Original Article

Comparison of the effects of caffeine, aminophylline, and saline on the recovery from total intravenous anesthesia in laparoscopic surgeries: A randomized controlled trial

R. Hari Prasad, Bharat Paliwal, Manoj Kamal, Pradeep Kumar Bhatia

Department of Anesthesiology and Critical Care, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

Abstract

Background and Aims: The return of consciousness (ROC) after general anesthesia (GA) is by stopping the administration of anesthetic agents. At present, no drug is given to reverse the loss of consciousness produced by general anesthetic agents. This study is conducted to find whether caffeine and aminophylline hasten the ROC.

Material and Methods: This study was conducted on 75 American Society of Anesthesiologists (ASA) I and II female patients undergoing laparoscopic hysterectomy, aged between 18 and 60 years. The patients were divided into three equal groups (Group C: caffeine citrate, Group A: aminophylline, and Group S: saline) of 25 each by a computer-generated random number table. GA was induced with propofol, fentanyl, and maintained with propofol infusion. On completion of the surgery, the neuromuscular blocking agent was reversed and then the infusion of propofol was stopped. The study drug was administered intravenously when the BIS 60 was achieved. Time to achieve BIS 90, return of first gag reflex, eye-opening on verbal command, and extubation after study drug administration were noted. Hemodynamic parameters and SpO2 were also monitored.

Results: The time for BIS 60 to 90 was 10 (4.25) min in the caffeine group, 13 (4.25) min in the aminophylline group, and 26 (9.0) min in the saline group. The time to return of gag reflex and time to extubation were shorter in the caffeine and aminophylline group compared to the saline group. The time to eye-opening on verbal command was shorter in the aminophylline group compared to the saline group. Hemodynamic parameters after infusion of the study drug were comparable in all three groups.

Conclusion: Caffeine hastens the recovery from total intravenous anesthesia with propofol and fentanyl in laparoscopic hysterectomy as effectively as aminophylline.

Keywords: Aminophylline, BIS, caffeine, propofol, recovery, reversal of loss of consciousness, and total intravenous anesthesia

Introduction

General anesthesia (GA) is a drug-induced reversible loss of consciousness (LOC). The exact mechanism of the LOC caused by anesthetic agents is not known yet. The most common site of action includes gamma-aminobutyric acid (GABA) receptors which cause hyperpolarization and in turn inhibition of transmission of an action potential.[1] The return of consciousness (ROC) at the end of the surgery is achieved by stopping the administration of propofol infusion, and the time taken for ROC depends on the context-sensitive time. (Context is the duration of propofol infusion.) In the current practice of anesthesia, no reversal agent is being used for the hypnotic agents to attain ROC. The regaining of consciousness from GA is a passive process, and patients recover from anesthesia with varying time courses, dependent upon several factors that are beyond

Address for correspondence: Dr. Bharat Paliwal,
Associate Professor, Department of Anaesthesiology and Critical Care, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India.
E-mail: docbpali@gmail.com

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the clinician's control, including but not limited to genetics, temperature, comorbidities, and age.[2] Owing to these factors, the time taken for emergence from propofol varies among the patients. Confusion, emergence delirium, patient agitation, delayed extubation, and aspiration are some risks associated with delayed recovery from GA.

This study was conducted in search of a drug that can be given to safely reverse the LOC in humans. Dopamine, amphetamine, physostigmine, modafinil, and methylphenidate have also been tried previously as a reversal drug for general anesthesia without much success.[2-4] The methylxanthine group of drugs has shown promising results in a few studies with volatile anesthetic agents. Aminophylline and caffeine are two of the commonly used drugs belonging to the methylxanthine group.

