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Effect of Aminophylline on Incidence of Apnea and Recovery Time during Propofol Sedation for Gastrointestinal Endoscopy

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ABSTRACT
Background: Apnea may occur during propofol sedation for endoscopy, which can be harmful to the patient and disruptive to the procedure.
Objective: To test the hypothesis that a small dose of aminophylline before propofol sedation may result in a lower incidence of apnea, as well as faster emergence from sedation.
Patients and Methods: The researchers conducted a single-center, prospective randomized controlled study on 76 adult ASA I or II patients with age ranged from 20 to 65 years old. They were admitted for upper gastrointestinal or colonoscopic endoscopies. All patients were sedated with 25µg fentanyl, 1mg/kg propofol bolus over 30 seconds, then propofol boluses (0.5 mg/kg) according to need. Patients were divided into two groups: Control group [Group C (n=38)], and a study group [Group Am (n=38)] who received 0.5 mg/kg aminophylline preoperatively. Apneas were counted during each procedure, and emergence from sedation was assessed with modified Aldrete score.
Results: There was a statistically significant decrease in the overall incidence of apneas with aminophylline premedication (P = 0.025), as well as a reduction in the number of apneas per bolus of propofol (P = 0.006). However, there was no statistically significant difference regarding the average time to modified Aldrete score both when tested after 5 minutes or after 10 minutes after discharge from the endoscopy room.
Conclusion: Premedication with a small dose of intravenous aminophylline significantly reduces the incidence of apnea during propofol sedation for gastrointestinal endoscopies, while its effect on emergence from sedation is not significant.
Keywords: Propofol sedation, Aminophylline, Gastrointestinal endoscopy.

INTRODUCTION

Propofol is a potent anesthetic with dose-dependent respiratory depression [(1)].

After intravenous injection of propofol, apnea occurs; the incidence and duration of apnea depend on the dose, rate of injection, and other premedications [(2)]. An anesthetic dose of propofol results in a 25% to 30% incidence of apnea in the absence of surgical or painful stimuli. Metabolic depression also decreases the $PaCO_2$ elevation. The duration of apnea with propofol may be prolonged to more than 30 seconds with the addition of opioids as premedication [(3)].

As with other sedative and anesthetic drugs, spontaneous ventilation for a patient under propofol sedation is dependent on a balance between the drug's respiratory depressant effects and decrease in carbon dioxide production (due to metabolic depression) versus the stimulatory effects of increased $PaCO_2$ resulting from apnea and stimulation from nociception. Propofol also depresses the respiratory response to hypoxia by acting on the carotid body chemoreceptors [(4)].

Endoscopy is the most common medical procedure performed under sedation. A safe and competent anesthetic service has to ensure rapid patient turnover and discharge, in addition to a high operator (endoscopist) and patient satisfaction. Medical practitioners from across the medical spectrum, ranging from operators to nurses to anesthesiologists, have been providing sedation for endoscopies, and the safety of some of these practices has been assessed [(5,6)]. In Ain Shams University Hospitals, nearly all endoscopy patients are managed by anesthesiologists, staff and residents, regardless of patient risk, type of procedure or planned depth of sedation, or specialty of the operator (surgical, internal medicine, and pediatric). This is consistent with the increasing involvement of anesthesiologists in endoscopy services around the world [(7)].

While a sedative dose of propofol (0.5 - 1 mg/kg) administered for a patient undergoing gastrointestinal endoscopy is significantly lower than an induction dose (1-2.5 mg/kg) [(8)], still, respiratory depression happens and apneic episodes are encountered, albeit less frequently and less severely. Nonetheless, even those less-encountered respiratory depression and episodes of apnea, which invariably result in hypoxia and a decrease in SpO_2, are potentially harmful to the patient and disruptive of the anesthetic practice and the endoscopic procedure.

The attending anesthesiologist has to ensure that the patient's airway is clear and patent, and at times, resort to stimulating or improving ventilation with painful techniques like jaw thrust. These maneuvers frequently decrease the level of sedation, and may lead to the patient's discomfort, awakening, and movement, disrupting the endoscopic procedure. Not infrequently, the anesthesiologist needs to give an additional dose of propofol, risking repeating the same unfavorable sequence of events. Aminophylline acts centrally as an adenosine antagonist [(9)]. Several clinical trials have shown that aminophylline decreases the depth and duration of propofol sedation [(10)]. Other studies have shown that aminophylline may be used to decrease the

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incidence of postoperative apnea in preterm neonates [11]. Aminophylline was also used to speed recovery from anesthesia in patients who had received propofol TIVA (total intravenous venous anesthesia) [12]. However, data on the impact of premedication with aminophylline, on the immediate postinduction respiratory effects of propofol anesthesia and sedation is scanty.

