CEOG Clinical and Experimental Obstetrics & Gynecology

Original Research

Effect of aminophylline on restoration of spontaneous respiration and recovery profiles during anesthesia without using muscle relaxants in patients undergoing brief gynecological procedure

Y.S. Jeon[1] , **E.H. Jun**[1] , **J.H. Kim**[1] , **S.T. Choi**[1] , **J.H. In**[1,*]

[1] *Department of Anesthesiology and Pain Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul (Republic of Korea)*

Summary

Purpose of Investigation: The purpose was to evaluate the effects of aminophylline on returning of spontaneous respiration and recovery profiles during propofol-fentanyl-sevoflurane anesthesia without muscle relaxants in patients undergoing day care gynecological surgery. *Materials and Methods*: Sixty-six patients were enrolled. Either aminophylline 3 mg/kg (group A) or saline (group C) was administered to each patient. Tidal volume (Vt), respiratory rate (RR), and end tidal carbon dioxide ($ETCO_2$), apneic time, recovery time, discharge time and modified observer's assessment of alertness/sedation scale (MOAA/S) were evaluated. *Results*: Apneic time and recovery time were significantly shorter in Group A than in Group C ($P < 0.01$). MOAA/S, tidal volume ($P = 0.02$) and $ETCO_2$($P = 0.03$) were significantly improved in Group A compared with Group C. *Conclusion*: Aminophylline effectively reduced apneic and recovery time, thereby improving respiratory and recovery profiles during anesthesia with propofol, fentanyl, and sevoflurane in brief day care surgeries.

Key words: Aminophylline; Hypercapnia; Anesthesia recovery period.

Introduction

Day care surgeries are becoming increasingly common due to benefits including shorter hospital stays, lower morbidity rates, and relatively inexpensive costs. Because these procedures are brief and superficial, clinical anesthetic maintenance is usually performed using a technique that allows spontaneous breathing through a face mask or laryngeal mask airway (LMA). The use of muscle relaxants in short surgeries is inappropriate because succinylcholine has well-known side effects, and a minimum effective dose of non-depolarizing muscle relaxants can lead to postoperative residual paralysis after brief operations.

To guarantee immobility of patients without using muscle relaxants, we use a single bolus containing fentanyl, propofol, and a high concentration of sevoflurane during induction of anesthesia. The combination of these anesthetic agents often causes respiratory depression that may lead to delayed recovery of spontaneous breathing, hypercapnia, or hypoxemia; therefore, attempts to restore respiratory effort and maintain normocapnia are required during propofol-fentanyl-sevoflurane anesthesia.

Aminophylline is currently used as the drug of choice for bronchospasm, offering the effect of direct relaxation of the smooth muscles of the bronchial airways and pulmonary blood vessels. Along with a bronchodilating effect, aminophylline presents an arousal effect [1-3] and a preventive effect of apnea in neonates [4, 5]. Aminophylline is also a muscle agonist. This is important as a healthy patient may not experience a significant amount of bronchodilation of smooth muscles that would account entirely for the changes seen in recovery of spontaneous breathing but a muscle agonist affects would. Evidence in literature also supports muscular effects such as increases in contractility and action and whole animal evidence [6, 7, 8].

We designed this study to evaluate the effects of aminophylline on restoration of spontaneous respiration and recovery profiles during propofol-fentanyl-sevoflurane anesthesia without muscle relaxants in patients undergoing brief gynecological surgery.

Materials and Methods

The present study protocol was reviewed and approved by the ethics committee of the Catholic University of Korea, St Vincent Hospital, Seoul, Korea (IRB No. VC15MISI0078). Written informed consent was obtained from all participants. Sixty six patients classified by the American Society of Anesthesiologists (ASA) as status I or II, aged 30 to 70 years, who were scheduled for brief gynecological day care surgery - loop electrosurgical exci-

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLVII, n. 4, 2020
doi: 10.31083/j.ceog.2020.04.5417

sion procedure (LEEP) - were enrolled in this study and randomly assigned to two groups (Group C: control group, n = 33; Group A: aminophylline group, n = 33). Randomization was computer generated and kept in opaque envelops until just before anesthesia. Patients were blinded as to which group they were allocated. Patients with severe cardiovascular, pulmonary, neurologic, renal, hepatic, upper airway disorder or who were taking psychoactive drugs were excluded from this study.

