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A Comparison of the Effects of Low and High Doses of Aminophylline on Recovery Time and the Bispectral Index Score Following Iso flurane Anesthesia

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Abstract

Background: Aminophylline expedites the recovery from total intravenous and inhalation anesthesia.
Objectives: The aim of this study was to evaluate low and high doses of aminophylline on extubation time, time to discharge from recovery, and the bispectral index score (BIS) in patients who received isoflurane anesthesia.
Patients and Methods: After ethical approval and informed consent were obtained, this prospective, randomized, blinded clinical study was conducted in Sina hospital in Iran. Seventy-five patients who were scheduled for elective laparatomy surgery under isoflurane anesthesia were randomly allocated to receive either saline or 1 or 5 mg/kg of aminophylline (n = 25 for each) at the end of their anesthesia. The time to tracheal extubation and BIS after the administration of the study drug and the total time required until discharge from the post anesthesia care unit (PACU) were recorded.
Results: Seventy-five patients completed the study. Compared to saline, patients who received 1 and 5 mg/kg of aminophylline demonstrated decreased extubation times (mean ± SD) (12.26 ± 7.33 vs. 11.15 ± 8.62 and 10.4 ± 4.78 min, respectively, P = 0.001) with higher BIS values (P = 0.001). However, the recovery and discharge times from the PACU were no different between the aminophylline and saline groups.
Conclusions: The administration of high doses of aminophylline after laparatomy procedures with isoflurane anesthesia expedited the extubation time with no effects on discharge from the PACU.

Keywords: Aminophylline, Bispectral Index, Isoflurane, Postanesthesia Nursing

1. Background

Isoflurane has been advocated as a routine anesthetic drug in surgery patients. This volatile anesthetic can have adverse postoperative cognitive behavioral effects that may affect task performance; its rapid elimination may also speed up the postoperative recovery time, which in turn could reduce the discharge time in large and overcrowded operating rooms (1-3). Both pharmacologic (4) and non-pharmacologic (5-8) interventions have been reported to reduce recovery times. The Bispectral Index Score (BIS) is a new electroencephalogram parameter that was specifically developed to measure the hypnotic effects of anesthesia (9). BIS monitoring during anesthesia significantly improves recovery regardless of whether propofol (10) or volatile anesthesia (11) is used. Aminophylline is a methylxanthine found in coffee and tea, and it can partially antagonize the behavioral and hypnotic effects of benzodiazepines (12). This drug works clinically to centrally antagonize adenosine, which is a potent, endogenous central nervous system (CNS) depressant (13). When administered at the routine clinical therapeutic dose, aminophylline increases ventilation and the electromyography activity of both inspiratory and expiratory muscles (14). Several clinical studies have suggested that aminophylline can decrease the duration of recovery after total intravenous anesthesia with propofol and remifentanil, sevoflurane, and desflurane (15). However, aminophylline induces seizures, which are commonly fatal; no specific, pharmacologically antagonistic drug is known. Free radicals have recently been implicated in aminophylline-induced toxicities (16). Therefore, clinicians should be cautious in the administration of aminophylline.

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2. Objectives

This study was designed to compare the effects of low and high doses of aminophylline on extubation time, time to discharge from recovery, and the BIS in patients following isoflurane anesthesia

3. Patients and Methods

After obtaining approval from the institutional review board of Tehran University of Medical Sciences, this prospective, randomized, blinded clinical study was conducted at the Sina hospital affiliated with the Tehran University of Medical Sciences in Iran (400 beds and 4 surgical wards) from June 2013 to December 2014. This research study was registered in the Iranian registry of clinical trials under ID number IRCT201403073773N11. The study enrolled 75 American Society of Anesthesiologists (ASA) Classification I–II patients aged 18 - 70 years without cardiovascular, pulmonary, psychological, or neurological diseases who were scheduled for elective laparatomy for tumor resection of the gastrointestinal tract under general anesthesia. The exclusion criteria were a history of cognitive dysfunction; obesity (body mass index $\geq$ 30 kg/m^2); alcoholism; opioid addiction; and current treatment with β-agonists, anticholinergic agents, tranquilizers, anticonvulsants, or antidepressants.