With the established role of peri-recovery aminophylline in improving the respiratory functions of patients who had received hypnotics and sedatives like propofol, the researchers in this study found it appropriate to explore the drug's potential in improving the respiratory function and decreasing incidence of apnea and hypoxia in endoscopy patients. It was decided to start this line of research with a small dose of aminophylline (0.5 mg/kg) to avoid its impact on consciousness at higher doses [13], which might lead to anesthesia resistance and patients' awareness.

This work aimed to test the hypothesis that a small dose of aminophylline before propofol sedation may result in a lower incidence of apnea, as well as faster emergence from sedation.

PATIENTS AND METHODS

Study design and participants

This single-center prospective randomized controlled study was conducted in the Gastrointestinal Endoscopy Unit of Ain Shams University Hospitals during the period from July 2022 to October 2022.

Inclusion criteria for patients: The American Society of Anesthesiologists (ASA) physical status classification system I or II. Upper or lower gastrointestinal endoscopy. Age 20-65 years. BMI: 20-30 kg/m^2 and body weight: 50 – 100 kg

Exclusion criteria: Tachycardia (above 110 b/m) or any sort of arrhythmia. Hypotension (below 90/60 mmHg). Patients with a history of respiratory disease or clinical respiratory symptoms (as the disease and its management could require additional aminophylline doses or include other confounding drugs/conditions), as well as morbidly obese patients (to exclude obstructive sleep apnea cases). History of seizures.

Sampling and Randomization

The patients were divided into two groups: Control group [Group C (n=38)], not receiving aminophylline premedication, and the study group, [Group Am (n=38)], where patients received 0.5 mg/kg aminophylline preoperatively. Computer-generated randomization was used to assign participants to either group C or group Am.

Procedures

Only patients in group Am received a premedication dose of 0.5 mg/kg aminophylline 10 minutes before admission to the endoscopy room. In the endoscopy room, each patient was given 25 µg fentanyl, then put into position (lateral decubitus), and oxygen via nasal prongs (4L/min) was provided. Sedation was then instituted with an initial bolus of 1mg/kg propofol, injected over 30 seconds. Increments of 0.5 mg/kg of propofol were added if needed.

Every patient was monitored with pulse oximetry, ECG, and non-invasive blood pressure monitoring. Number of apneas after each propofol injection, as well as the number of times SpO_2 dipped below 92% were recorded. When an apnea, or SpO_2 less than 92%, was encountered after IV propofol injection, the patient was examined for any airway obstruction, and occasionally a jaw thrust was briefly administered till the patient resumed regular breathing. There were no cases of prolonged apnea or hypoxia, and there was no need for interruption of the endoscopy procedure for resuscitation for any of the patients.

After discharge from the endoscopy room, the patients were assessed for their modified Aldrete score (Table 1), 5 and 10 minutes after their admission to the PACU room.

Table (1): Post-anesthesia recovery score - Modified Aldrete Score [14].

Category	Description	Score
Consciousness	Fully awake and orientated (name, place, date)	2
	Arousal on calling	1
	Not responding	0
Activity	Moves all 4 extremities voluntarily or on command	2
	Moves 2 extremities	1
	Unable to move extremities	0
Respiration	Breathes deeply and coughs freely	2
	Dyspnea, limited breathing, or tachypnea	1
	Apneic or on mechanical ventilation	0
Circulation	Blood pressure ± 20% of pre-anesthetic level	2
	Blood pressure ± 20% - 49% of pre-anesthetic level	1
	Blood pressure ± 50% of pre-anesthetic level	0
Oxygen Saturation	SpO2 > 92% on room air	2
	Supplemental O_2 required to maintain SpO2 > 90%	1
	SpO2 <92% with O_2 supplementation	0
Maximum Score		10

Ethical approval:

Approval for this study was obtained from The Research Ethical Committee of Faculty of Medicine, Ain-Shams University (code number: FMASU R 105/2022), and written informed consents were obtained from patients. The study was also registered in the Pan African Clinical Trial Registry (identification number: PACTR202208823864076). This study was conducted in compliance with the code of ethics of the world medical association (Declaration of Helsinki) for human subjects.