Procedure

Preoperative medication was not used. On arrival at the operating room, 3 mg/kg of aminophylline or an equal volume of isotonic saline was administered intravenously to patients in Groups A and C, respectively. Prior to induction of anesthesia, routine monitors of electrocardiography, non-invasive blood pressure, pulse oximetry, and end-tidal carbon dioxide were connected to patients, and baseline values were recorded. Anesthesia was induced using a mixture of 2.0 mg/kg of 1% propofol and 1 μ/kg of fentanyl without a neuromuscular blocker. No additional opioid was provided after inducing anesthesia. After loss of consciousness, patients were mechanically ventilated with sevoflurane 8 vol% in 100% oxygen to maintain an end-tidal carbon dioxide partial pressure ($ETCO_2$) of 35 mmHg. Once end-tidal sevoflurane reached 2.5 vol% [9], mechanical ventilation was discontinued, and an LMA was inserted. After LMA was inserted, patients were allowed to breathe spontaneously with patients placed in lithotomy position. And then, anesthesia was maintained with 2.0% sevoflurane in 50% nitrous oxide in oxygen. Positive pressure ventilation was applied only if desaturation (SpO_2 less than 95%) or hypercapnia ($ETCO_2 > 50$ mm Hg) occurred. Sevoflurane and nitrous oxide were simultaneously discontinued at the end of surgery. After confirming appropriate patient emergence, the LMA was removed.

Assessment

Demographic data of age, body weight, height, and duration of anesthesia were recorded. Oxygen saturation, heart rate (HR), and mean arterial blood pressure (MBP) were monitored in all patients before anesthesia and at 5-minute intervals during anesthesia (T1, T2, T3, T4, T5; baseline, 5, 10, 15, and 20 minutes after induction of anesthesia, respectively). Tidal volume (Vt), respiratory rate (RR), and $ETCO_2$ were also measured from the beginning of anesthesia at 5-minute intervals. Time elapsed to reach sevoflurane 2.5 vol% from induction of anesthesia was noted. Apneic time was defined as the interval between mechanical ventilation discontinuance and the time at which the first effort of spontaneous respiration was detected and was recorded. Recovery profiles including recovery time (the time interval from cessation of anesthetics to eye opening in response to verbal command), discharge time, and modified observer's assessment of alertness/sedation scale (MOAA/S) were evaluated (Table 1). MOAA/S was evaluated at 15-minute intervals starting from arrival at the post-anesthesia care unit (PACU). The number of hypoxic or hypercarbic events in each group was recorded.

Statistical analysis

Data are presented as mean $\pm$ SD. Continuous variables (age, weight, height, duration of anesthesia, apneic time, recovery time, time to reach sevoflurane 2.5 vol%) were analyzed with Student's *t*-test. The categorical variable (MOAA/S scale) was compared using a chi-square test. Changes in HR, MBP, Vt, RR, and $ETCO_2$ were analyzed by repeated measures ANOVA. A P-value < 0.05 was considered statistically significant in all tests. Statistical analyses were performed using SPSS version 21 (SPSS Inc., Chicago, IL, USA).

Results

A total of 66 patients was enrolled in this study and randomly assigned to Groups A (n = 33) and C (n = 33). There were no significant differences between the two groups regarding age, body weight, height, or duration of anesthesia (Table 2). Recovery and respiratory profiles are presented in Table 3. Discharge time was not significantly different between two groups; however, recovery time was significantly shorter in Group A than in Group C (6.1 $\pm$ 2.8 min *vs.* 8.2 $\pm$ 3.0 min, $P < 0.01$). On arrival at the PACU, the MOAAS scale score was not significantly different between groups, but MOAAS scale scores measured 15 and 30 minutes after arrival at the PACU were significantly higher in Group A compared with Group C. Time to reach sevoflurane 2.5 vol% was not significantly different between groups. Group A showed a significantly shorter apneic time compared with Group C (68.8 $\pm$ 25.2 s *vs.* 93.9 $\pm$ 29.7 s, $P < 0.01$). Respiratory variables are presented in Figure 1. Change over time of tidal volume was significantly increased in Group A compared with Group C ($P = 0.02$). Difference in respiratory rate between Groups A and C had no clinical relevance. $ETCO_2$ values of the two groups were not statistically different at the beginning of anesthesia; however, overall changes in $ETCO_2$ over time was significantly lower in Group A compared with Group C ($P = 0.03$). No patient in Group A needed assistant ventilation to correct hypoxemia or hypercapnia, while $ETCO_2$ temporarily exceeded 50 mm Hg in one patient of Group C during the operation. Hemodynamic variables including HR and MBP showed no statistical differences between groups (Table 4).