Aminophylline, used clinically as a bronchodilator, centrally antagonizes adenosine which is a very potent endogenous central nervous system (CNS) depressant.[5] Caffeine, commonly present in coffee and green tea, is a CNS stimulant with cortical arousal action and hence leads to an increase in alertness and a decrease in fatigue. It is more specific than aminophylline in CNS effects and devoid of cardiovascular side effects seen with aminophylline. It is already known that administration of aminophylline by the end of the surgery increases BIS value significantly in patients receiving total intravenous anesthesia (TIVA) and reduces the recovery time from TIVA with propofol and remifentanil.[6] The widespread use of aminophylline is restricted because of its cardiovascular side effects. Hence, this study is designed to compare the effects of caffeine and aminophylline on the recovery profile from TIVA with propofol and fentanyl in humans. The bispectral index (BIS) is a reliable indicator of the level of consciousness and depth of anesthesia without subjective variability. The increase in BIS value from 60 to 90 was defined as the primary endpoint of reversal of consciousness in the study. Other clinical variables were also measured, including time to eye-opening, return of gag reflex, and extubation.

Material and Methods

This was a single-center, prospective, randomized, double-blind, controlled study conducted from July 2019 and June 2020 in Jodhpur. After the Institutional Ethics Committee's approval and clinical trial registry [CTRI/2019/06/019882] and obtaining written informed consent from the patients, a pilot study was conducted on 12 patients for sample size calculation. The mean and standard deviation of time for BIS 60 to 90 were calculated. The highest mean was 1560 s, the lowest mean was 503 s, and the overall mean was 766 s. It was calculated based on the difference in means among groups based on the formula:

$$n = \left[1 + \sqrt{(g-1)}\right]\left[\frac{Z_{(1-\frac{\alpha}{2})} + Z_{(1-\beta)}}{d^2}\right] + \left[\frac{Z_{(1-\frac{\alpha}{2})}\sqrt{(g-1)}}{2(1+\sqrt{\alpha(g-1)})}\right]$$

g = number of groups = 3; d = effect size = 0.922; α = 5%; β = 80%

Patients in the age-group of 18 to 60 years and ASA physical status class 1 or 2 were included in the study. After assessing eligibility, patients were excluded from the study based on the following criteria: substance abuse (opioid, alcohol, and tobacco), patients with known allergy or contraindications to any of the drugs used, and BMI less than 18 or more than 30. A total of 75 patients were randomly allocated into three groups according to intraoperative drug infused, using a computer-generated random number table [Figure 1]. Allocation concealment was performed using the sealed envelope method. In the operating room (OR), standard monitors like electrocardiogram (ECG), noninvasive blood pressure, and pulse oximetry, along with neuromuscular and BIS monitoring, were performed. Patients were pre-medicated with 50 μg/kg of midazolam, 0.1 mg/kg of dexamethasone, and 2 mcg/kg of fentanyl. The patients were induced with propofol 1.5–2 mg/kg IV bolus. Loss of eyelash reflex and BIS value of 40–50 were taken as the endpoint of induction. The tracheal intubation was facilitated with rocuronium 0.9 mg/kg after a successful bag and mask ventilation. The airway was secured with an appropriate size endotracheal tube. Mechanical ventilation was carried out with air–oxygen mixture (50:50) using Dräger anesthesia workstation with a tidal volume of 6–8 ml/kg while maintaining EtCO2 of 32 to 35 mm Hg. GA was maintained using propofol infusion based on regime proposed by Roberts *et al.*,[1] infusion of 10 mg/kg/h for 10 min, 8 mg/kg/h for next 10 min, and 6 mg/kg/h thereafter to maintain BIS value in a range of 40 to 60 during the intraoperative period and intermittent doses of fentanyl 1 mcg/kg. The intermittent doses of IV rocuronium were repeated based on TOF count from neuromuscular monitoring. After skin closure, neuromuscular reversal was performed using neostigmine 50 mcg/kg with glycopyrrolate 10 mcg/kg at the TOF count of 3–4. After the TOF ratio of 0.9, the infusion of propofol was stopped and the study drug was infused according to the group over 5 min when a BIS value of 60 was attained. Group C received caffeine citrate of 15 mg/kg, Group A received aminophylline of 3 mg/kg, and Group S received saline. For group concealment (blinding), the study drug (calculated as per body weight) was diluted

