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Original Contribution

Comparison of the recovery and respiratory effects of aminophylline and doxapram following total intravenous anesthesia with propofol and remifentanil☆,☆☆

Dae Woo Kim MD, PhD (Professor), Jin Deok Joo MD, PhD (Professor), Jang Hyeok In MD, PhD (Professor), Yeon Su Jeon MD, PhD (Professor), Hong Soo Jung MD (Clinical Assistant Professor), Kyeong Bae Jeon MD (Resident), Jae Sik Park MD (Resident), Jin Woo Choi MD, PhD (Associate Professor) *

Department of Anesthesiology and Pain Medicine, The Catholic University of Korea St. Vincent Hospital, Suwon, 442–723, South Korea

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ABSTRACT

Study Objective: To compare the effects of aminophylline and doxapram on recovery, respiration, and bispectral index (BIS) values in patients after total intravenous anesthesia (TIVA) with propofol and remifentanil.
Design: Prospective, randomized, blinded clinical trial.
Setting: Operating room of a university hospital.
Patients: 90 adult, ASA physical status 1 and 2 patients scheduled for elective laparoscopic vaginal hysterectomy.
Interventions: TIVA was performed with the induction target of remifentanil 3 ng/mL and propofol 6 μg/mL, followed by the maintenance target of remifentanil 1–3 ng/mL and propofol 3–5 μg/mL at the effect site, and with BIS scores in 40–50 range. Patients were randomized to three groups to receive intravenous (IV) aminophylline 3 mg/kg (n = 30), IV doxapram 1 mg/kg (n = 30), or normal IV saline (control; n = 30).
Measurements and Main Results: After administration of the study drugs, return to spontaneous ventilation differed significantly among the three groups. The times to eye opening and hand squeezing on verbal command were similar. The time to extubation was shortened in both the doxapram and aminophylline groups ($P < 0.05$). Tidal volumes were increased in the doxapram group at 5–14 minutes and the aminophylline group at 5–12 minutes ($P < 0.05$). Respiratory rates were increased at 2 to 8 minutes and then showed a decrease at the 12 to 14-minute mark in both the doxapram and aminophylline groups ($P < 0.05$). No difference was noted between the two groups. BIS values were increased in both the doxapram and aminophylline groups at 4–10 minutes ($P < 0.05$). Heart rates were increased in the doxapram group for the first 8 minutes and at 1–2 minutes in the aminophylline group ($P < 0.05$).
Conclusion: Aminophylline 3 mg/kg or doxapram 1 mg/kg shortened the time to spontaneous ventilation and improved early recovery from TIVA without appreciable side effects. The more rapid emergence correlates with higher BIS values when compared with the saline control group. The arousal and respiratory effects of aminophylline were comparable to those of doxapram.

1. Introduction

Total intravenous anesthesia (TIVA) with propofol and remifentanil allows for rapid and predictable titration of anesthesia. However, we have noted a greater delay in return to spontaneous breathing after TIVA than with sevoflurane or desflurane anesthesia.

Propofol is a potent intravenous (IV) anesthetic with dose-dependent respiratory depression [1], and remifentanil produces similar dose-dependent respiratory depression [2]. The synergistic interaction of remifentanil and propofol in TIVA causes more depression of the ventilatory response to hypercapnia. Therefore, a pharmacological means to hasten recovery without side effects is desirable.

Caffeine, like aminophylline, is a methylxanthine found in coffee and green tea, and it can partially antagonize the behavioral and hypnotic effects of ethanol [3–5]. Aminophylline, which is used clinically as a bronchodilator, centrally antagonizes adenosine, which is a very potent, endogenous central nervous system (CNS) depressant [6,7]. It was reported in 1981 that aminophylline antagonized the hypnotic action of diazepam [8]. Several clinical studies have suggested that aminophylline decreases the depth and duration of sedation produced by propofol [9]. Aminophylline is usually used in anesthetic practice to treat bronchospasm [10,11]; in preterm neonates it decreases the incidence of postoperative apnea [12–14].

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* Correspondence: Jin Woo Choi, MD, PhD, 93–6, Chi-Dong, Paldal-Ku, Suwon, 442–723, South Korea. Tel.: +82 31 249 7212; fax: +82 31 258 4212.
E-mail address: cjwooo@catholic.ac.kr (J.W. Choi).

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Doxapram is a central and peripheral respiratory stimulant and a nonspecific CNS stimulant, which antagonizes the hypnotic or respiratory depressant effect of anesthetics such as diazepam, barbiturates, and halothane [15–18]. This study was designed to compare the effects of aminophylline and doxapram on recovery, respiration, and bispectral index (BIS) monitoring in patients following TIVA with propofol and remifentanil.

2. Materials and methods

This prospective, randomized, blinded clinical study was approved by the Institutional Review Board of the Catholic University of Korea St. Vincent Hospital, and written, informed consent was obtained from all patients. A total of 90 ASA physical status 1 and 2 patients without cardiovascular, pulmonary, or neurological diseases, who were scheduled for elective laparoscopic vaginal hysterectomy, were enrolled.

No premedication was given. In the operating room, a routine monitoring system was attached to each patient, including continuous electrocardiography, noninvasive arterial blood pressure (BP), pulse oximetry, and capnography. To evaluate the depth of anesthesia, a BIS monitor (A-3000; Aspect Medical Systems, Norwood, MA, USA) was used.