Discussion

This study demonstrated the effectiveness of aminophylline in reducing apneic and recovery times and in improving respiratory and recovery profiles during anesthesia with propofol, fentanyl, and sevoflurane in brief day care surgeries. For short operations, anesthesia is usually administered by mask or laryngeal mask airway without muscle relaxants, allowing patients to breathe spontaneously. However, the synergistic effect of fentanyl, propofol, and high concentration of sevoflurane could decrease the venti-

Table 1. — *Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S).*

	Score
Agitated	6
Responds readily to name spoken in normal tone (Alert)	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to deep stimulus	0

Table 2. — *Patient characteristics.*

	Group A (n = 33)	Group C (n = 33)	*P*
Age (yrs)	46.5 ± 11.3	47.6 ± 12.5	0.71
Body weight (kg)	57.4 ± 9.2	56.8 ± 8.4	0.81
Height (cm)	160.6 ± 4.7	158.8 ± 4.8	0.13
Duration of anesthesia (min)	26.9 ± 10.5	23.4 ± 15.9	0.29

Data are presented as mean ± SD. Group A, aminophylline group; Group C, control group.

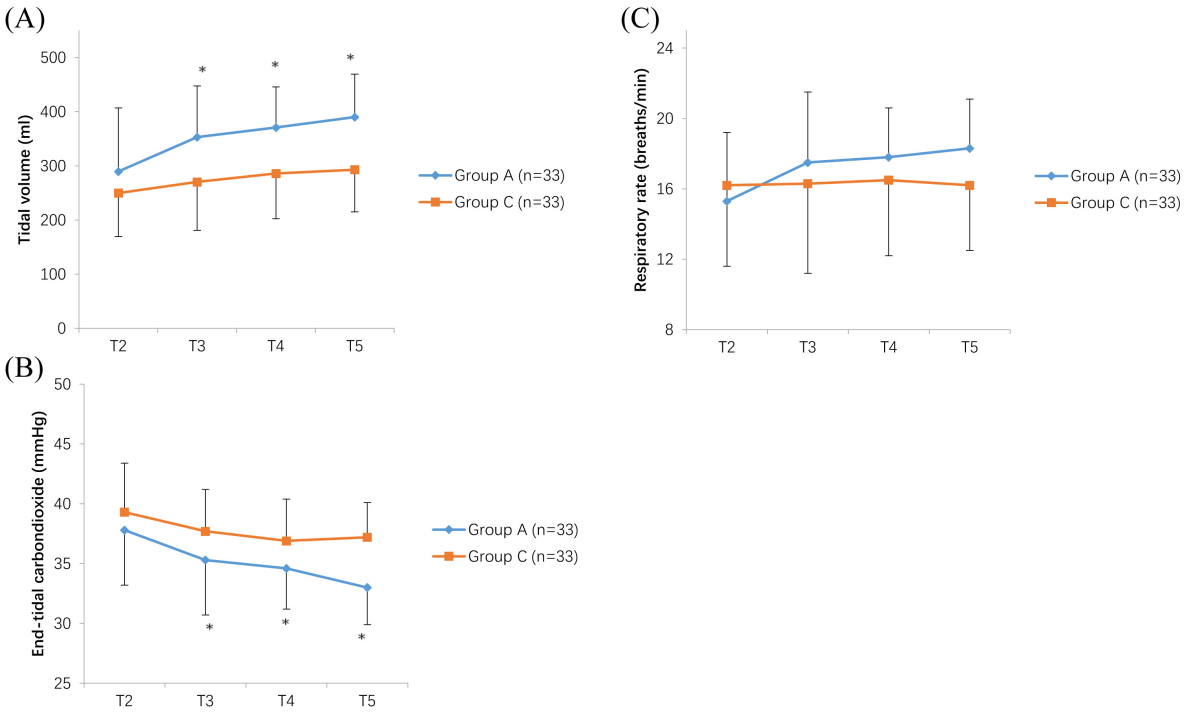

Figure 1. — Perioperative changes of respiratory variables. (A) Tidal volume (B) Respiratory rate (C) End tidal carbon dioxide ($ETCO_2$). Group A, aminophylline group; Group C, control group. T2, 5 minutes after induction of anesthesia; T3, 10 minutes after induction of anesthesia; T4, 15 minutes after induction of anesthesia; T5, 20 minutes after induction of anesthesia. *$P < 0.05$ compared to Group C. Overall changes over time of tidal volumes and $ETCO_2$ were significantly higher in Group A compared with Group C, while there was no significant difference in respiratory rate between the groups.