to prepare the same volume (50 ml) and infused at the same rate (10 ml/min). The drug infusions were prepared and administered based on the computer-generated random sequence by an anesthesiologist not involved in the study. The noninvasive blood pressure (NIBP), heart rate (HR), BIS, and oxygen saturation (SpO2) were recorded at baseline, every minute after starting infusion of study drug until 10 min of infusion and every 5 min thereafter until shifting the patient to the high dependence unit (HDU). After stopping propofol infusion, the time taken for the BIS value to increase from 60 to 90, to the return of first gag reflex, to eye-opening on verbal command, and the time to extubation were noted. The patients were shifted to HDU after ROC (BIS 90). Postoperatively, NIBP, electrocardiogram (ECG), and SpO2 were recorded at 1, 5, 10, and 20 min. The trial was completed after achieving the calculated sample size.

Statistical analysis was performed by using SPSS (version 26). Data are expressed as mean with standard deviation for normally distributed data and as median with interquartile range (IQR) for non-normally distributed data. The test of normality used for data was the Shapiro–Wilk test. ANOVA and Chi-square test were used for non-categorical and categorical data, respectively. For data that were not normally distributed, a nonparametric Kruskal–Wallis test was used as a test of significance. Intergroup analysis was performed by Bonferroni post hoc analysis for ANOVA. P value < 0.05 was considered significant.

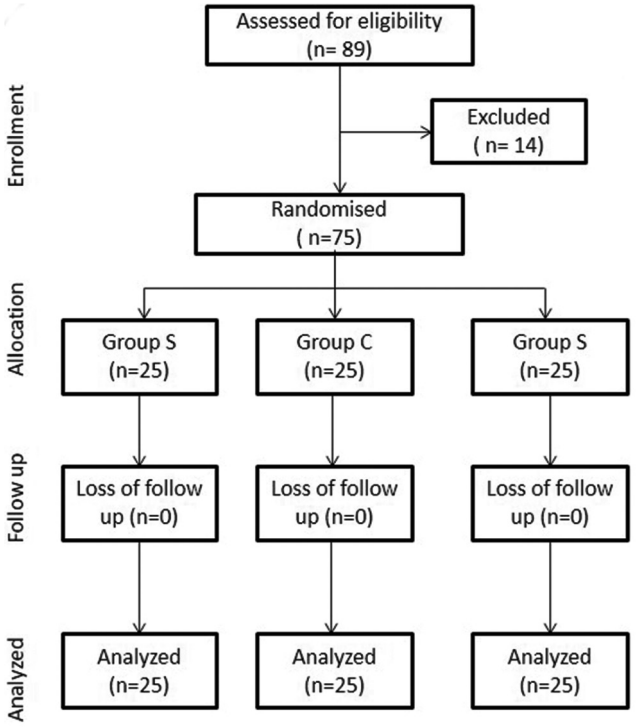

Figure 1: Consort flow diagram

Results

All 75 patients included in the study were female. The mean and SD of age, weight, and duration of surgery were compared between groups. There was no significant difference between the groups (both P value > 0.05). The distribution of the ASA class of patients was similar in all three groups with no statistical difference between groups. There was also no statistically significant difference in comorbidities including diabetes mellitus, hypertension, hyperthyroid, and hypothyroid ($P > 0.05$ for all demographic, comorbid variables) among groups [Table 1].

The median (IQR) of time duration between BIS value 60 and 90 of Group S, Group C, and Group A was 26 (9.0) min, 10 (4.25) min, and 13 (4.25) min, respectively. It was significantly different between the aminophylline and saline group ($P < 0.001$) and between the caffeine and saline group ($P < 0.001$). The BIS value in various time points was significantly higher in Group A and Group C compared to Group S. However, there was no statistically significant difference between Group C and Group A ($P = 0.293$) [Table 2, Figure 2]. The time for the return of gag reflex was significantly different between the aminophylline and saline group ($P = 0.045$) and between the caffeine and saline group ($P = 0.006$), but not between the caffeine and aminophylline group ($P = 1.000$).

