolus dose of fentanyl 2 μg·kg^{-1} without propofol-induced sedation. All patients breathed 3 l·min^{-1} oxygen spontaneously via a face mask during the anesthesia. HR, mAP, $EtCO_2$, and RR were recorded before and 5, 10, 15, and 30 min after the administration of fentanyl or saline. Minimum SpO_2 was also recorded throughout the study period. Airway obstruction was defined as existing when no $EtCO_2$ waveform was detected, despite respiratory efforts for more than 10 s. Apnea was defined as present when no $EtCO_2$ waveform was detected without any respiratory efforts for more than 30 s. If SpO_2 decreased to less than 90% or apnea continued for more than 2 min, airway manipulation, such as extension or rotation of the head, was carried out. If these maneuvers were not enough, airway support or manual ventilation was adopted until the obstruction or apnea was resolved.

Patient characteristics were analyzed using one-way ANOVA for comparison between groups. The results were analyzed statistically using two-way ANOVA, followed by contrast for comparison between and within groups. Descriptive data were analyzed with Fisher's exact test with Bonferroni correction. Data are expressed as mean ± SD, with $P < 0.05$ indicating statistical significance.

Results

There were no significant differences between the groups with respect to age, height, or weight. Preanesthetic parameters (HR, mAP, EtCO2, RR, and SpO_2) and block height were also similar in the three groups (Table 1).

Changes in hemodynamic and respiratory variables are summarized in Fig. 1. After propofol-induced sedation, mAP was significantly lower in groups P and PF than in group F ($P = 0.0002$ and 0.0001, respectively). HR gradually decreased in all three groups, and this change was comparable in the groups. In terms of respiratory variables, the most significant changes appeared in group PF. $EtCO_2$ was higher in groups PF and F than in group P ($P = 0.0003$ and 0.0004, respectively). RR was significantly lower in group PF than in groups F and P ($P = 0.0001$), and a significant difference was also found between group F and group P ($P = 0.0001$).

After propofol-induced sedation, from patients in group P and five in group PF showed partial airway obstruction, including sneezing or abnormal breathing patterns, which was treated by extension or rotation of the head. This airway manipulation was not enough for one patient in group P, who required manual airway support for a while. The incidence of apnea and airway obstruction after fentanyl administration is shown in Fig. 2. No patient in group P showed apnea. In contrast, six patients (60%) in group PF and one patient (10%) in group F developed apnea, which continued for 58 ± 14 s and 42 s, respectively. Apnea occurred more frequently in group PF than in groups P and F ($P = 0.0021$ *vs*

Table 1. Patient characteristics, hemodynamic and respiratory data, and block height after spinal anesthesia[a]

Characteristic	Propofol	Fentanyl	Propofol plus fentanyl
Number	10	10	10
Age (yr)	44.7 (6.3)	42.6 (4.1)	46.8 (3.2)
Weight (kg)	55.0 (9.6)	59.5 (10.2)	59.6 (8.6)
Height (cm)	155.7 (4.7)	156.2 (5.7)	154.1 (5.7)
HR (bpm)	77.1 (19.0)	86.9 (21.8)	87.4 (14.5)
mAP (mmHg)	87.6 (19.6)	97.4 (17.3)	94.1 (17.8)
$EtCO_2$	36.6 (3.6)	35.8 (3.4)	36.7 (3.0)
RR (bpm)	14.0 (2.7)	14.0 (4.1)	16.2 (4.3)
SpO_2 (%)	99.9 (0.3)	99.7 (0.4)	99.6 (0.5)
Block height	T6.0 (0.6)	T6.1 (0.7)	T5.9 (0.7)

[a] Values are expressed as means (SD). There were no significant differences among the groups.