latory response, resulting in hypercapnia. It is, therefore, necessary to modify the respiratory profiles by whether pharmacological or mechanical means. Controlled ventilation in a patient anesthetized without muscle relaxants is inappropriate for use since it could induce auto-peep. As a pharmacological means, respiratory stimulant could be a proper option, as it expects to antagonize the hypnotic or depressive respiratory effect of sedatives.

Table 3. — *Recovery and respiratory profiles.*

		Group A	Group C	*P*
		(n = 33)	(n = 33)	
Recovery				
	Recovery time (min)	6.2 ± 2.8	8.2 ± 3.0	< 0.01
	Discharge time (min)	32.2 ± 4.8	33. ± 5.3	0.23
	MOAA/S on arrival at PACU	0.6 ± 0.7	0.4 ± 0.6	0.38
	MOAA/S at 15 min	4.0 ± 0.7	3.4 ± 0.7	0.02
	MOAA/S at 30 min	4.8 ± 0.6	4.3 ± 0.5	0.01
Respiratory				
	Apneic time (sec)	68.8 ± 25.2	93.9 ± 30.0	< 0.01
	TSevo2.5 (sec)	104.2 ± 40.0	96.5 ± 39.1	0. 43

Data are presented as mean ± SD. Group A, aminophylline group; Group C, control group. MOAA/S, modified observer's assessment of alertness/sedation scale. TSevo2.5; time to reach end tidal sevoflurane 2.5 vol%.

Table 4. — *Perioperative changes of hemodynamic variables.*

	Heart rate (bpm)		Mean arterial blood pressure (mmHg)	
	Group A (n = 33)	Group C (n = 33)	Group A (n = 33)	Group C (n = 33)
T1	64.9 ± 7.4	61.8 ± 7.0	80.7 ± 14.5	80.1 ± 13.9
T2	71.3 ± 9.5	67.2 ± 9.6	91.3 ± 16.2	86.6 ± 12.0
T3	65.2 ± 8.8	64.5 ± 8.5	79.8 ± 13.2	80.7 ± 13.5
T4	64.3 ± 8.1	62.6 ± 6.1	80.0 ± 12.2	80.6 ± 13.6
T5	65.5 ± 8.2	65.1 ± 6.2	77.2 ± 11.3	80.9 ± 17.2

Data are presented as mean ± SD. Group A, aminophylline group; Group C, control group. T1, baseline; T2, 5 minutes after induction of anesthesia; T3, 10 minutes after induction of anesthesia; T4, 15 minutes after induction of anesthesia; T5, 20 minutes after induction of anesthesia. Overall hemodynamic changes over time demonstrated no significant difference in heart rate or mean arterial blood pressure between two groups.

A sedative dose of propofol can induce decreases in tidal volume and ventilatory response to CO_2 by 58% of baseline awake control while increasing respiratory rate to 30% higher than that at baseline [10]. Propofol's estimated concentration of effect site for inducing respiratory depression is 3.8 mcg/mL, slightly higher than that required to induce loss of consciousness with a 50% probability when used alone [11, 12]. In contrast, the respiratory pattern caused by the opioid is characterized by a decrease in breathing frequency. A change in respiratory rate is the most sensitive aspect of opioid-induced respiratory depression [13], whereas the change of tidal volume varies according to opioid dose [14]. Ferguson and Drummond reported that fentanyl 0.5 mcg/kg prolonged the durations of inspiration and expiration by 30% and 95%, respectively [15]. Fentanyl-mediated depression at this low dose may be further exacerbated when combined with propofol and lead to a synergistic interaction of respiratory depressant effects [16]. Sevoflurane at 1 MAC also causes respiratory depression in a dose-dependent manner. Furthermore, in conditions similar to our study, high concentrations of sevoflurane (6-8 vol%) may augment the respiratory depressant effects of opioid and propofol [17, 18] and may delay the recovery of spontaneous respiration. In this study, one patient in Group C required assistance ventilation due to retention of CO_2 during anesthesia compared with no patients in Group A, but there was no significant difference between the two groups.