Statistical analysis

We analyzed our recorded data using the Statistical Package for Social Sciences, version 24.0 (SPSS Inc., IBM Corporation). Quantitative data were expressed as mean ± standard deviation (SD). Independent samples T-test of significance was used when comparing two means. Categorical data were presented as frequencies and appropriate proportions. Comparison between proportions was done using Chi-square test. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. P value ≤ 0.05 was considered significant while p-value < 0.001 was considered highly significant.

RESULTS

Seventy-six patients (52.6% [N = 40] males) were recruited (July – October 2022) into the study and were aged 20 to 65 years (Table 2).

Table (2): Baseline characteristics

	Group C	Group Am	P-value
Sex • Male • Female	22 (55%) 16 (44.4%)	18 (45%) 20 (55.6%)	0.358[a]
Age (Years)	54.11 ± 8.42	56.87 ± 6.23	0.108[b]
Body mass index (BMI) (kg/m^2)	23.82 ± 4.47	24.95 ± 5.18	0.313[b]

a. Chi-Square test. b. Independent T-test

Sixty patients (78.9%) underwent upper gastrointestinal endoscopies [Group C 31 patients (81.5%) and Group Am 29 patients (76.3%)]. 16 patients underwent colonoscopies [Group C 7 patients (18.4%), Group Am 9 patients (23.6%)] (Table 3). Overall, there was no statistically significant difference in the type of procedure across both groups (P = 0.57). Also, the average duration for endoscopies across both groups was quite similar (Group C 12.28 ± 4.74 minutes, Group Am 13.24 ± 5.18, P = 0.4).

Table (3): Types of Endoscopies

	Group C	Group Am	P value
Procedure • Upper GI • Colonoscopy	31 (81.5%) 7 (18.4%)	29 (76.3%) 9 (23.6%)	0.57[a]
Average duration of procedure, time (mean ± SD)	12.28 ± 2.94	13.24 ± 3.21	0.4[b]

a. Chi-Square test. b. Independent T-test

The number of endoscopies where oxygen saturation dipped below 92% was small, with no statistical difference between the two groups [Group C 6 patients (15.7%) and group Am 4 patients (10.5%), P value = 0.49]. However, the difference in the overall incidence of apnea between the groups was highly significant [Group C 16 patients (42.1%) and group Am 7 (18.4%), P = 0.025] (Table 4). While the difference in the number of propofol boluses per procedure between the two groups was barely insignificant (Group C 2.46 ± 0.95 and group Am 2.89 ± 1.01, P value + 0.054). There was a statistically significant difference in the number of apneas per bolus of propofol between the two groups (Group C 0.25 ±- 0.33 and group Am 0.079 ± 0.18, P value = 0.006) (Table 4).

Table (4): Respiratory Complications

	Group C (n=38)	Group Am (n=38)	P value
Number of endoscopies where $SpO_2 < 92\%$	6 (15.7%)	4 (10.5%)	0.49[a]
Number of Apneic Patients	16 (42.1%)	7 (18.4%)	0.025[a]
Number of Propofol boluses/endoscopy procedure (mean ± SD)	2.46 ± 0.60	2.89 ± 0.51	0.054[b]
Number of Apneas/bolus of propofol (mean ± SD)	0.25 ± 0.05	0.079 ± 0.018	0.006[b]

a. Chi-Square test. b. Independent T-test

However, there was no statistically significant difference regarding modified Aldrete score after discharge from the operating room, both when tested after 5 minutes (Group C 9.04 ± 0.94 and group Am 8.89 ± 0.69, P value = 0.445), or after 10 minutes (Group C 9.49 ± 0.38 and group Am 9.43 ± 0.44, P = 0.5) (Table 5).

Table (5): Emergence from sedation

	Group C (n=38)	Group Am (n=38)	P value
Aldrete Score at 5 min	9.04 ± 0.94	8.89 ± 0.69	0.445
Aldrete Score at 10 min	9.49 ± 0.38	9.43 ± 0.44	0.5

DISCUSSION

While, a sedative dose of propofol (0.5 - 1 mg/kg) administered for a patient undergoing gastrointestinal endoscopy is significantly lower than an induction dose, still, respiratory depression and apneic episodes are frequently encountered. To reduce the respiratory adverse effects associated with propofol sedation and to shorten the time to recovery for patients undergoing gastrointestinal endoscopy, the researchers of this trial tested a premedication dose of 0.5 mg/kg aminophylline.

In previous studies, respiratory complications associated with propofol sedation were reported in a myriad of ways, with widely varying incidence rates. In studies of gastrointestinal endoscopies, **Külling *et al.*** [15] in their huge study, of 27,061 endoscopy procedures, reported a drop of oxygen saturation below 90% in only 623 (2.3%) of the procedure, while **Tandon *et al.*** [16] reported that 19 (out 130) patients had respiratory incidents that required intervention.

