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ORIGINAL ARTICLE

Effects of aminophylline on cognitive recovery after sevoflurane anesthesia

Mohamed R. El Tahan

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Abstract
Purpose Aminophylline accelerates the recovery from sevoflurane anesthesia. We studied the effects of escalating doses of aminophylline on cognitive and clinical recovery after sevoflurane anesthesia.
Methods After ethical approval and informed consent, 150 patients scheduled for elective surgery under sevoflurane-fentanyl anesthesia were randomly allocated to receive saline or 2, 3, 4 or 5 mg/kg of aminophylline ($n = 30$ for each) at the end of anesthesia (T_0). Short Orientation Memory Concentration Test (SOMCT) scores, entropy values, end-tidal sevoflurane concentrations (EtSevo), times to eyes opening and extubation, respiratory rate (RR) and tidal volume (TV) were recorded.
Results Compared to placebo, patients receiving 2, 3, 4 and 5 mg/kg of aminophylline had higher SOMCT scores [median (25th percentile/75th percentile) 20.6 (19/23), 21.5 (21/22), 24.5 (24–25), 25.5 (25/26), respectively, vs. 13.5 (13/14) at 30 min after extubation, and 24 (22/26), 25 (24/26), 27.5 (27–28), 27.5 (27/28), respectively, vs. 18.5 (18/19) at 45 min after extubation], higher entropy values for the first 10 min after T_0, lower EtSevo for the first 4 min after T_0, shorter times to eyes opening [5 (4.0/6.0), 5 (4.0/6.0), 4 (2.0/5.5), and 4 (2.0/6.0), respectively, vs. 9.8 (8.0/11.0) min], shorter times to extubation, shorter times to home discharge ($P < 0.001$), and higher RR and larger TV values. Patients who received 4 and 5 mg/kg of aminophylline showed higher SOMCT scores, 6 min shorter times to eyes opening and to extubation, and 58 min shorter times to home discharge.
Conclusion The administration of escalating doses of aminophylline accelerates postoperative cognitive recovery from sevoflurane anesthesia, as measured by the SOMCT, due to increased ventilatory elimination of sevoflurane.

Keywords Aminophylline · Sevoflurane · Anesthesia · Cognitive function · Recovery · Entropy

M. R. El Tahan (✉)
Anesthesiology Department, College of Medicine,
University of Dammam, P.O. 40289, Dammam,
Al Khobar 31952, Saudi Arabia
e-mail: mohamedrefaateltahan@yahoo.com

M. R. El Tahan
Anesthesiology Department, College of Medicine,
Mansoura University, Mansoura, Egypt

Introduction

Since volatile anesthetics can have adverse postoperative cognitive effects that may affect task performance, their rapid elimination could accelerate postoperative cognitive recovery, which in turn could reduce the time to home discharge after fast-tracking procedures [1–3].

Sevoflurane has been advocated for the routine anesthesia of ambulatory surgery patients. Experimental studies have shown that sevoflurane interferes with adenosine transport or key enzymes in adenosine metabolism, thereby increasing extracellular adenosine levels, which in turn activate adenosine A_1 receptors [4]. Compared to desflurane [5] and xenon [2] anesthesia, sevoflurane anesthesia is associated with slower emergence and delayed early postoperative cognitive recovery.

Studies over the last 20 years have shown that aminophylline significantly improves the clinical recovery from sevoflurane anesthesia [6, 7]. However, this agent is still not used on a widespread basis.

Aminophylline at 2–5 mg/kg accelerates the recovery from sevoflurane anesthesia [6–9] through increased

ventilatory elimination of sevoflurane and its action as an adenosine monophosphate-dependent phosphodiesterase inhibitor [10]; however, this may be associated with increases in heart rate (HR) [6–9]. The increase in the elimination of sevoflurane by aminophylline shortens the recovery, as it is known that aminophylline increases diaphragmatic contractility, minute ventilation, tidal volume and respiratory frequency [11].

Rapid recovery of consciousness after sevoflurane anesthesia may theoretically be associated with faster cognitive recovery and a shorter hospital stay. The ability of aminophylline to accelerate cognitive recovery after balanced anesthesia with sevoflurane has not yet been studied.

We hypothesized that the administration of escalating doses of aminophylline may improve cognitive recovery from sevoflurane anesthesia while inducing only minimal changes in HR. To test this, this study investigated the effect—in patients undergoing ambulatory surgery with sevoflurane anesthesia—of 2, 3, 4, and 5 mg/kg aminophylline on postoperative cognitive recovery, as measured by the Short Orientation Memory Concentration Test (SOMCT), response entropy (RE), state entropy (SE), end-tidal sevoflurane concentrations (EtSevo), hemodynamic values, and the times to eyes opening, extubation, and home discharge.