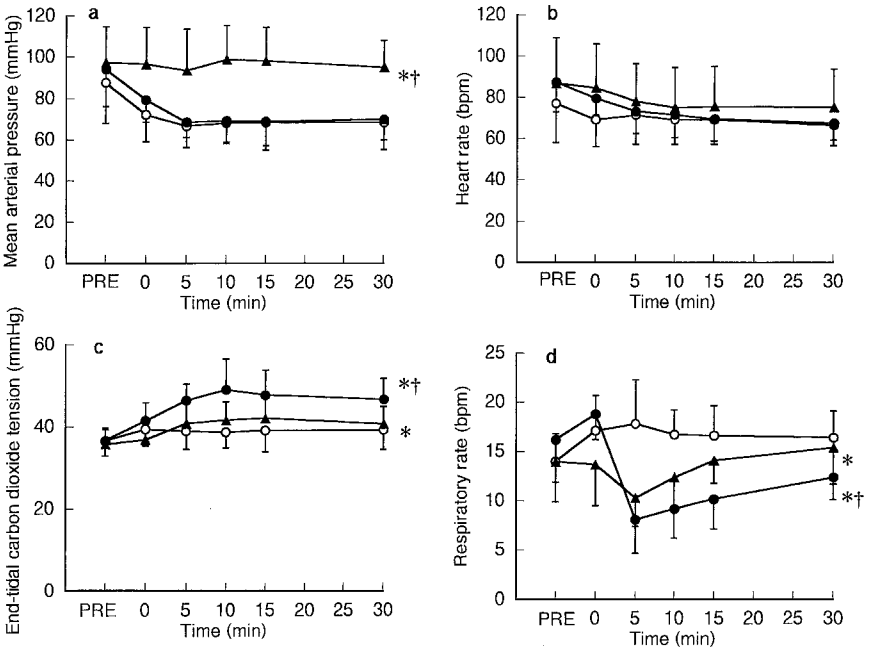

Fig. 1. Plot of mean arterial pressure, heart rate, end-tidal carbon dioxide tension, and respiratory rate (mean ± SD) before (pre-propofol sedation) and for 30 min after the administration of fentanyl or placebo. **a** Mean arterial pressure was lower in the groups with propofol-induced sedation (groups P and PF) than in the group without propofol-induced sedation (group F). **b** Heart rate was gradually decreased in all groups, and there were no significant differences between groups. **c** End-tidal carbon dioxide tension increased most in group PF. **d** Respiratory rate was decreased most in group PF. *PRE*, Pre-propofol sedation; 0, pre-fentanyl administration; *open circles*, propofol; *solid circles*, propofol + fentanyl; *triangles*, fentanyl. $*P < 0.01$ compared with group P. $\dagger P < 0.01$ compared with group F

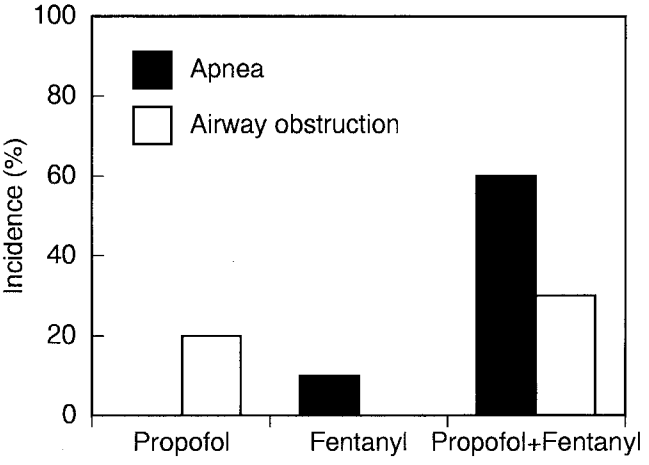

Fig. 2. Incidence of apnea and airway obstruction in the three groups. The combination of fentanyl with propofol-induced sedation augments the risk of apnea ($P = 0.0021$ *vs* groups P and F combined), but not airway obstruction

groups P and F combined). All apnea episodes occurred within 5 min of fentanyl administration. Airway obstruction did not occur in group F, whereas three patients (30%) in group PF and two patients (20%) in group P developed airway obstruction. No significant difference was found between groups P and PF. The minimum SpO_2 was 98.8 ± 1.5%, 98.9 ± 2.0%, and 97.8 ± 2.3% in groups P, F, and PF, respectively. There were no significant differences among the groups ($P = 0.0829$). No patients showed oxygen desaturation of less than 90%.

