Received: 16 February 2023 | Revised: 14 May 2023 | Accepted: 8 June 2023

DOI: 10.1002/hsr2.1362

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

The effect of aminophylline on the recovery profile after hysterectomy: A randomized controlled double-blinded study

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Abstract

Background and Aims: In anesthesia practice, aminophylline is clinically used to treat bronchospasm. However, due to its antagonistic effect on adenosine, studies have recently focused on the drug's ability to enhance the recovery profile. The aim of this study was to investigate the hypothesis that the administration of aminophylline leads to better recovery after general anesthesia in hysterectomy.

Methods: This randomized controlled double-blinded study, was conducted at Alzahra academic hospital in Guilan, Iran. During December 2022 to March 2023, 70 eligible women scheduled for elective abdominal hysterectomy were divided into two groups. Group A: received 3 mg/kg IV aminophylline diluted in 100 mL of normal saline and Group C: received 100 mL IV normal saline. The time to recovery of consciousness, tracheal extubation and discharge from post anesthesia care unit were recorded. In addition, heart rate, and mean arterial blood pressure were measured at 10 point times including; baseline (T0), immediately before the administration of aminophylline (T1), every 5 min until the end of the surgery (T2,T3,T4,T5,T6), and every 15 min in PACU(T7,T8,T9).

Results: There was no significant difference in terms of demographic data between the study groups. Comparing the two groups, the time of ROC was shorter in Group A than group C; 5.95 ± 1.12 and 8.5 ± 1.77 for Groups A and C, respectively ($p < 0.001$). The extubation time was shorter in Group A than group C; 7.79 ± 1.48 and 10.55 ± 3.02, for Groups A and C, respectively ($p < 0.001$). In addition, the discharge time was also shorter in group A than Group C; 30.17 ± 5.24 and 37.57 ± 4.41 for Groups A and C, respectively ($p < 0.001$). Not serious side effects were reported among 71.4% of cases in Group A and 51.4% in Group C ($p = 0.086$).

Conclusion: Administration of aminophylline at a dose of 3 mg/kg IV improves the recovery profile after abdominal hysterectomy without serious adverse effects.

KEYWORDS

aminophylline, general anesthesia, recovery

1 | INTRODUCTION

Operating rooms (OR) are one of the most important parts of a hospital, which contribute to both the revenue and workload. Delayed emergence and prolonged recovery are anesthesia-related complications that result in prolonged OR turnover and increased costs. Several underlying mechanisms, pharmacological, and non-pharmacological have been known for delayed emergence.[1] However, it may occur as a benign condition even when all standards of general anesthesia (GA) have been considered. Therefore, when the anesthesiologist faces this challenge, an accurate diagnosis must be made to establish appropriate immediate management.[2] It is well known that inefficient management of turnover time in the OR which is related to the recovery time from anesthesia and preparation of the OR for the next patient, leads to patients' dissatisfaction, long waiting lists, and wasted costs. Therefore, optimizing the use of OR time is a valuable goal and investigation to find a cost-effective and safe central nervous system (CNS) stimulant agent for rapid recovery from anesthesia is crucial.[3,4] Recovery from anesthesia is defined as a state of consciousness when the patient is awake and aware of his surroundings.[5] Emergence from anesthesia points to the final stage of anesthesia when the patient progresses from unconsciousness to full wakefulness and effective spontaneous breathing.[6] Despite significant progress in the field of anesthesia, the main neurobiological mechanisms of GA, getting unconscious, and emergence from anesthesia are not well recognized.[7] In this regard, a few studies have investigated the arousal properties of aminophylline which is clinically administrated as a bronchodilator. Aminophylline consists of theophylline and ethylenediamine in a ratio of 2:1. Theophylline acts as a histone deacetylase activator, phosphodiesterase inhibitor, and adenosine receptor blocker.[8,9] However, several questions still remain unanswered, such as the best timing and the optimal dosage of aminophylline that has the most efficacy and the least adverse effects.

2 | MATERIALS AND METHODS

After the approval of the Research Ethics Committee of Guilan University of Medical Sciences, the study protocol was documented as IR.GUMS.REC.1401.464, and registered as the number: IRCT20170314033069N5, this randomized controlled double-blinded study was carried out at Alzahra academic center. It was a referral hospital specific for all types of elective and emergency gynecologic and obstetrics surgeries. During December 2022 to March 2023, women candidates for elective abdominal hysterectomy under GA were screened for eligibility.