Materials and methods

This study followed the human trial requirements that are detailed in the CONSORT statement (http://www.consort-statement.org). After obtaining approval from the local institutional ethical committee, 150 ASA I–II patients aged 18–55 years who were scheduled for elective ambulatory surgery that required general anesthesia and would last >1 h were enrolled in this prospective double-blinded, placebo-controlled, randomized study. Written informed consent was obtained from all participants. This study was registered with http://www.clinicaltrials.gov in November 2010 (ref. NCT01022151).

The study involved five groups of patients who, at the end of surgery, were injected intravenously with saline 0.9% (placebo group) or 10, 15, 20, or 25 mg/mL aminophylline (aminophylline 2, 3, 4, and 5 mg/kg groups, respectively). To determine the sample size needed for this study, a pilot study revealed that the primary outcome variable of the present study, namely SOMCT [12] responses 30 min after extubation, was normally distributed in all groups with a standard deviation of 2.3. A priori power analysis indicated that a sample size of 27 for each group was sufficiently large to detect a 2.5-point difference in SOMCT means, with a type I error of 0.05/15 possible comparisons ($P = 0.0033$) and a power of 80%. To account for patient drop-out during the study, 10% more patients were added. Thus, all groups had 30 patients. The participants were allocated randomly into the five groups by drawing sequentially numbered, sealed, opaque envelopes containing a computer-generated randomization code.

The exclusion criteria were: history of significant cardiovascular, respiratory, neurological or psychiatric disease; cognitive dysfunction; pregnancy; obesity (body mass index $\geq$30 kg/m^2); recent infection or fever; alcoholism; drug dependence; previous adverse reactions to the study drugs; current treatment with xanthines, β-agonists, anticholinergic agents, tranquilizers, anticonvulsants or antidepressants; habitual coffee consumption exceeding 2 cups per day; inability to read; and presence of a serious hearing or vision impairment. All operations were performed by the same surgeons.

The primary outcome variable, the SOMCT—which measures cognitive function in terms of orientation, memory, and concentration—consists of six questions, and the total score ranges from 0 to 28. Higher SOMCT scores indicate better function. Scores exceeding 20 are considered normal (see the "Appendix") [12]. The SOMCT was explained and administered to all patients 30 min before induction and 30, 45, 60 and 90 min after extubation by an investigator who was blinded to the study solutions and not involved in the management of the patients. The secondary outcome variables were RE, SE, EtSevo, and times from sevoflurane discontinuation (T_0) to eyes opening, extubation, and home discharge.

The following procedure was followed for all patients. No premedications were given. Lactated Ringer's solution was infused at a rate of 2–3 mL/kg/h. The patients were monitored by electrocardiography, pulse oximetry, noninvasive measurement of blood pressure, and nasopharyngeal temperature measurement. RE and SE were monitored using specific entropy sensors that were placed on the patient's forehead according to the manufacturer's instructions. General anesthesia was induced with propofol (2–3 mg/kg), fentanyl (2–3 μg/kg), and rocuronium (0.6 mg/kg), and tracheal intubation was performed when the train-of-four (TOF) revealed maximal blockade. Based on entropy readings, where the end-points were an SE of $\leq$50 and an SE-RE difference of <10 [13], anesthesia was maintained with a 0.5–1.5 minimum alveolar concentration of sevoflurane (MAC-Sevo) in combination with 40% air in oxygen in a semi-closed circuit with a total gas flow of 1 L/min. The patient's lungs were ventilated mechanically to maintain end-tidal concentrations of carbon dioxide at 35–40 mmHg. Rocuronium was given incrementally to maintain suppression of the second twitch in TOF. Normothermia was maintained by using forced-air warming blankets. Intravenous lornoxicam 16 mg, paracetamol 15 mg/kg and granisetron 1 mg were given to all patients during surgery. Supplementary doses of muscle relaxant were not administered from 30 min before the end of the