Table 1: Distribution of demographic characteristics, ASA class, and comorbid illnesses among the groups

Variables	Group S	Group C	Group A	*P*
N (number)	25	25	25	
Age (years) Mean±SD	46.5±7.4	44.3±7.1	44.6±6.5	0.472
Weight (Kg) Mean±SD	60.3±10.1	57.9±9.3	58.0±10.6	0.638
Duration of surgery (min) Mean±SD	147±17	150±16	143±32	0.751
ASA (Percentage)				
Class I	16 (64%)	17 (68%)	16 (64%)	0.945
Class II	9 (36%)	8 (32%)	9 (36%)	
Hypothyroid (Percentage)				
Absent	22 (88.0%)	22 (88.0%)	22 (88.0%)	1.0
Present	3 (12.0%)	3 (12.0%)	3 (12.0%)	
Hyperthyroid (Percentage)				
Absent	24 (96.0%)	24 (96.0%)	25 (100.0%)	1.0
Present	1 (4.0%)	1 (4.0%)	0 (0.0%)	
Diabetes mellitus (Percentage)				
Absent	22 (88.0%)	23 (92.0%)	22 (88.0%)	1.0
Present	3 (12.0%)	2 (8.0%)	3 (12.0%)	
Hypertension (Percentage)				
Absent	22 (88.0%)	21 (84.0%)	21 (84.0%)	1.0
Present	3 (12.0%)	4 (16.0%)	4 (16.0%)	

However, it was shorter in the caffeine group compared to the aminophylline group. The time to eye-opening on verbal command and time to extubation were least in aminophylline and maximum in the saline group without any difference between the caffeine and aminophylline group ($P = 0.445$).

There was no difference in HR and SBP (systolic blood pressure) in baseline value among groups [Figure 3a and b]. The number of patients with a heart rate of more than 100/min was compared among groups at different time frames. The caffeine group had a maximum number of patients with a heart rate of more than 100/min at the 7th min. However, there was no significant difference between groups except at the 5th min when the heart rate was maximum in the caffeine group followed by the aminophylline group and least in the saline group. There was no significant difference in systolic and diastolic blood pressure among the three groups. There were no significant changes in the SBP and DBP (diastolic blood pressure) after study drug infusion in between groups (all P value > 0.05) [Figure 3c and e]. There was no significant difference in mean arterial blood pressure among the three groups (P value > 0.05) [Figure 3d]. There was no statistically significant difference in postoperative hemodynamic monitoring including heart rate, systolic blood pressure, and diastolic blood pressure among the three groups (all P value > 0.05) [Figure 4].

Discussion

The methylxanthine group of drugs including theophylline, aminophylline, and caffeine has a CNS stimulation effect which has been explored as a reversal agent for ROC. Studies have shown that caffeine reduces the time for emergence from inhalational anesthesia with isoflurane in humans and by propofol in rats.[7] The exact mechanism of the LOC caused by anesthetic agents is not known yet. One of the proposed mechanisms of action of hypnotic drugs is action on GABA receptors causing hyperpolarization of neurons in the brain inhibiting transmission of action potentials.[8] Other neurotransmitters implicated in the mechanism of action of

Table 2: Recovery profile parameters among groups

Variables	Group S (Min) Median (IQR)	Group C (Min) Median (IQR)	Group A (Min) Median (IQR)	*P*
Time to BIS 90	26 (9.0)	10 (4.25)	13 (4.25)	*P*<0.001
Time to return of gag reflex	6.0 (2.85)	3.6 (2.6)	4.0 (3.5)	*P*=0.005
Time to eye-opening	6 (2.85)	5.0 (3.85)	4.6 (3.88)	*P*=0.044
Time to extubation	7.0 (2.75)	5.5 (3.0)	5.0 (3.8)	*P*=0.006