Aminophylline is a xanthine derivative that directly relaxes bronchial smooth muscle by inhibiting phosphodiesterases, thereby relieving bronchospasm and asthma. Aminophylline-induced augmentation of ventilation is attributed to improving effects on central neural drive and contractility of respiratory muscles by increasing intracellular calcium content [19, 20]. Aminophylline induced increase of diaphragm contractility was revealed in one in vitro animal study [8]. This muscle agonist effects of aminophylline may play a role in turning the central stimulus into actual respiratory action as well as a underlying mechanism of the drug. Previous studies have presented various outcomes regarding the effects of aminophylline on respiratory variables. Aminophylline promotes larger tidal volume and faster breathing frequency [7, 20], although Okubo *et al*. reported that aminophylline did not produce a significant increase in tidal volume or respiratory frequency despite an increase in maximum inspiratory pressure [21]. In this study, improvement of Group A patient respiratory profiles was achieved by a significant in-

crease in tidal volume rather than an effect on respiratory rate, which did not correspond with some results from previous studies [20]. Aminophylline is also effective in preventing apnea of prematurity [22]. Apnea in preterm infants is related to immaturity of the central respiratory control [23], which contributes to an obtunded respiratory response to CO_2 [24]. The main role of aminophylline in this theory is to increase the central ventilatory drive, which could explain the shorter apneic time in patients receiving aminophylline in this study [25].

Aminophylline has been shown to reduce the depth of sedation by antagonizing adenosine receptors [26, 27] and inhibiting GABA-ergic neurotransmission [28]; hence, it acts as a stimulant of the central nervous system to induce vigilance [29]. Previous studies have reported that aminophylline increased the propofol dose needed to induce loss of consciousness and contributed to a reduction in depth of propofol anesthesia [3]. Aminophylline's effects are not restricted to intravenous anesthetics but extend to inhalational anesthetics [30, 31]. It has been suggested that aminophylline can produce an anti-hypnotic effect and hasten recovery time [27, 32]. Our data showed that aminophylline has a favorable effect on fast awakening and sedation scale score, although there was no significant difference in discharge time between groups.

Aminophylline is well known to have positive inotropic and chronotropic effects; however, studies on the cardiovascular effect of aminophylline show conflicting results depending on the research subjects or the study approach [33, 34]. Previous studies have reported that aminophylline caused a decrease in MBP with an improvements in effect on coronary circulation [35], while Rutherford JD *et al*. reported moderately increased vascular resistance (except for the renal bed) with aminophylline administration in an animal study [33]. Interestingly, they noted that the vasoconstrictive effect of aminophylline in the coronary bed at low doses was reversed as the dose increased. Regarding HR, most authors report coincident results that verify the increasing effect of aminophylline [33, 35, 36], whereas Conrad and Prosnitz demonstrated no clinically significant change in HR in a human study [34]. In the present study, there were no statistically significant differences in HR and MBP between groups, although the overall heart rate of Group A patients slightly exceeded that of Group C patients over time.

Conclusion

In conclusion, our results showed that administration of aminophylline effectively shortened apneic time and improved respiratory profiles, thereby offering advantages in prevention of apnea or hypercapnia in patients undergoing brief day care surgery. In addition, the arousal effect of aminophylline enhanced early recovery from propofol-fentanyl-sevoflurane anesthesia and reduced the depth of sedation without any adverse effects on hemodynamic stability.

Acknowledgments

The authors would like to express their deep and sincere gratitude to all the peer reviewers and editors for their opinions and suggestions.

Conflict of Interest

The authors declare no competing interests.