surgery onwards. During skin closure, when the TOF ratio ranged between 0.3 and 0.5, the neuromuscular blockade was antagonized with 50 μg/kg neostigmine and 10 μg/kg glycopyrrolate. When the last skin suture was performed, sevoflurane was discontinued and the patient's lungs were ventilated with 100% oxygen using a gas flow of 5 L/min. Subjects were allocated randomly to five groups ($n = 30$ for each) by drawing sequentially numbered, sealed, opaque envelopes containing a computer-generated randomization code to receive intravenous injection of 0.2 mL/kg of a study solution containing either saline 0.9% solution (placebo group) or 10, 15, 20, or 25 mg/mL of aminophylline (aminophylline 2, 3, 4, and 5 groups, respectively). All study solutions were injected within 1 min of the discontinuation of sevoflurane (T_0). The patient was not stimulated during this period. The test solutions looked identical and were prepared in identical syringes labeled "study drug." The attending anesthesiologists who administered the anesthetics and established awakening were not involved in patient data collection. All staff were unaware of the randomization code. The average intraoperative HR and the changes in RE, SE, EtSevo, HR, mean arterial blood pressure (MAP), respiratory frequency and tidal volumes were recorded every min after T_0 for 15 min. Tracheal extubation was performed immediately when all extubation criteria were achieved (TOF ratio $\geq$ 0.9, spontaneous ventilation, the ability to follow verbal commands, eyes opening, head lift $\geq$5 s, and handgrip). The level of consciousness was assessed by using simple verbal commands ("open your eyes," "move your hand") and was repeated up to three times with increasing forcefulness if the subject failed to respond. Recovery from anesthesia was assessed by the times from T_0 to spontaneous eye opening, squeezing the investigator's hand on receiving a verbal command, and tracheal extubation. After transfer to the post-anesthesia care unit (PACU), the patient was assessed every 5 min using the modified Aldrete score [14] until it reached at least 9 points; the time needed to reach 9 points was recorded. Postoperative analgesia was provided by 0.5 mg/kg i.v. boluses of meperidine. HR, MAP, respiratory rate, peripheral oxygen saturation, and the degree of sedation [as measured by using a four-point verbal rating score (VRS) composed of "awake," "drowsy," "rousable," or "deep sleep"] were recorded at the end of anesthesia, on extubation, on admission to the PACU, and every 15 min until discharge to the ward. Regarding discharge to the ward, no attempt was made to speed up this process: the patient was only discharged from the PACU if he/she was alert, orientated to the time and place, conversant, and cooperative, if the vital signs had been stable for at least 30 min, if the patient could sit up without dizziness or nausea, if the pain was considered tolerable, and the modified Aldrete score was $\geq$9. The patient was deemed to be ready to go home according to Philip and co-workers [15] if the vital signs had been stable for at least 1 h, the pain was controllable by oral analgesics, there was no or only mild nausea or emesis, and the patient could walk without dizziness and retain oral fluids. The time from T_0 to PACU discharge was recorded, as were the total doses of meperidine used, the time from T_0 to home discharge, the time from T_0 to home readiness, and postoperative complications, including arrhythmia, tremors, nausea, vomiting, seizures, shivering, agitation, or hypoxemia (SpO_2 <90%).

Statistics

The data were tested for normality by using the Kolmogorov–Smirnov test. Generalized linear models were used to test the probability distribution of the predictors of the SOMCT. Repeated-measures analysis of variance (ANOVA) served to analyze serial changes in the SOMCT, entropy variables, Etsevo, HR, MAP, respiratory rate, tidal volume, oxygen saturation, and VRS at different times after T_0. Fisher's exact test was used for categorical data. Repeated-measures ANOVA was used for continuous parametric variables, and the differences were then tested by Tukey's Honestly Significant Difference post hoc test to evaluate the effects of time, group, and interaction. The repeated lag autocorrelation (time series) mixed effects model showed similar results to those obtained by ANOVA. Kruskal–Wallis one-way ANOVA was performed for intergroup comparisons for the nonparametric variables, including RE, SE, EtSevo, SOMCT, times to eye opening, hand squeeze, extubation and to reach an Aldrete score $\geq$9, and the total doses of used meperidine; post hoc pair-wise comparisons were performed using the Wilcoxon rank sum t test. Linear regression served to analyze the correlation between the SOMCT (independent variable) and the secondary endpoints; namely, RE, SE, and EtSevo after T_0, and the times from T_0 to PACU discharge, home readiness, and home discharge (dependent variables). Linear regression was used to analyze the correlation between the incidence of postoperative shivering and agitation and the EtSevo after T_0, SOMCT and the times from T_0 to spontaneous eye opening, response to a verbal command, tracheal extubation, PACU discharge, home readiness, and home discharge. The data were expressed as mean $\pm$ SD, number (%), median (range), or median (25th percentile/75th percentile). A value of $P < 0.05$ was considered to indicate statistical significance.

Results

All 150 patients completed the study. The five groups did not differ significantly in terms of gender, mean age,