Test of significance: Kruskal–Wallis test

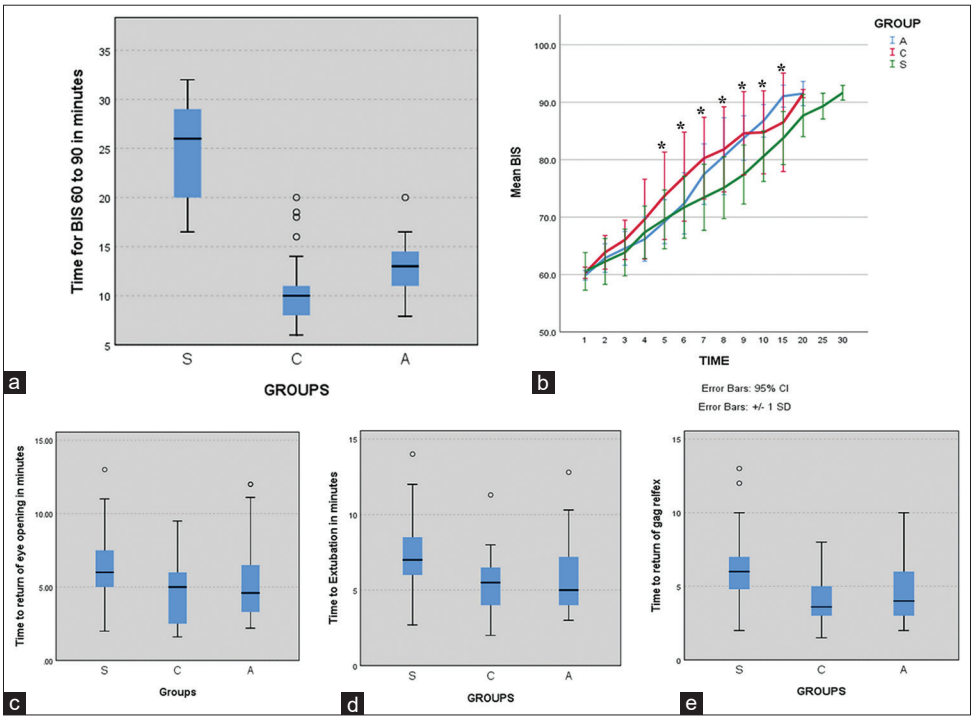

Figure 2: Box plot of primary and secondary recovery parameters among groups; 2a: Time to increase BIS from 60 to 90. 2b: BIS values at various time points after study drug administration. 2c: The time to return of eye-opening. 2d: Time to extubation. 2e: Time to return of gag reflex. Data are expressed as median (IQR)