Written informed consent was obtained from all participants. A routine monitoring system was used, including electrocardiography, noninvasive arterial blood pressure, pulse oximetry, and capnography. To measure the depth of anesthesia, the BIS [Brain function assessment (BFA) monitor SAADAT Co. Ltd., 16765-965, Tehran, Iran] was used. After at least two min of pre-oxygenation, all patients were intubated after the administration of 2 μ/kg fentanyl, 3 mg/kg thiopental sodium, 0.5 mg/kg atracurium, and 1 mg/kg lidocaine. During the operation, isoflurane was adjusted to maintain a BIS between 45 and 60 (If the BIS was more than 10 seconds outside the scope, the isoflurane dosage was changed). Repeated doses of fentanyl (1 μ/kg) were administered at more than 20% of the baseline heart rate or mean arterial pressure. Neuromuscular blockade was achieved with 8 μg/kg/minute atracurium. During the final 20 minutes of the operation, no additional muscle relaxant was administered. At the end of the painful stimulations of surgery, the inhalation of isoflurane was stopped and the study drug was given intravenously over two minutes. The neuromuscular block was then reversed with 50 μ/kg neostigmine and 0.015 mg/kg atropine. The study involved three groups of patients who had been randomized according to a computer-generated table of random numbers. The low-dosage aminophylline group (n = 25) received 1 mg/kg intravenous (IV) aminophylline. The high-dosage aminophylline group (n = 25) was given 5 mg/kg IV aminophylline, and the control group (n = 25) received normal IV saline. One physician administered the drug. The other colleagues were unaware of which drug had been given and simply evaluated the patients.

The following parameters were assessed: time to tracheal extubation and BIS after administration of the drug. Following transfer to the post-anesthesia care unit (PACU), the patient was evaluated using the modified Aldrete score every 5 minutes (17) until at least $\geq$ 9 points had been reached to allow safe discharge from the PACU. Postoperative analgesia was provided by an IV injection of 0.5 mg/kg meperidine. Patients were only discharged from the PACU if they were alert, oriented, and cooperative; when their vital signs were stable; and if their pain was considered tolerable.

3.1. Statistical Analysis

To estimate the sample size, we wanted to show a difference of at least two minutes in the recovery times among the three groups. With a two-tailed α = 0.05 and a power of 80%, 25 patients in each group were required. The demographic data were analyzed by chi square test. BIS values were evaluated using a repeated-measures analysis of variance (ANOVA). The extubation time was also compared with a repeated-measures ANOVA. The Kaplan-Meier test was used to determine the patient's recovery time from the anesthesia. Data are expressed as means $\pm$ standard deviation. In all tests, a P-value $<$ 0.05 was considered statistically significant.

4. Results

The demographic data of patients were comparable among the three groups, and no significant differences were noted (Table 1).

Seventy-five patients completed the study. Compared to saline, patients who received 1 and 5 mg/kg of aminophylline had decreased extubation times (mean $\pm$ SD) (12.26 $\pm$ 7.33 vs. 11.15 $\pm$ 8.62 and 10.4 $\pm$ 4.78 minutes, respectively, P = 0.001) with higher BIS values (P = 0.001). However, the recovery and discharge times from the PACU were no different between the aminophylline groups and the saline group.

The time to extubation and the amount of time it took for the BIS reach to 90 after administration of the study drug were significantly shorter in the aminophylline groups vs. the control group (Table 2). Recovery time and discharge from PACU were also not different between all three groups (Figure 1).

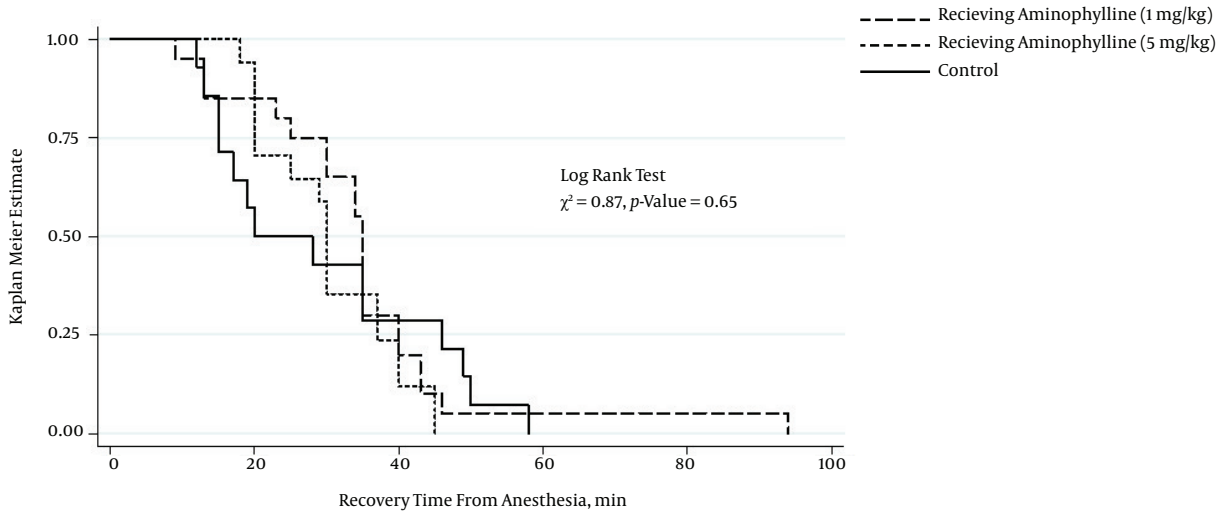

Figure 1. A Comparison of the Anesthesia Recovery Time in the Three Groups

Table 1. Patient Characteristics[a]