Table 1 Patients characteristics

	Placebo ($n = 30$)	Aminophylline 2 ($n = 30$)	Aminophylline 3 ($n = 30$)	Aminophylline 4 ($n = 30$)	Aminophylline 5 ($n = 30$)
Age (years)	41.7 (4.3)	39.3 (7.1)	42.9 (5.4)	37.9 (8.6)	38.1 (6.6)
Sex (male/female)	19/11	23/7	20/10	21/9	23/7
Weight (kg)	74.9 ± 10.32	76.0 ± 8.02	77.4 ± 7.63	79.8 ± 5.31	76.5 ± 6.90
Height (cm)	167.3 ± 5.55	169.5 ± 4.31	166.2 ± 6.63	169.1 ± 3.73	171.3 ± 5.42
ASA physical status (I/II)	17/13	15/15	18/12	20/10	19/11
Types of surgery					
General	5	3	4	2	3
Breast surgery	2	3	0	0	1
Ear, nose and throat	15	16	15	19	17
Gynecological	2	3	3	1	2
Orthopedic	6	5	8	8	7
Duration of surgery (min)	131.0 ± 44.8	137.7 ± 41.2	128.6 ± 30.6	123.3 ± 43.7	133.3 ± 29.7
Duration of anesthesia (min)	147.7 ± 51.3	151.9 ± 59.9	140.0 ± 42.8	131.9 ± 68.1	145.5 ± 48.5

Data are presented as median (range), number, and mean ± SD

Aminophylline 2, aminophylline 2 mg/kg; aminophylline 3, aminophylline 3 mg/kg; aminophylline 4, aminophylline 4 mg/kg; aminophylline 5, aminophylline 5 mg/kg; ASA, American Society of Anesthesiologists

weight, height, or ASA physical status, type of surgery, and durations of surgery and anesthesia (Table 1). The groups also did not differ significantly in terms of baseline RE, SE, EtSevo (Figs. 1a, b, 2, respectively), HR, MAP, respiratory rate, and tidal volumes (Table 2).

Compared to the placebo group, the four aminophylline groups had significantly higher RE and SE values and significantly lower EtSevo values for the first 10 min after T_0 ($P < 0.001$) (Figs. 1a–b, 2, respectively). Moreover, compared to the patients who received 2–3 mg/kg aminophylline, the patients receiving 4–5 mg/kg aminophylline had significantly higher RE and SE values ($P < 0.001$), and significantly lower EtSevo values ($P < 0.001$) for the first 4 min after T_0 (Figs. 1a–b, 2, respectively).

The baseline SOMCT scores of the five groups were similar. However, compared to the placebo group, the aminophylline groups had significantly higher postoperative SOMCT scores 30 and 45 min after extubation ($P < 0.001$) (Fig. 3). Patients who received 4–5 mg/kg aminophylline had significantly higher SOMCT scores than all the other groups 30 and 45 min after extubation ($P = 0.002$) (Fig. 3).

Linear regression analysis revealed significant correlations between the SOMCT values 30, 45, 60 and 90 min after extubation and the secondary endpoints, namely RE, SE, and EtSevo in the 15 min after T_0. SOMCT showed a significant positive correlation with RE and SE 2–15 min after T_0, and a significant negative correlation with EtSevo 2–7 min after T_0 (Table 3). SOMCT values 30, 45, and 60 min after extubation showed a significant negative correlation with the times from T_0 to PACU discharge, home readiness, and home discharge (Table 3).

The five groups were similar with regard to average intraoperative HR and perioperative oxygen saturation. The five groups also did not differ significantly in terms of the perioperative HR and MAP values (Table 2), but the patients who received aminophylline had significantly faster respiratory rates and larger tidal volumes after the administration of the study's solution and at the time of extubation than the placebo patients ($P < 0.04$) (Table 2).

However, compared to the placebo group, the aminophylline groups all recovered from sevoflurane anesthesia significantly faster, as indicated by the times to eyes opening, response to verbal commands, extubation, attainment of an Aldrete score ≥9, PACU discharge, home readiness, and home discharge ($P < 0.001$) (Table 2). The patients who received 4–5 mg/kg aminophylline had significantly shorter recovery times compared to the other groups ($P < 0.05$) (Table 2).

The placebo group had significantly higher VRS values after extubation and at arrival in the PACU than the aminophylline groups ($P < 0.01$). The five groups required similar total meperidine doses (Table 2).

All five groups were similar in terms of the overall incidence of arrhythmia, tremors, nausea and vomiting, seizures, and hypoxemia, but the placebo group patients were significantly more likely to develop shivering and agitation than the aminophylline groups (Table 2).

Linear regression analysis showed nonsignificant correlations between the incidence of postoperative shivering