Discussion

Our results showed that propofol, but not fentanyl, induced airway obstruction and decreased blood pressure, even at the doses required for sedation. The incidence of apnea was augmented when fentanyl and propofol were used together.

Propofol may produce ventilatory depression such as reductions in carbon dioxide sensitivity and suppression of hypoxic ventilatory response at infusion rates of 6 to 12 $mg \cdot kg^{-1} \cdot h^{-1}$ or plasma propofol levels above 2.2 $\mu g \cdot ml^{-1}$ [3,6]. Those concentrations, however, would be considerably higher than the 1 $\mu g \cdot ml^{-1}$ predicted in this study [7]. Pavlin et al. [8] reported adequate spontaneous ventilation at plasma propofol levels of 0.6 to 0.8 $\mu g \cdot ml^{-1}$. Fentanyl, 2 $\mu g \cdot kg^{-1}$, may also produce hypoxemia in young adults breathing room air, but does not elicit apnea [9]. Therefore, each dose of propofol and fentanyl we used in this study was not likely to blunt the respiratory responses to hypoxemia or to induce apnea.

The combination of sedatives with opiates is supposed to induce potent respiratory depression. Bailey et al. [9] found that frequent hypoxemia and apnea occurred after sedation with midazolam (0.05 $mg \cdot kg^{-1}$) and fentanyl (2 $\mu g \cdot kg^{-1}$) in young volunteers breathing room air. Pavlin et al. [8] also showed that the combination of propofol (target plasma levels, 0.6 $\mu g \cdot ml^{-1}$) with alfentanil (target plasma levels, 40 $ng \cdot ml^{-1}$) caused greater depression of the carbon dioxide response curve and a greater decline in minute ventilation than either agent alone. Our findings are consistent with these

results, suggesting that fentanyl and propofol synergetically inhibit ventilation. Apnea frequently occurred after the administration of fentanyl during propofol-induced sedation, although none of the patients developed hypoxemia, because all patients received oxygen via a face mask throughout the anesthesia. Application of oxygen is indispensable during sedation, and only $3\,l \cdot min^{-1}$ oxygen can prevent hypoxemia when fentanyl is combined with propofol for sedation.

Some authors have reported that airway maintenance was excellent, with no evidence of coughing, laryngospasm, airway obstruction, or apnea during propofol sedation [1,10]. However, similar to most anesthetic agents, propofol narrows or closes the upper airway at the level of the soft palate [4]. Indeed, airway narrowing or obstruction occurred in some patients during sedation with propofol alone in our study, suggesting that propofol potentially induces airway obstruction even at the dose required for sedation and therefore that adequate airway management should be applied. In contrast, the addition of fentanyl to propofol did not increase the incidence of airway obstruction. Thus, fentanyl is unlikely to potentiate the risk of airway obstruction during propofol sedation, although it does potentiate the risk of apnea.

Propofol causes dose-related hemodynamic depression, which is augmented by fentanyl. Billard et al. [5] observed that the administration of $2\,\mu g \cdot kg^{-1}$ fentanyl before propofol induction ($2.0–3.5\,mg \cdot kg^{-1}$ bolus) produced significant hemodynamic depression. Consistent with previous reports, our results showed that propofol, but not fentanyl, decreased mean arterial pressure. However, the administration of fentanyl during propofol-induced sedation had no effect on mean arterial pressure or heart rate. Differences in the study protocol may have contributed to this discrepancy; we used a lower concentration of propofol ($3\,mg \cdot kg^{-1} \cdot h^{-1}$) and administered fentanyl during propofol-induced sedation.

A limitation of this study was the difficulty of assessing the level of sedation. Although every patient achieved diminished eyelash reflex during propofol infusion, the deeper levels of sedation could not be identified. Because we maintained a constant infusion rate of propofol during the study period, some patients may have been more deeply sedated than we expected. Monitoring consciousness using a bispectral index would be useful to maintain a constant level of sedation.

In conclusion, the administration of fentanyl, $2\,\mu g \cdot kg^{-1}$, during propofol-induced sedation increased the hazards of respiratory depression and apnea. The application of oxygen and adequate airway management are indispensable to prevent hypoxemia and airway obstruction when administrating fentanyl during propofol-induced sedation.

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