Submitted: November 19, 2019
Accepted: March 11, 2020
Published: August 15, 2020

References

[1] Turan A., Memiş D., Karamanlýodthlu B., Pamukçu Z., Süt N.: "Effect of aminophylline on bispectral index". *Acta Anaesthesiol. Scand.*, 2004, *48*, 408.
[2] Stirt J.A.: "Aminophylline is a diazepam antagonist". *Anesth. Analg.*, 1981, *60*, 767.
[3] Turan A., Kasuya Y., Govinda R., Obal D., Rauch S., Dalton J.E., *et al*.: "The effect of aminophylline on loss of consciousness, bispectral index, propofol requirement, and minimum alveolar concentration of desflurane in volunteers". *Anesth. Analg.*, 2010*, 110,* 449.
[4] Lim D.S., Kulik T.J., Kim D.W., Charpie J.R., Crowley D.C., Maher K.O.: "Aminophylline for the prevention of apnea during prostaglandin E1 infusion". *Pediatrics*, 2003, *112*, e27.
[5] Schmidt B., Roberts R.S., Davis P., Doyle L.W., Barrington K.J., Ohlsson A., *et al*.: "Caffeine therapy for apnea of prematurity". *N. Engl. J. Med.*, 2006, *354*, 2112.
[6] Yuzkat N., Kati I., Isik Y., Kavak S., Goktas U., Cengiz N.: "Effects of theophylline with methylprednisolone combination therapy on biomechanics and histopathology in diaphragm muscles of rats". *Inflammation*, 2016, *39*, 1635.
[7] Gorini M., Duranti R., Misuri G., Valenza T., Spinelli A., Goti P., *et al*. : "Aminophylline and respiratory muscle interaction in normal humans". *Am. J. Respir. Crit. Care Med*., 1994, *149*, 1227.
[8] Sigrist S., Thomas D., Howell S., and Roussos C.: "The effect of aminophylline on inspiratory muscle contractility". *Am. Rev. Respir. Dis*., 1982, *126*, 46.
[9] Aantaa R., Takala R., Muittari P.: "Sevoflurane EC50 and EC95 values for laryngeal mask insertion and tracheal intubation in children". *Br. J. Anaesth.*, 2001, *86*, 213.
[10] Goodman N.W., Black A.M., Carter J.A.: "Some ventilatory effects of propofol as sole anaesthetic agent". *Br. J. Anaesth.*, 1987, *59*, 1497.
[11] Lee M.H., Yang K.H., Lee C.S., Lee H.S., Moon S.Y., Hwang S.I., Song J.H.: "The effect-site concentration of propofol producing respiratory depression during spinal anesthesia". *Korean J. Anesthesiol.*, 2011, *61*, 122.
[12] Vuyk J., Engbers F.H., Lemmens H.J., Burm A.G., Vletter A.A., Gladines M.P., Bovill J.G.: "Pharmacodynamics of propofol in female patients". *Anesthesiology*, 1992, *77*, 3.
[13] Lalley P.M.: "Mu-opioid receptor agonist effects on medullary respiratory neurons in the cat: evidence for involvement in certain types of ventilatory disturbances". *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, 2003, *285*, R1287.
[14] Bouillon T., Bruhn J., Roepcke H., Hoeft A.: "Opioid-induced respiratory depression is associated with increased tidal volume variability". *Eur. J. Anaesthesiol.*, 2003, *20*, 127.
[15] Ferguson L.M., Drummond G.B.: "Acute effects of fentanyl on breathing pattern in anaesthetized subjects". *Br. J. Anaesth.*, 2006, *96*, 384.
[16] Ma D., Sapsed-Byrne S.M., Chakrabarti M.K., Whitwam J.G.: "Synergistic interaction between the effects of propofol and midazolam with fentanyl on phrenic nerve activity in rabbits". *Acta Anaesthesiol. Scand.*, 1998, *42*, 670.
[17] Walpole R., Olday J., Haetzman M., Drummond G.B., Doyle E.: "A comparison of the respiratory effects of high concentrations of halothane and sevoflurane". *Paediatr. Anaesth.*, 2001, *11*, 157.