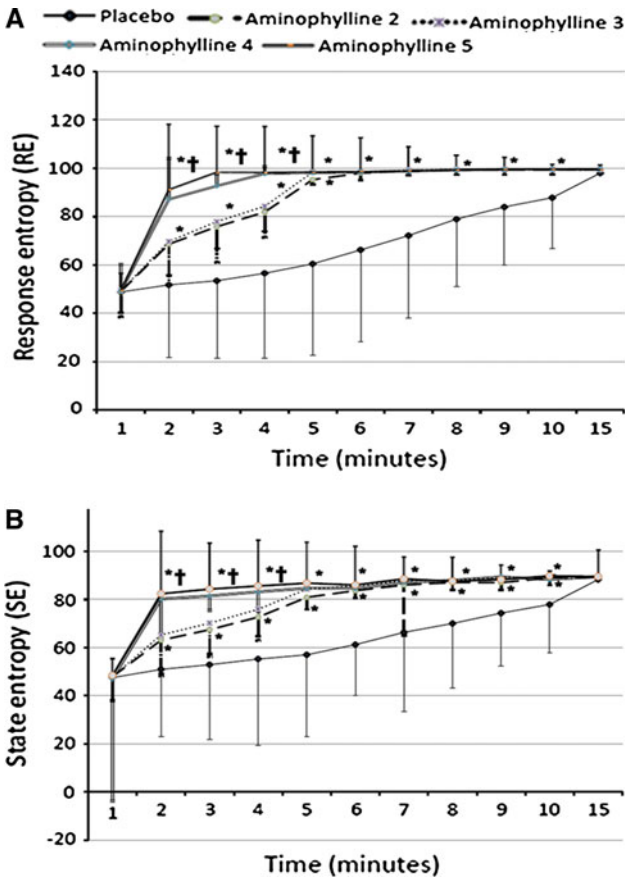

Fig. 1 **a** Response entropy (RE) changes, **b** state entropy (SE) changes ($n = 30$ in each). Data are presented as median (range). *$P < 0.001$ was considered significant compared with the placebo group, †2 mg/kg and 3 mg/kg aminophylline groups. Aminophylline 2, aminophylline 2 mg/kg; aminophylline 3, aminophylline 3 mg/kg; aminophylline 4, aminophylline 4 mg/kg; aminophylline 5, aminophylline 5 mg/kg

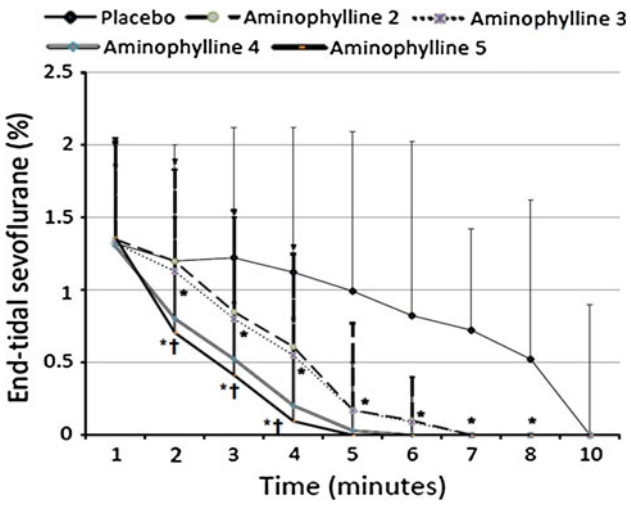

Fig. 2 The end-tidal concentration of sevoflurane (EtSevo) changes ($n = 30$ in each). Data are presented as median (range). *$P < 0.01$ was significant compared with the placebo group, †2 mg/kg and 3 mg/kg aminophylline groups. Aminophylline 2, aminophylline 2 mg/kg; aminophylline 3, aminophylline 3 mg/kg; aminophylline 4, aminophylline 4 mg/kg; aminophylline 5, aminophylline 5 mg/kg

and agitation and the times from T_0 to spontaneous eye opening, response to a verbal command, tracheal extubation, PACU discharge, home readiness, and home discharge ($P < 0.05$). The incidence of postoperative shivering and agitation showed a significant positive correlation with EtSevo values 4–10 min after T_0 ($P < 0.02$), and a significant negative correlation with SOMCT scores at 30 and 45 min after extubation ($P < 0.03$) (Table 4).

Discussion

The effect of aminophylline on postoperative cognitive recovery has not yet been studied. The present study showed that the postoperative use of escalating doses of aminophylline after sevoflurane anesthesia accelerated postoperative cognitive recovery, induced higher entropy and respiratory rate values and lower EtSevo and sedation scores, and shortened the times to eyes opening, response to verbal commands, extubation, achievement of an Aldrete score ≥9, PACU discharge, home readiness, and home discharge. This indicates that aminophylline may be useful for patients undergoing day case surgery or those vulnerable to postoperative cognitive dysfunction. In particular, it was observed that the larger doses of aminophylline (4–5 mg/kg) were associated with a faster and better recovery pattern, and that this was associated with non-significant changes in HR. Unsurprisingly, postoperative cognitive recovery, as measured by the SOMCT, correlated significantly positively with entropy values and negatively with EtSevo and the times to PACU discharge, home readiness, and home discharge.