Inclusion criteria: Women aged 30 to 70, I&II American Society of Anesthesiologists (ASA class) who underwent abdominal hysterectomy under GA due to nonmalignant indications (irregular bleeding with nonresponse to medical treatments, adenomyosis, uterine myomato, etc) and who gave informed consent.

Exclusion criteria: Hysterectomy due to malignancy, any history of allergy to aminophylline or drug components, liver dysfunction, smokers, patients with a history of arrhythmia, epilepsy, unexpected conditions such as bleeding and unstable hemodynamics, significant complications such as arrhythmia and seizures, any situations that other surgeons rather than obstetrics (urology, general surgery, vascular surgery, etc) involved.

Randomization and blinding: A nurse, who was not engaged in the study, allocated intervention and placebo by the computer-generated random quadruple blocks sequence (https://www.sealedenvelope.com) with a ratio of 1:1 through a list of eligible women.

Anesthesia management: On the arrival of the patient to the OR, standard monitoring including electrocardiogram (ECG), noninvasive blood pressure (NIBP), and pulse oximetry (SaO2), was applied, a cannula with proper gauge was secured, and hydration with crystalloids was started. After the initial preoxygenation with 100% oxygen, anesthesia was inducted by midazolam 1 mg, fentanyl 3 μg/kg, 1.5 mg/kg propofol, and 0.5 mg/kg atracurium and tracheal was intubated. The anesthesia was maintained by isoflurane 0.8 MAC, in an O_2/NO_2 mixture, and the ETCO2 values were kept at 36–40 mmHg. It should be noted that, due to the impact of surgeons' experience on the outcomes, all the surgeries were performed by a single surgeon. After the hysterectomy, patients in Group C received 100 mL of normal saline IV and in Group A, the patients received 3 mg/kg IV aminophylline (Caspian Pharmaceutical Company, Iran, 250 mg in 10 mL Amp) diluted in 100 mL of normal saline. At the end of the surgery, atropine 0.02 mg/kg, and neostigmine 0.04 mg/kg were administered for the reversal of neuromuscular block. They were transferred to the postanesthesia care unit (PACU) and were discharged after obtaining a score of 10 based on Aldrete criteria.

Measurement point times and outcomes: The primary outcome; the time to recovery of consciousness (ROC) (in minutes), which was defined as the time from discontinuation of anesthetic agents until the eye-opening to verbal commands. The time to tracheal extubation and discharge from PACU which both were measured from the time of stopping anesthesia, were the other main outcomes. Hemodynamic parameters including heart rate (HR) and mean arterial pressure (MAP) were documented at baseline (T0), immediately before the administration of aminophylline (T1), every 5 min until the end of the surgery(T2,T3,T4,T5,T6), and every 15 min in PACU (T7,T8,T9). Adverse events such as light-headedness, vomiting, chest discomfort, arrhythmia, hypotension, or hypertension were also recorded.

2.1 | Statistical analysis

To analyze the data SPSS version 21 was used. Data were described in terms of the mean ± standard deviation or frequencies. Two independent *T* test were used to analyze continuous quantitative data in case of normal distribution and in case of non-normal distribution, the equivalent nonparametric test was performed. χ^2

test was used to compare categorical data. The nonparametric data were presented as median (range) and the parametric data as mean ± standard deviation. All the tests were done two-sided. A $p < 0.05$ was considered significant and $p < 0.01$ were considered statistically highly significant.

3 | RESULTS

Finally, 70 eligible women who underwent abdominal hysterectomy completed the survey (Figure 1). In terms of demographic data including age, BMI, ASA classification, and the there was no significant difference between the two groups (Table 1). Comparing two groups, group A showed higher HR at T5 ($p = 0.002$) to T8 ($p < 0.001$) than group C and this difference was statistically highly significant. Although a higher HR was recorded in group A at T1 to T4 and T9, the difference was not significant ($p > 0.05$). In terms of MAP, group A significantly showed higher values compared to group C at T5 ($p = 0.003$). There was a statistical difference between the studied groups at T2 to T9 but it was not significant ($p > 0.05$) (Tables 2 and 3). Comparing the two groups, the time to ROC was shorter in Group A than Group C; 5.95 ± 1.12 versus 8.5 ± 1.77 respectively ($p < 0.001$). The extubation time was shorter in Group A than group C; 7.79 ± 1.48 versus 10.55 ± 3.02, respectively ($p < 0.001$). In addition, the discharge time was also shorter in Group A than Group C; 30.17 ± 5.24 and 37.57 ± 4.41, respectively ($p < 0.001$) (Table 4). Transient side effects such as mild headache or nausea were observed among 71.4% of cases in Group A and 51.4% in Group C ($p = 0.086$). (Table 5). None of our patients required intraoperative intervention such as administration of inotropes or vasodilators/vasopressors.