Characteristics	Control Group	Aminophylline Group (1 mg/kg)	Aminophylline Group (5 mg/kg)
Age, y	39.5 ± 8.2	40 ± 10.5	41.2 ± 7.2
Gender			
Female	12	14	13
Male	13	11	12
Weight, kg	59.5 ± 9.5	57.6 ± 5.8	58.3 ± 6.4
Duration of anesthesia, minute	135.8 ± 8.5	141.2 ± 2.4	143.5 ± 3.5
Total dose of meperidine used, mg	25 (14/25)	30 (19/25)	35 (22/25)

[a]Values are expressed as means ± SD.

5. Discussion

The improvement of the postoperative recovery period using aminophylline has been studied in many clinical trials. Surprisingly, the present study showed that the postoperative administration of both low and high doses of aminophylline after isoflurane anesthesia for laparatomy surgery had no impact on the patients' recovery time. However, aminophylline hastened the extubation time and produced higher BIS values in this study than those seen in the control group.

The injection of aminophylline after a phase of deep general anesthesia may partially antagonize the hypnotic and sedative effects of anesthesia and lead to a statistically significant increase in the BIS value (18, 19), which reinforced the findings of the present study. Hupfl demonstrated the effects of aminophylline on the bispectral index during inhalational and total intravenous anesthesia and reported that it was associated with a significant increase in the BIS up to 10 minutes following the aminophylline injection (20).

The major mechanism of the neuronal excitability induced by aminophylline seems to be the inhibition of gamma-Aminobutyric acid-ergic and adenosine receptors (21, 22). Porkka-Heiskanen et al. reported that the antagonism of adenosine by theophylline is well known and results in excitatory effects on neuronal activity, which stimulate the CNS to induce vigilance and increase the time spent awake (23).

Escalating doses of aminophylline have been used in many studies; El Tahan administered 2, 3, 4, and 5 mg/kg of aminophylline after sevoflurane and total intravenous anesthesia, which accelerated the patients' postoperative cognitive recovery, induced higher respiratory rate values and lower sedation scores, and shortened the times to eye opening, extubation, achievement of an Aldrete score $\geq$ 9, and PACU discharge after ambulatory surgeries (20, 24, 25). The type of operation in many of these trials was a non-laparotomy procedure with a short duration, which raised a major question: In our study, why did aminophylline increase the recovery period after laparotomies that used isoflurane anesthesia? One of the most common complications of aminophylline is abdominal discomfort (26, 27) that may present as nausea, vomiting, and abdomi-

Table 2 . BIS Changes, Extubation, and Recovery Times[a]

Times	Control Group	Aminophylline Group (1 mg/kg)	Aminophylline Group (5 mg/kg)	P-Value
Extubation time, minute	12.26 ± 7.33	11.15 ± 8.62	10.4 ± 4.78	0.001
Time to reach BIS 90, minute	14.4 ± 4.2	11.5 ± 5.6	10.6 ± 3.7	0.001

[a]Values are means ± SD.

nal pain. According to the results of our study, the use of an opioid in the aminophylline groups was higher than it was in the placebo group (Table 1), which indicates that these patients were more anxious, which likely led to the delay in their PACU discharge.

In conclusion, the administration of varying doses of aminophylline after laparatomy surgeries that used isoflurane anesthesia expedited the extubation time but was associated with a delay in discharge from the PACU.

5.1. Limitations

The present study had some important limitations. First, we did not observe any adverse effects of aminophylline, such as tachycardia, cardiac arrhythmia, hypertension, hallucinations, and excitation, during the recovery period. Second, we did not verify the plasma concentrations of aminophylline in the PACU.

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Footnotes

Authors' Contribution: Design and study collection, Farsad Imani, Azadeh Ahmmadi Tabatabaie, Pejman Pourphakhr; management, Farsad Imani, Azadeh Ahmadi Tabatabaie; analysis of the data, Azadeh Ahmadi Tabatabaie; preparation, review, and approval of the manuscript, Reza Shariat Moharari, Farhad Etezadi, Mohammad Reza Khajavi, Farsad Imani.

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