There are several electroencephalography-based methods for monitoring the depth of anesthesia: Bispectral Index, Entropy, and Narcotrend. One study has shown that the Entropy method reduces the times to eye opening and response to command along with the dose of anesthetic drugs [16]. Entropy consists of two parameters, namely SE, which reflects the degree of hypnosis in the patient, and RE, which reflects the electromyographic response of the facial muscles to noxious stimulation [17]. Both parameters can distinguish between the awake and unconscious states [18]. In the present study, escalating doses of aminophylline both significantly increased the entropy values and shortened the recovery times. Similarly, several other studies reported higher Bispectral Index values and faster recovery after intravenous aminophylline administration [6–9, 19].

All five groups in the present study had similar perioperative HR values. Another investigator also failed to find

Table 2 Patient data

	Placebo ($n = 30$)	Aminophylline 2 ($n = 30$)	Aminophylline 3 ($n = 30$)	Aminophylline 4 ($n = 30$)	Aminophylline 5 ($n = 30$)
Average intraoperative heart rate (min)	76 ± 12.56	74 ± 10.15	69 ± 13.76	70 ± 11.42	72 ± 12.78
Time to eyes opening (min)	9.8 (8.0/11.0)	5 (4.0/6.0)[a]	5 (4.0/6.0)[a]	4 (2.0/5.5)[ab]	4 (2.0/6.0)[ab]
Response time (min)	10.9 (9.2/12.2)	6.2 (5.2/7.2)[a]	6.0 (5.0/7.0)[a]	5.2 (3.2/7.2)[ab]	5.0 (3.0/7.0)[ab]
Time to extubation (min)	11.3 (9.5/12.5)	7.0 (6.0/7.9)[a]	6.8 (5.5/7.8)[a]	5.9 (4.0/7.2)[ab]	5.5 (3.5/7.5)[ab]
Time to reach an Aldrete score ≥9 (min)	15.3 (13.2/17.2)	9.2 (8.2/10.0)[a]	9.0 (8.0/10.0)[a]	8.0 (6.0/9.9)[ab]	7.7 (5.7/9.4)[ab]
Total dose of meperidine used (mg)	25 (15/30)	25 (15/26.2)	25 (20/30)	25 (20/30)	25 (20/30)
Time to PACU discharge (min)	58.2 ± 4.90	42.4 ± 1.81[b]	41.2 ± 2.04[b]	32.6 ± 2.33[ab]	30.7 ± 2.94[ab]
Time to home readiness (min)	142.7 ± 9.99	118.8 ± 7.04[b]	120.6 ± 5.61[b]	96.3 ± 4.11[ab]	94.7 ± 4.82[ab]
Time to home discharge (min)	178.5 ± 15.34	145.9 ± 16.80[b]	147.4 ± 14.94[b]	121.9 ± 18.84[ab]	119.2 ± 20.32[ab]
Heart rate (beat/min)					
At the end of anesthesia	68 ± 6.37	65 ± 8.69	68 ± 6.33	69 ± 7.82	69 ± 6.70
After administering the study solution	74 ± 6.68	73 ± 5.39	77 ± 4.49	74 ± 6.15	76 ± 5.50
After extubation	96 ± 5.94	97 ± 3.71	97 ± 8.64	95 ± 8.10	98 ± 7.71
Upon arrival at PACU	80 ± 5.92	82 ± 6.63	79 ± 4.96	79 ± 6.55	77 ± 4.90
Upon arrival at the ward	71 ± 5.95	70 ± 4.71	73 ± 6.80	67 ± 5.53	69 ± 4.71
Mean arterial blood pressure (mmHg)					
At the end of anesthesia	85 ± 9.11	89 ± 10.12	93 ± 8.77	88 ± 9.00	91 ± 10.73
After administration of study solution	89 ± 10.55	91 ± 11.24	95 ± 10.94	92 ± 12.80	93 ± 9.85
After extubation	107 ± 10.52	110 ± 9.32	99 ± 12.03	106 ± 9.95	102 ± 8.90
Upon arrival at PACU	81 ± 7.54	79 ± 8.36	85 ± 9.03	83 ± 8.44	81 ± 7.84
Upon arrival at the ward	90 ± 6.32	89 ± 8.45	90 ± 7.74	92 ± 6.95	91 ± 9.53
Respiratory rate (breaths/min)					
At the end of anesthesia	13.6 ± 1.65	14.9 ± 1.83	13.0 ± 1.93	14.9 ± 1.43	14.8 ± 1.12
After administration of study solution	14.0 ± 1.93	17.9 ± 1.88[c]	18.4 ± 1.65[c]	19.8 ± 1.73[c]	20.0 ± 1.90[c]
After extubation	15.8 ± 1.32	18.7 ± 1.77[c]	19.9 ± 1.43[c]	22.3 ± 1.10[c]	21.1 ± 1.63[c]
Upon arrival at the PACU	16.3 ± 1.12	16.5 ± 1.43	17.3 ± 1.96	16.6 ± 1.15	17.2 ± 1.33
Upon arrival at the ward	16.6 ± 1.35	15.6 ± 1.47	17.0 ± 1.80	16.6 ± 1.23	17.0 ± 1.95
Tidal volume (ml)					
At the end of anesthesia	381.9 ± 50.57	395.4 ± 41.71	410.8 ± 40.44	406.9 ± 27.81	413.1 ± 36.57
After administration of the study solution	395.6 ± 42.23	440.8 ± 46.52[c]	456.2 ± 45.01[c]	486.8 ± 32.39[c]	478.1 ± 34.12[c]
At extubation	411.6 ± 56.76	494.0 ± 52.13[c]	541.8 ± 49.59[c]	534.66 ± 35.58[c]	535.5 ± 48.30[c]
Shivering	3	1[c]	1[c]	1[c]	0[a]
Agitation	4	1[a]	0[a]	0[a]	0[a]