Patients were randomized to three groups according to a computer-generated table of random numbers. The aminophylline group (n = 30) received IV aminophylline 3 mg/kg, the doxapram group (n = 30) received IV doxapram 1 mg/kg, and the control group (n = 30) received normal IV saline. Induction was performed with a target-controlled infusion (TCI) of remifentanil, followed by propofol (Orchestra Infusion Workstation V03.OS-1; Fresenius, Vial, France), which included a protocol in the infusion instrument that was chosen by the Schnider model for propofol and the Minto model for remifentanil. Target-controlled infusion mode was used on both effect-site concentration infusions. The induction target of remifentanil was 3 ng/mL and propofol 6 μg/mL, followed by a maintenance target of remifentanil 1–3 ng/mL and propofol 3–5 μg/mL at the effect site; during the operation, these infusions were titrated to maintain BIS scores in the 40–50 range.

Neuromuscular blockade was obtained with rocuronium 0.6 mg/kg. After endotracheal tube insertion, ventilation was adjusted to maintain end-tidal CO_2 at 35 ± 5 mmHg using 2 L/min of oxygen (O_2) and 2 L/min of room air. During the last 30 minutes of the operation, no additional muscle relaxant was administered. At 10 minutes before the end of surgery, neuromuscular block was reversed with IV pyridostigmine 0.2 mg/kg and glycopyrrolate 0.04 mg/kg to allow for the return to spontaneous breathing. At the end of surgery, the propofol and remifentanil infusions were stopped and the study drug was given intravenously over one minute.

Recovery from anesthesia was assessed by an anesthesiologist who was unaware of patients' study group allocations. The following parameters were evaluated: time to return to spontaneous breathing, eye opening on verbal command, hand squeezing on verbal command, and tracheal extubation after administration of the study drug. Heart rate (HR), BP, and BIS values were determined before surgery and at 5-minute intervals during surgery. At each minute after injection of the study drug, for a period of 16 minutes the above-mentioned parameters were determined. Respiratory rate (RR) and tidal volume (V_T) were also recorded from the time of injection of the study drug to extubation.

To estimate group size, a pilot study was conducted to measure the time it took for the occurrence of spontaneous breathing for 10 patients in the control group. The standard deviation (SD) of the time to return to spontaneous breathing was 2.2 minutes. For our power calculation, we assumed an equal SD for the time to return to spontaneous breathing in the other two groups. We wanted to show a difference of two minutes among the three groups in the time to return to spontaneous breathing. With a two-tailed $\alpha = 0.05$ and a power of 80%, 25 patients per group were needed. Assuming the possibility of patients being excluded from the study, we enrolled 30 patients per group. Data are expressed as means and SD. Demographic data were analyzed by x^2-test. Heart rate, BP, BIS values, RR, and V_T were all analyzed by repeated-measures analysis of variance (ANOVA); the Newman-Keuls test was applied when ANOVA reached significance. The time to return to spontaneous breathing, eye opening on verbal command, hand squeezing on verbal command, and extubation were also compared using repeated-measures ANOVA. In all tests, a P-value < 0.05 was considered significant.

3. Results

Patient characteristics were comparable among the three groups, with no significant differences noted (Table 1).

After study drug administration, the return to spontaneous breathing occurred first in the doxapram group, then the aminophylline group, and finally the control group, with significant differences noted among the three groups. Eye opening and hand squeezing on verbal command were observed in the same order, with significant differences noted among the three groups. However, the time to extubation was significantly shorter in the doxapram and aminophylline groups versus the control group ($P < 0.05$; Table 2).

Tidal volumes after study drug injection were increased significantly in the doxapram group, at 5–14 minutes, and in the aminophylline group, at 5–12 minutes, when compared with the control group. Respiratory rates were increased significantly at 2–8 minutes and decreased significantly at 12–14 minutes in both the doxapram and aminophylline groups versus the control group ($P < 0.05$; Fig. 1). However, there were no differences between the doxapram and aminophylline groups.

With respect to BIS, no significant differences were noted among the three groups at baseline, ie, before injection of the study drugs. BIS values after injection of the study drugs were increased significantly in both the doxapram and aminophylline groups when compared with the control group at 4–10 minutes ($P < 0.05$), with no intergroup differences observed between the doxapram and aminophylline groups. Heart rates after study drug injection were increased significantly in the doxapram group for the first 8 minutes and at 1–2 minutes in the aminophylline group when compared with the control group ($P < 0.05$; Fig. 2). However, there was no significant difference in BP among the three groups.

4. Discussion

The synergistic interaction of remifentanil and propofol in TIVA causes a greater depression of the ventilatory response to hypercapnia, further delaying recovery. It therefore seemed logical to evaluate whether recovery from TIVA, with a rapid recovery profile, might be modified by a CNS stimulant such as aminophylline or doxapram. The main finding of this study was that both the aminophylline and

Table 1
Patient characteristics

	Control group (n = 30)	Doxapram group (n = 30)	Aminophylline group (n = 30)
Age (yrs)	42.2 ± 10.2	40.0 ± 11.3	43.1 ± 7.8
Height (cm)	158.2 ± 4.8	161.5 ± 6.0	158.3 ± 5.6
Weight (kg)	57.0 ± 10.0	57.7 ± 8.7	57.8 ± 8.6
Duration of anesthesia (min)	86.1 ± 28.6	82.2 ± 30.9	99.2 ± 15.9

Values are means ± SD.
The control group received normal intravenous (IV) saline, the aminophylline group received IV aminophylline 3 mg/kg, and the doxapram group received IV doxapram 1 mg/kg.