[18] Manyam S.C., Gupta D.K., Johnson K.B., White J.L., Pace N.L., Westenskow D.R., Egan T.D.: "Opioid-volatile anesthetic synergy: a response surface model with remifentanil and sevoflurane as prototypes". *Anesthesiology*, 2006, *105*, 267.
[19] Nishii Y., Okada Y., Yokoba M., Katagiri M., Yanaihara T., Masuda N., *et al*.: "Aminophylline increases parasternal intercostal muscle activity during hypoxia in humans". *Respir. Physiol. Neurobiol.*, 2008, *161*, 69.
[20] Yokoba M., Katagiri M., Ichikawa T., Takakura A., Ishii N., Kurosaki Y., *et al*.: "Aminophylline increases respiratory muscle activity during hypercapnia in humans". *Pulm. Pharmacol. Ther.*, 2015, *30*, 96.
[21] Okubo S., Konno K., Ishizaki T., Kubo M., Suganuma T., Takizawa T.: "Effect of theophylline on respiratory neuromuscular drive". *J. Clin. Pharmacol.*, 1987, *33*, 85.
[22] Shivakumar M., Jayashree P., Najih M., Lewis L.E.S., Bhat Y.R., Shashikala, K.A.: "Comparative efficacy and safety of caffeine and aminophylline for apnea of prematurity in preterm (≤ Aminophylline increases respiratory muscle activity during hypercapnia in humans weeks) neonates: a randomized controlled trial". *Indian Pediatr.*, 2017, *54*, 279.
[23] Kattwinkel J., Nearman H.S., Fanaroff A.A., Katona P.G., Klaus M.H.: "Apnea of prematurity: comparative therapeutic effects of cutaneous stimulation and nasal continuous positive airway pressure". *J. Pediatr.*, 1975, *86*, 588.
[24] Rigatto H., Brady J.P., de la Torre Verduzco R.: "Chemoreceptor reflexes in preterm infants: II. The effect of gestational and postnatal age on the ventilatory response to inhaled carbon dioxide". *Pediatrics*, 1975, *55*, 614.
[25] Gerhardt T., McCarthy J., Bancalari E.: "Effect of aminophylline on respiratory center activity and metabolic rate in premature infants with idiopathic apnea". *Pediatrics,* 1979, *63*, 537.
[26] Biaggioni I., Paul S., Puckett A., Arzubiaga C.: "Caffeine and theophylline as adenosine receptor antagonists in humans". *J. Pharmacol. Exp. Ther.*, 1991, *258*, 588.
[27] Niemand D., Martinell S., Arvidsson S., Ekström-Jodal B., Svedmyr N.: "Adenosine in the inhibition of diazepam sedation by aminophylline". *Acta Anaesthesiol. Scand.*, 1986, *30*, 493.
[28] Taketo M., Matsuda H., Yoshioka T.: "Calcium-independent inhibition of GABA(A) current by caffeine in hippocampal slices". *Brain Res.*, 2004, *1016*, 229.
[29] Porkka-Heiskanen T.: "Adenosine in sleep and wakefulness". *Ann. Med.*, 1999, *31*, 125.
[30] El Tahan M.R.: "Effects of aminophylline on cognitive recovery after sevoflurane anesthesia". *J. Anesth.*, 2011, *25*, 648.
[31] Turan A., Memiş D., Karamanlioglu B., Colak A., Pamukçu Z., Turan N.: "Effect of aminophylline on recovery from sevoflurane anaesthesia". *Eur. J. Anaesthesiol.*, 2002, *19*, 452.
[32] Hüpfl M., Schmatzer I., Buzath A, Burger H., Hörauf K., Ihra G., *et al*.: "The effects of aminophylline on bispectral index during inhalational and total intravenous anaesthesia". *Anaesthesia,* 2008, 63, 583.
[33] Rutherford J.D., Vatner S.F., Braunwald E.: "Effects and mechanism of action of aminophylline on cardiac function and regional blood flow distribution in conscious dogs". *Circulation*, 1981, *63*, 378.
[34] Conrad K.A., Prosnitz E.H.: "Cardiovascular effects of theophylline. Partial attenuation by beta-blockade". *Eur. J. Clin. Pharmacol.*, 1981, *21*, 109.
[35] Oei H.H., Hale T.H., Gandhi S.S., Pilla T.J., Wegria R.: "Effect of aminophylline on coronary circulation and cardiac metabolism". *Arch. Int. Pharmacodyn. Ther.*, 1977, *229*, 95.
[36] Rutherford J.D., Vatner S.F., Braunwald E.: "Effects of aminophylline in the conscious dog after coronary occlusion". Am. J. Cardiol., 1981, *48*, 1071.

Corresponding Author:
JANG HYEOK IN, M.D.
Department of Anesthesiology and Pain Medicine
St. Vincent's hospital, College of Medicine
The Catholic University of Korea
Seoul (Republic of Korea)
e-mail: ijangh@hanmail.net