Data are presented as mean ± SD, median (25th percentile/75th percentile), and number

Aminophylline 2, aminophylline 2 mg/kg; aminophylline 3, aminophylline 3 mg/kg; aminophylline 4, aminophylline 4 mg/kg; aminophylline 5, aminophylline 5 mg/kg; response time, the times from T_0 to spontaneous eye opening; PACU, post-anesthesia care unit

[a] $P < 0.001$ compared with the placebo group

[b] $P < 0.02$ compared with the aminophylline 2 and aminophylline 3 groups

[c] $P < 0.04$ compared with the placebo group

significant changes in HR after administering 3 mg/kg aminophylline [6], but another study reported that 2 mg/kg aminophylline significantly increased HR [7]. Turan and coworkers indicated previously that high aminophylline doses (4–5 mg/kg) were followed by significant short-term HR increases [8, 9].

The present study revealed that aminophylline was associated with lower EtSevo values. This may relate to the concurrent increases in ventilatory frequency and tidal volumes and hence the faster elimination of sevoflurane. Thus, in an experimental study, aminophylline at the usual therapeutic dosage elicited increases in minute ventilation, tidal volume and respiratory frequency, both during resting breathing and at equivalent levels of hypercapnic stimulated breathing [11]. The increase in the elimination of sevoflurane by aminophylline shortened the recovery, as it

is known that aminophylline increases diaphragmatic contractility and pulmonary blood flow [11].

The increased use of sevoflurane has been accompanied by an increase in emergence agitation which varies widely between 2 and 80% depending on the scoring system and the anesthetic technique used, and is more frequently observed in children [20]. Although the rapid emergence sometimes induces shivering and agitation, only sevoflurane is associated with a high incidence of emergence agitation in infants and young children compared with propofol, which could not fully explained with the noted rapid emergence form sevoflurane [21]. Similarly, we failed to find a significant correlation between the incidence of shivering and agitation and the recovery times after sevoflurane anesthesia. Just like other groups who reported significant reductions in the incidence of postoperative shivering with earlier sevoflurane discontinuation [22], we found a significant positive correlation between the incidence of shivering and agitation and EtSevo values and a significant negative correlation with SOMCT scores at 30 and 45 min after extubation. Moreover, aminophylline significantly reduced the overall incidence of shivering and agitation after sevoflurane anesthesia by improving the quality of cognitive recovery and lowering end tidal sevoflurane concentration.

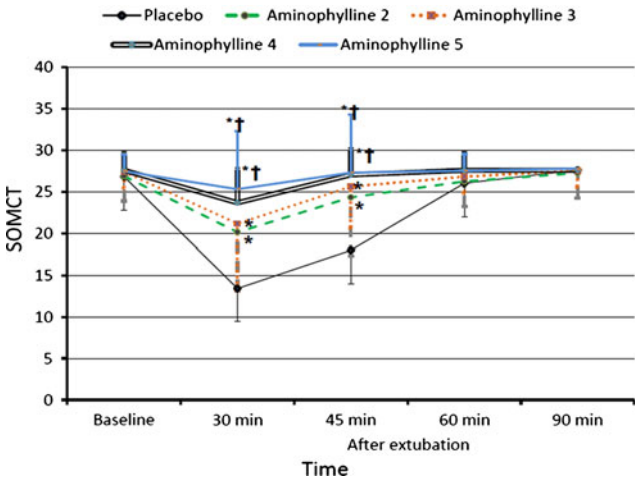

Fig. 3 Perioperative changes in the Short Orientation Memory Concentration Test (SOMCT) scores ($n = 30$ in each). Data are presented as median (range). *$P < 0.002$ significant compared with the placebo group, †2 mg/kg and 3 mg/kg aminophylline groups. Aminophylline 2, aminophylline 2 mg/kg; aminophylline 3, aminophylline 3 mg/kg; aminophylline 4, aminophylline 4 mg/kg; aminophylline 5, aminophylline 5 mg/kg

In the present study, the earlier cognitive recovery due to aminophylline was associated with shorter times to home discharge. It should be noted that meperidine was used for postoperative analgesia, in accordance with the institution's protocol. This could potentially adversely affect cognitive recovery after sevoflurane anesthesia, but it was observed that all five groups consumed similar amounts of meperidine.