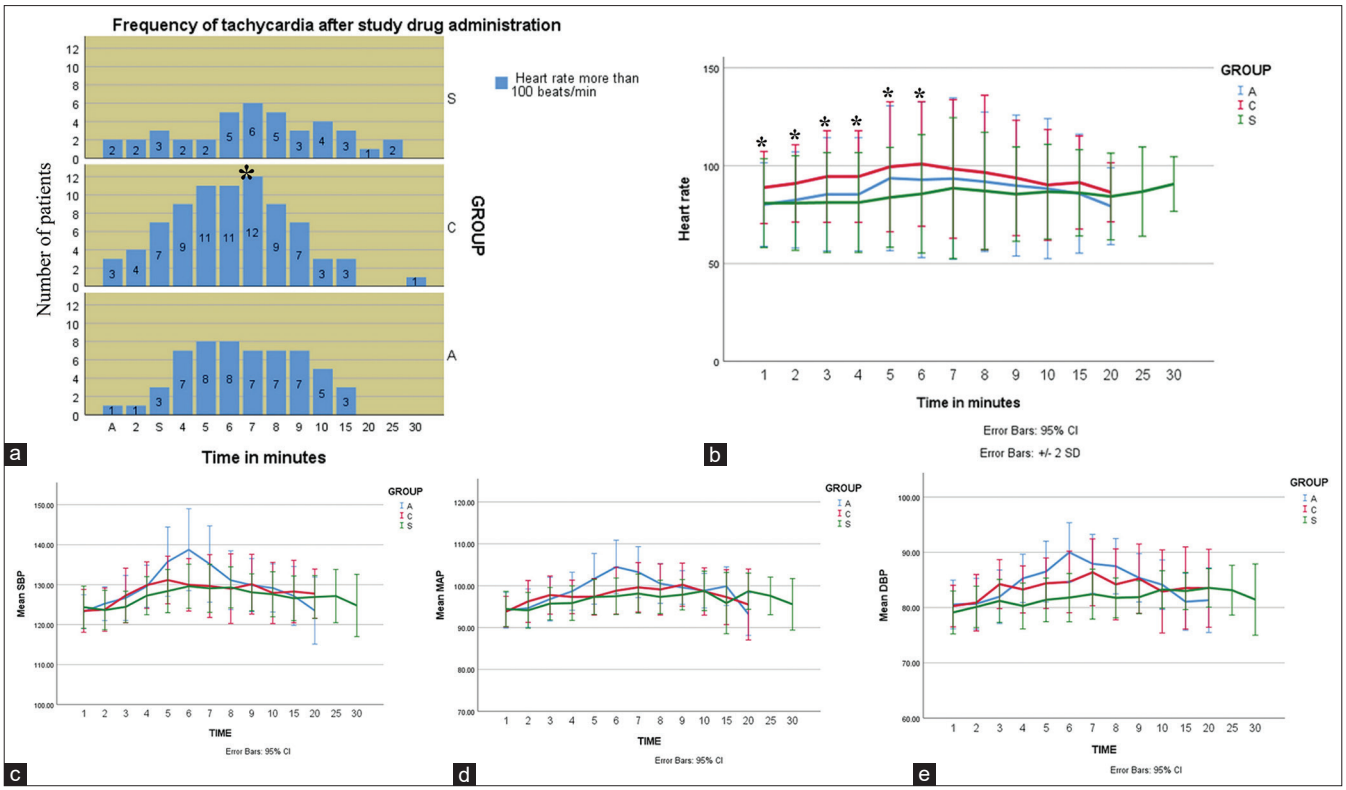

Figure 3: Hemodynamic parameters after study drug administration among groups: 3a: Frequency of tachycardia. 3b: Heart rate at various time points. 3c: Systolic blood pressure at various time points. 3d: Mean arterial blood pressure at various time points. 3e: Diastolic blood pressure at various time points. Data are expressed as mean and SD. *: *P* value < 0.05 (one-way ANOVA)

general anesthetics are dopamine, noradrenaline, serotonin, and acetylcholine.[9,10] Caffeine has calcium-independent inhibition of GABA receptors in the hippocampus.[11] At present, it is clinically used in neonates as a respiratory stimulant for the treatment of apnea of prematurity.[12,13]

BIS is a processed electroencephalographic signal that monitors the depth of anesthesia and correlates with the level of awareness during anesthesia. The increase in BIS value from 60 to 90 was chosen as the point of emergence as it is not a subjective parameter and hence does not vary based on observers. The study drug was not administered when BIS was below 60 because then most of the receptors might be occupied by propofol, leading to a lesser number of receptors available for the study drug to act. Though the time to achieve BIS 90 was reduced 23% in the caffeine group in comparison with the aminophylline group, it was statistically insignificant (p = 0.293). There are no previous studies that compared the effect of caffeine and aminophylline on emergence from TIVA. BIS was recorded every minute after infusion of the study drug in all three groups. There was a leftward shift of mean BIS value after infusion of the study drug. It was maximum in the caffeine curve followed by aminophylline and saline [Figure 2b]. This indicates that BIS values reached 90 earlier in caffeine compared to aminophylline and saline. The median time for the BIS value to increase from 60 to 90 was 61% lower in the caffeine group compared to the saline group. The results are similar to a previously conducted study by Robert Fong *et al.*[7] where BIS value increased rapidly after administration of caffeine during emergence from isoflurane anesthesia. Caffeine has been shown to accelerate the emergence from GA in rats by 55% to 60% when 2% isoflurane is used for 60 min.[14] Based on our study results, caffeine not only hastens the return of consciousness from isoflurane anesthesia but also from TIVA with propofol and fentanyl. The time required to achieve BIS 90 in the aminophylline group was reduced by 50% in comparison with the saline group [Table 2]. The administration of aminophylline has been shown to increase BIS values significantly in patients receiving TIVA with propofol.[6,15-17]

Fong *et al.*[7] considered the return of gag reflex as a definitive indicator of emergence from isoflurane anesthesia and found a significant difference between caffeine and saline groups with a 42% reduction in the caffeine group. The time to return of gag reflex was significantly shorter in both the study groups compared to the saline group. There is no previous data for the effect of aminophylline on time to return of gag reflex compared with our study.