Outside sedation for endoscopies, other studies reported on respiratory complications resulting from propofol sedation, **Yuce *et al.*** [17] on dilatation and curettage patients reported that the incidence of respiratory complications was as low as 1.31%, all the way. **Frey *et al.*** [18] on cataract patients showed that the incidence was as high as 54.55%.

The results of our trial showed that while the incidence of hypoxia, in the form of oxygen saturation dipping below 92% wasn't greatly different between both groups, the number of apneic episodes encountered during sedation with propofol was significantly lower in the group of patients who received aminophylline premedication. The number of procedures in which apnea was recorded was significantly lower in the aminophylline group [Group C 16 patients (42.1%), Group Am 7 (18.4%), P = 0.025]. Also, there was a statistically significant lower mean number of apneas per bolus of propofol in the study group (Group C 0.25 ± 0.33 and group Am 0.079 ± 0.18, P = 0.006). This decrease in the incidence of respiratory adverse effects associated with propofol sedation in patients can be largely attributed to the respiratory stimulant effects of aminophylline.

While there are no comparable studies on the addition of a premedication dose of aminophylline in sedation for endoscopies, there are a few studies that were reported on the effect of preoperative effect of aminophylline on patients receiving general anesthesia for major surgeries. **Kasim *et al.*** [19] tested preoperative aminophylline on the recovery profile after major pelvic abdominal surgeries and found that it enhanced recovery from anesthesia. In addition to a control group, their study included two groups who were given considerably high doses of aminophylline (Group A1: 2 mg/kg and group A2: 4 mg/kg). At the end of their surgical procedures, patients who received aminophylline awakened more quickly (measured as a Bispectral index of 80) and were extubated earlier as well [19].

Another study by **Jung *et al.*** [12] on laparoscopic vaginal hysterectomy patients showed that the addition of 3 mg/kg of aminophylline resulted in a significantly faster recovery of spontaneous breathing (almost half the time in the control group).

Other studies tested the respiratory stimulant effect of aminophylline in the context of general anesthesia, but the drug was administered toward the end of surgeries, like in the study by **Sahmeddini *et al.*** [20] on inguinal herniorrhaphies. They studied the effect of aminophylline injection (4 mg/kg) toward the end of their surgeries and reported a significant effect on time to eye opening and extubation.

In the above studies, their decision to test higher dosage of aminophylline can be justified by the fact that the patients were fully anesthetized for lengthy surgeries, unlike in our study where patients were sedated for shorter procedures.

Our trial has failed to show a similar positive effect of aminophylline on recovery from sedation. We assumed that emergence from sedation could be improved with a small aminophylline premedication dose, based on the CNS stimulant effect of aminophylline. However, there was no statistically significant difference between the modified Aldrete score after discharge from the operating room, both when tested after 5 minutes (Group C 9.04 ± 0.94 and group Am 8.89 ± 0.69, P = 0.445), or after 10 minutes (Group C 9.49 +/- 0.38, Group Am 9.43 +/- 0.44, P value = 0.5).

These results, however, should be interpreted while keeping in mind the limitations of our study, mainly the small aminophylline dosage and the preoperative timing of injection. We opted for a small aminophylline dose to avoid resistance to sedation, an effect that was evident in our study, in the form of increased propofol boluses per procedure, though in a statistically insignificant way (Group C 2.46 ± 0.98 and group Am 2.89 ± 1.01, P = 0.054).

CONCLUSIONS

Premedication with a small dose of aminophylline significantly reduced apneas during propofol sedation,

however, its effect on emergence from sedation was not statistically significant.

RECOMMENDATIONS

Based on this clinical trial, the researcher recommends routine use of 0.5 mg/kg aminophylline premedication for patients undergoing endoscopy under propofol sedation, to decrease the incidence of apnea, provided the patients have no contraindications to the use of the drug.

Anesthesia providers, while confident in their current practice, should still consider adjuvants and premedication that help reduce and avoid complications whenever possible, and embrace efficient techniques especially in theaters with high turnover.

Optimal use of aminophylline could help achieve a speedy recovery from sedation and minimize intraoperative respiratory complications while avoiding a shallow depth of sedation and increased sedative agent consumption. Striking that balance would need further research on both the dosage and timing of aminophylline injection that may be achieved by repeating our trial with more study groups receiving incrementally higher doses of aminophylline at various entry points.

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