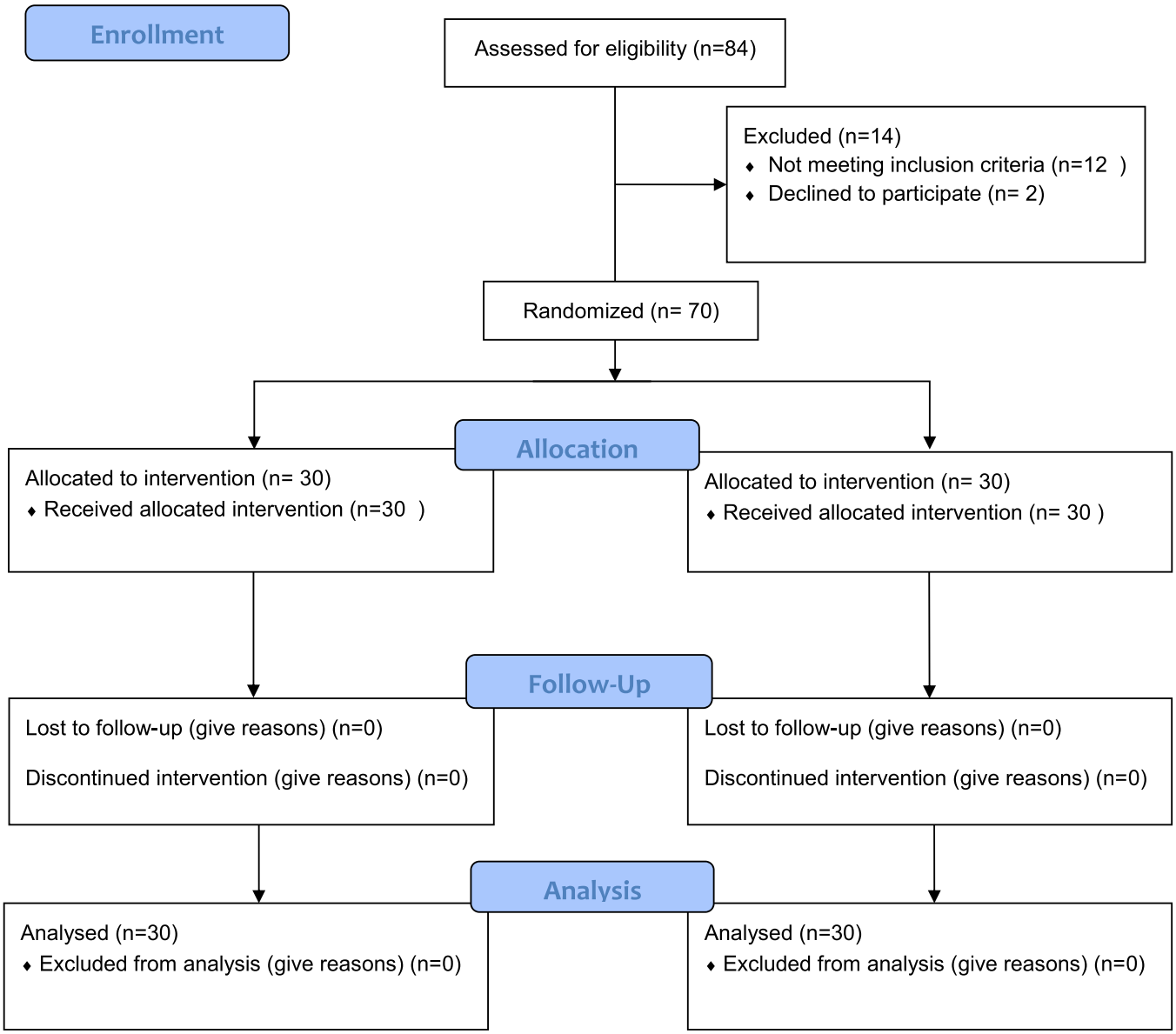

FIGURE 1 CONSORT flow diagram of the survey.