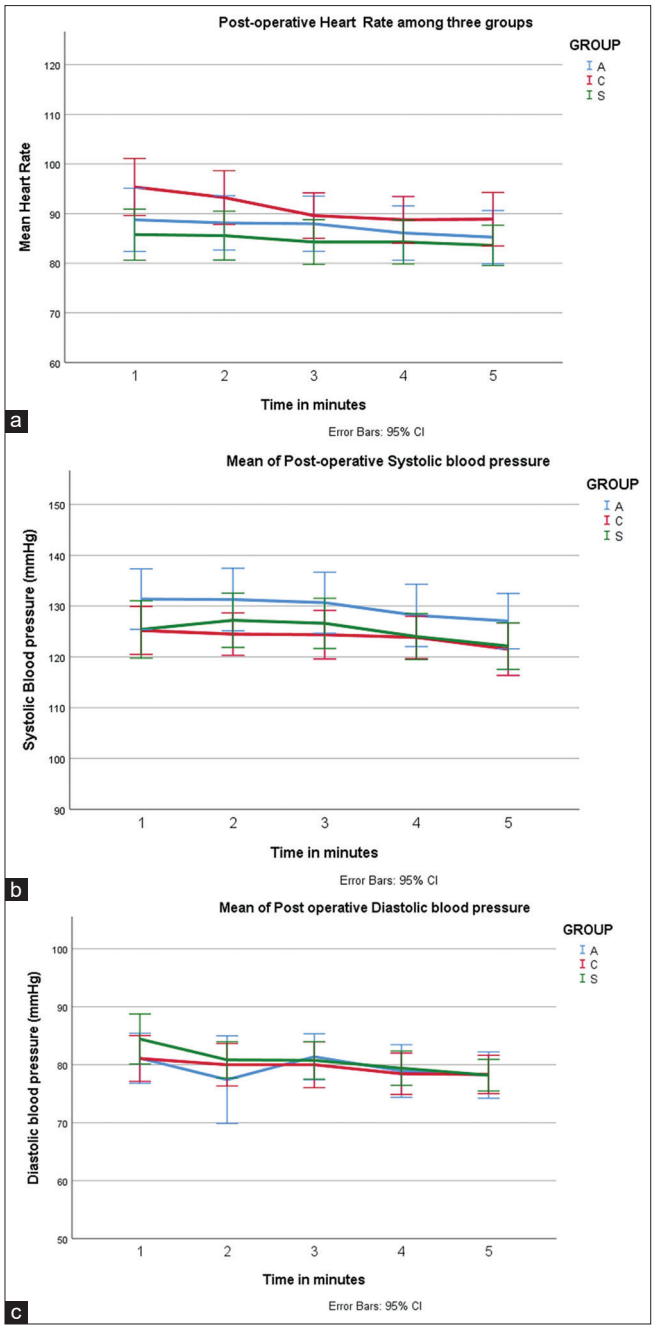

Figure 4: Postoperative hemodynamic parameters. 4a: Mean of heart rate. 4b: Mean of systolic blood pressure. 4c: Mean of diastolic blood pressure

The median (IQR) of time to eye-opening was 16.6% faster in the caffeine group compared to the saline group, while others were insignificant. However, in a previously conducted study, there was a significant difference in eye-opening time between the aminophylline and saline groups. One of the reasons may be because of higher aminophylline doses (4–5 mg/kg) in previous studies compared to our study (3 mg/kg).[15-17] The time for extubation was shorter in both the caffeine and aminophylline groups in comparison with the saline group. However, it was similar between the caffeine and aminophylline groups.