While the present study showed that the recovery times from sevoflurane anesthesia were shortened by only 6 min by aminophylline, this was associated with a broader clinical impact. First, the postoperative cognitive recovery was improved, since the higher SOMCT scores 30 and 45 min after extubation were increased by 25 and 17%,

Table 3 Linear regression analysis between the Short Orientation Memory Concentration Test (SOMCT) and secondary endpoints

	SOMCT 30 min	SOMCT 45 min	SOMCT 60 min	SOMCT 90 min
Response entropy				
Correlation coefficient	0.507	0.721	0.804	0.226
P value	<0.001	<0.001	<0.001	<0.01
State entropy				
Correlation coefficient	0.649	0.493	0.819	0.276
P value	<0.001	<0.001	<0.001	<0.01
End-tidal concentration of sevoflurane				
Correlation coefficient	−0.859	−0.518	−0.826	−0.362
P value	<0.001	<0.001	<0.001	<0.006
Time to PACU discharge				
Correlation coefficient	−0.197	−0.221	−0.209	−0.061
P value	0.004	0.001	0.001	0.379
Time to home readiness				
Correlation coefficient	−0.252	−0.273	−0.262	−0.116
P value	<0.001	<0.001	<0.001	0.095
Time to home discharge				
Correlation coefficient	−0.299	−0.322	−0.310	−0.147
P value	<0.001	< 0.001	<0.001	0.073

Significant when $P < 0.05$

PACU, post-anesthesia care unit

Table 4 Linear regression analysis for postoperative shivering and agitation and end-tidal concentration of sevoflurane and SOMCT

	Etsevo at 4 min	Etsevo at 8 min	Etsevo at 10 min	SOMCT 30 min	SOMCT 45 min
Shivering					
Correlation coefficient	0.199	0.221	0.216	−0.173	−0.189
P value	0.016	0.007	0.003	0.034	0.021
Agitation					
Correlation coefficient	0.172	0.236	0.245	−0.153	−0.185
P value	0.038	0.004	0.003	0.041	0.020

Significant when $P < 0.05$

EtSevo, end-tidal concentration of sevoflurane; SOMCT, the Short Orientation Memory Concentration Test scores

respectively. Second, the times to arrival in the PACU and home discharge were shortened by 17 and 45 min, respectively. Third, our results show that the improved discharge times can be attributed to improved cognitive recovery.

The present study suffers from some important limitations. First, short-term changes in cognition may relate to emergence delirium, which was not addressed in the present study. Emergence delirium is a change in mental status characterized by a reduced awareness of the environment and a disturbance in attention. Second, the neuropsychological tests that are used most widely to assess the early and late recovery of cognitive function after anesthesia include Trieger's Dot Test and the Digit Symbol Substitution Test [23]. However, these tests can be impractical, as they require more time than other tests. The SOMCT was used in the present study because it is simple and does not involve a written component. Moreover, Katzman and colleagues [12] have validated the SOMCT as a measure of cognitive impairment, as they showed it could discriminate between mild, moderate, and severe cognitive deficits. In addition, several previous studies have used the SOMCT to assess postoperative cognitive dysfunction after anesthesia [2, 5, 24].

Thus, further studies are needed to examine the effect of aminophylline on early and late cognitive recovery after sevoflurane, desflurane and intravenous anesthesia; these studies should employ neuropsychological tests other than the SOMCT, and should focus on specific types of surgery.

In conclusion, the administration of escalating doses of aminophylline accelerates postoperative cognitive recovery from sevoflurane anesthesia, as measured by the SOMCT, due to increased ventilatory elimination of sevoflurane.

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Appendix

See Table 5.

Table 5 Short Orientation Memory Concentration Test (SOMCT)

What is the current year?	Correct answer scores 4; incorrect answer scores 0.
What is the current month?	Correct answer scores 3; incorrect answer scores 0.
What time is it?	Correct answer scores 3; incorrect answer scores 0.
Count backwards from 20 to 1*	Maximum score 4
Say the months of the year* backwards	Maximum score 4
Repeat the information given in the preceding sentence†	Maximum score 10

The blinded assessor tells the patient the current time of day, day and year; gives a phrase comprising five items of information (name, surname, street number and name and town (e.g., Fahad Al Qahtani, 23th, Makkah str., Al Khubar); and 5 min later asks the questions in the same order in the previous table

* One point subtracted for each mistake; more than 4 mistakes still score 0

† Two points subtracted for each mistake (name, surname, street name, street number and town)

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