TABLE 1 Demographic variables and operation time.

Variable		Aminophylline (n = 35)	Control (n = 35)	p Value
Age (year) mean ± SD		51.51 ± 8.42	50.25 ± 7.69	0.517
BMI (kg/m^2) mean ± SD		28.44 ± 4.15	28.04 ± 4.17	0.689
ASA class number (percent)	I	20 (57.1)	23 (65.7)	0.461
	II	15 (42.9)	12 (34.3)	
Duration of surgery (min) mean ± SD		170.65 ± 8.95	168.28 ± 9.73	0.293

Abbreviation: ASA, American Society of Anesthesiologists.

TABLE 2 Comparison of changes in heart rate (bmp) from T0 to T9 between the two groups.

Time	Heart rate		p Value
	Aminophylline (n = 35) mean ± SD	Control (n = 35) mean ± SD	
Baseline(T0)	80.25 ± 7.73	81.37 ± 6.64	0.52
Before study drug administration(T1)	79.2 ± 7.35	79 ± 5.82	0.90
The first 5 min after injection(T2)	79.54 ± 7.29	79.02 ± 6.59	0.758
The Second 5 min after injection(T3)	81.42 ± 6.72	79.2 ± 6.19	0.154
The third 5 min after the injection(T4)	82.54 ± 6.37	79.94 ± 6.03	0.084
The fourth 5 min after the injection(T5)	85.28 ± 6.39	80.42 ± 5.88	0.002
The fifth 5 min after injection(T6)	89.48 ± 6.25	79.6 ± 5. 9	<0.0001
The first 15 min of recovery(T7)	88.17 ± 6.18	79.2 ± 5.68	<0.0001
The second 15 min of recovery(T8)	84.97 ± 6.43	79 ± 5.82	<0.0001
the third 15 min of recovery(T9)	80.85 ± 6.2	78.45 ± 5.72	0.097
In-group statistical estimation	<0.0001	<0.0001	
Intergroup statistical estimation	<0.0001		

TABLE 3 Comparison of changes in mean arterial blood pressure (mmHg) from T0 to T9 between the two groups.

Time	Aminophylline (n = 35) mean ± SD	Control (n = 35) mean ± SD	p Value
Baseline(T0)	79.05 ± 5.9	79.91 ± 7.65	0.602
Before study drug administration(T1)	77.11 ± 5.84	77.97 ± 7.31	0.59
The first 5 min after injection(T2)	77.74 ± 5.99	77.25 ± 7.28	0.762
The Second 5 min after injection(T3)	78.54 ± 5.89	76.6 ± 7.03	0.215
The third 5 min after the injection(T4)	79.2 ± 5.87	76.0 ± 7.68	0.054
The fourth 5 min after the injection(T5)	80.11 ± 5.87	75.37 ± 7.17	0.003
The fifth 5 min after injection(T6)	79.71 ± 5.59	76.68 ± 7. 14	0.053
The first 15 min of recovery(T7)	79.34 ± 5.63	76.68 ± 7.05	0.086
The second 15 min of recovery(T8)	78.2 ± 5.35	77.22 ± 6.89	0.513
the third 15 min of recovery(T9)	77.31 ± 5.63	76.74 ± 6.8	0.705
In-group statistical estimation	<0.0001	0.002	
Intergroup statistical estimation	<0.0001		

TABLE 4 Comparison of recovery variables between the two groups.

Variables	Group	Mean ± SD	*p* Value
Time to ROC (min)	Aminophylline	5.95 ± 1.12	<0.0001
	Control	8.5 ± 1.77	
Extubation time (min)	Aminophylline	7.79 ± 1.48	<0.0001
	Control	10.55 ± 3.02	
Discharge time (min)	Aminophylline	30.17 ± 5.24	<0.0001
	Control	37.57 ± 4.41	

Abbreviation: ROC, recovery of consciousness.

TABLE 5 Comparison of the reported side effects between the two groups.