It was postulated that drugs that increase the intracellular cAMP concentration can potentially reverse the LOC sustained by hypnotic agents. In that category, three drugs including caffeine, preladenant, and forskolin were studied for time to recover from GA in rats and caffeine was most effective in reversing the effects of GA induced with isoflurane in rats.[17] However, there is no study conducted to date on whether caffeine improves the emergence from TIVA by propofol. Caffeine acts through adenosine receptors in the brain causing CNS stimulation by antagonizing it and also inhibits both extra-synaptic and synaptic GABAergic inhibitory postsynaptic currents independent of calcium ions.[11] Caffeine causes wakefulness and sustains an awake state by acting on adenosine A2A receptors in the nucleus accumbens.[18] This may be the mechanism by which caffeine hastens the recovery from TIVA with propofol and fentanyl.

After starting administration of the study drug, tachycardia (HR >100/min) was occurring more in the caffeine group than in the aminophylline group. In contrary to the CNS-specific action of caffeine, the rise in heart rate was more in the patient who received caffeine rather than aminophylline. Despite tachycardia, none of the patients in the caffeine group had ST segment changes in ECG. Fong et reported no change in heart rate and blood pressure with caffeine unlike in our study.[18] The difference might be due to the difference in airway devices. Fong *et al.* used a laryngeal mask airway for ventilating patients, while our patients were intubated with an endotracheal tube. One of the probable causes of tachycardia could be the extubation response to the endotracheal tube. Aminophylline was found to cause tachycardia in a previous study conducted to find its role in early recovery from general anesthesia.[17-19] Aminophylline stimulates the sympathetic nervous system, which is responsible for metabolic and cardiovascular side effects.[20] One of the reasons for the statistically insignificant difference in heart rate is that it might be due to the slower rate of administration or drug dilution in our study and the lower dose of aminophylline (3 mg/kg) used. Theophylline and caffeine are rapidly distributed in body water but poorly distributed in the fat. The onset of action is immediate once the plasma concentration is achieved. However, it takes time because it is given only as an infusion and not as a bolus. So the exact onset of action depends on the duration of drug infusion. Secondly, the primary outcome of our study was not to look for significant changes in hemodynamic parameters. Hence, another probable reason may be that the calculated sample size according to the BIS value may be inadequate to make out significant hemodynamic fluctuations. There was no statistically significant difference between the caffeine and the aminophylline group in HR, systolic, diastolic, and

mean arterial blood pressure between groups after 7 min of drug infusion (all P value > 0.05). Once extubation was performed, the patients were monitored inside the OR till BIS reached 90, and then they were shifted to the high dependence unit (HDU). In HDU, during the postoperative period, the HR and blood pressure were similar in all three groups. Both the caffeine and aminophylline groups did not have a significant rise in heart rate and blood pressure/ECG changes or other complications during the postoperative period in HDU.

Our study has certain limitations. First, as it is performed with propofol as a hypnotic agent the safety and efficacy of caffeine as a reversal agent against other IV agents including thiopentone, etomidate, and ketamine need further studies. Second, no recommendation about the effective dose of the study drug to reverse the LOC can be made. Further studies are required to find the safe therapeutic dose of caffeine as a reversal agent against propofol. Third, the BIS value at which patients were extubated was not recorded in this study. Fourth, the finding of our study cannot be extrapolated to other types of surgeries, male patients, and pediatric patients. Lastly, the plasma concentration of propofol, caffeine, and aminophylline was not recorded. Their level may be affected by different pharmacodynamics and pharmacokinetic profiles of participants. A larger sample size could probably make up for such differences.

Conclusions

Caffeine hastens the recovery from TIVA with propofol and fentanyl as effectively as aminophylline measured in terms of BIS and other clinical recovery periods with minimally increased heart rate as compared with the saline group. If a reversal agent like caffeine is tested and proved for its safety and efficacy, it can open a new scope in the field of the present practice of anesthesia.

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Conflicts of interest
There are no conflicts of interest.

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