Side effects	Status	Aminophylline Number (percent)	Control Number (percent)	*p* Value
	Yes	25 (71.4)	18 (51.4)	0.086
	No	10 (28.6)	17 (48.6)	

4 | DISCUSSION

The main finding of this study was that aminophylline resulted in an improvement in recovery parameters after GA. Overall, changes in ion channels, cellular systems, neurotransmitters, and secondary messengers are known as mechanisms of action of drugs. The underlying mechanism for the arousal and antihypnotic properties of aminophylline is thought to be the inhabitation of central adenosine receptors in the CNS. Meanwhile, it has been reported that caffeine-like effects of the drug, decrease GABA-ergic neurotransmission.[10–12] The results of this study were consistent with previous reports that made similar observations, and support the hypothesis that aminophylline antagonizes the effects of anesthetic agents. Our study showed that aminophylline can be administrated safely in abdominal hysterectomy. Although an increase in HR and MAP values was observed in group A, no intervention was required. It was revealed that administration of aminophylline at a dose of 3 mg/kg IV decreased the time to ROC time, tracheal extubation and discharge from PACU, compared to the control group. Kim and colleagues reported that aminophylline 3 mg/kg IV shortened the recovery time from GA in laparoscopy vaginal hysterectomy. They supported the respiratory effects of aminophylline, which is a methyl xanthine as a potent substance that centrally antagonizes adenosine.[13] Jeon and colleagues evaluated the effect of aminophylline 3 mg/kg IV on recovery profile and apnea time in brief gynecological procedures. They reported significantly better results in the treatment group compared to placebo.[14] Truant and colleagues demonstrated that aminophylline improves recovery from sevoflurane anesthesia and leads to early emerging from anesthesia. They also reported that this intervention was associated with better postoperative cognitive function and higher bispectral index (BIS) values.[15] Kadhim et al.[16] reported that aminophylline 4 mg/kg IV shortened the time to eye opening and extubation in orthopedic surgeries under GA. Aghabiklooel et al.[17] reported that aminophylline reverses the sedative effects of benzodiazepines and speed up the process of consciousness. Kasim et al.[18] showed that in patients receiving aminophylline 4 mg/kg IV before induction of anesthesia in pelvic-abdominal surgeries, the time to reach BIS of 80 was significantly shorter than the control group, and the time to extubation was significantly longer in control group. They supported the safe use of aminophylline for early ROC. Ghaffaripour et al.[12] reported that recovery time and BIS scores improved when aminophylline was given. Hupfl et al.[19] demonstrated the effects of aminophylline on BIS during inhalational and total intravenous anesthesia which was associated with significant increase in BIS up to 10 min after aminophylline injection. Imani et al.[20] showed that time to extubation decreased following administration of aminophylline at the dose of 1–5 mg/kg IV compared to control group in laparotomy surgeries. As mentioned above, the results of these studies are not the same. Definitely, the type of surgery, the duration of anesthesia and surgery, the chosen anesthetics, the time of aminophylline administration and the dosage as well as the experience of surgical team are all among influential factors. The evaluated parameters and the outcomes focused on were also different in these studies.

5 | LIMITATION

This study had a small sample size; the studied population was restricted to female gender and abdominal hysterectomy. Furthermore, women with significant comorbidities were excluded.

6 | CONCLUSION

Administration of aminophylline enhances the recovery profile in abdominal hysterectomy under general anesthesia without significant adverse side effects.

To confirm the safety and efficacy of this intervention to speed the emergence from anesthesia in clinical practice, further studies with a larger sample size in different surgical situations are recommended.

AUTHOR CONTRIBUTIONS

Misa Naghdipour Mirsadeghi: Conceptualization; writing—original draft. **Gelareh Biazar**: Conceptualization; writing—original draft. **Soheil Soltanipour**: Formal analysis. **Reyhaneh Shahrokhi Rad**: Writing—review & editing. **Zahra Hamidi Madani**: Data curation; writing—review & editing. **Laya Nikbin**: Data curation.

ACKNOWLEDGMENTS

All authors have read and approved the final version of the manuscript. Dr Gelare Biazar had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis. Also, the authors would like to thank Anesthesiology Research Center members of Guilan

University of Medical Sciences; Ms. Mohadese Ahmadi and Ms. Mahin Tayefeh Ashrafie for their collaboration in this study. This study was financially supported by the Vice-Chancellorship of Research and Technology, at Guilan University of Medical Science.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Related data of this project are available on request.

TRANSPARENCY STATEMENT

The lead author Gelareh Biazar affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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How to cite this article: Mirsadeghi MN, Biazar G, Soltanipour S, Rad RS, Madani ZH, Nikbin L. The effect of aminophylline on the recovery profile after hysterectomy: a randomized controlled double-blinded study. *Health Sci Rep*. 2023;6:e1362. doi:10.1002/hsr2.1362