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Original Article

Intravenous Caffeine Infusion Accelerates Emergence from Total Intravenous Anesthesia: A Randomized, Double-blind, Placebo-controlled Study

Rahman Abbasivash, Mir Mousa Aghdashi, Alireza Mahoori, Ebrahim Hassani, Parisa Eghtesaddoust and Shahram Shokohi*

Department of Anesthesiology and Critical Care, Emam University Hospital, Urmia University of Medical Sciences, Urmia, West Azerbaijan, Iran

Abstract

Background: Emerging from general anesthesia remains a passive process. Recent studies show the importance of dopaminergic pathways in sleep–wake cycles. The effect of caffeine in increasing the level of consciousness and cognitive function has been well documented. The purpose of the current study was to evaluate the effect of intravenous caffeine, a dopamine receptor stimulant, on accelerating recovery from Total Intravenous Anesthesia (TIVA) with propofol.

Methods: Fifty patients, aged between 20 to 50 years old scheduled for elective laparoscopic cholecystectomy, were enrolled in this double-blind clinical trial, and forty-eight were analyzed. The study group, consisting of 24 patients, received 500 *mg* IV caffeine infusion 15 minutes before the end of the surgery. The control group, comprising 24 patients, received an equal volume of saline infusion. Emergence profile was evaluated and compared in two groups. The depth of anesthesia was determined by Bispectral Index (BIS) monitoring.

Results: Our research demonstrated that in the study group, the time intervals for increasing BIS values from 60 to 80, endotracheal extubation, eye-opening on verbal command, and achieving an Aldrete's discharge score ≥ 8 were significantly less than the control group. Short Orientation Memory Concentration Score (SOMCT) was lower in the control group as well. Incidence of nausea, vomiting and, shivering had no significant difference between the two groups.

Conclusion: Since emergence from general anesthesia is a passive process, caffeine may be used as a measure for active reverse of general anesthesia at clinical practice.

Keywords: Aldrete's score, Bispectral index, Emergence, Intravenous caffeine, Short orientation memory concentration test, Total intravenous anesthesia

*** Corresponding author**

Shahram Shokohi, MD
Department of Anesthesiology, Emam University Hospital, Urmia University of Medical Sciences, Urmia, West Azerbaijan, Iran
Email: shokohi725@yahoo.com

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Introduction

Emergence from general anesthesia is a passive and slow process during which the application of the anesthetics is stopped so that the effects of the anesthetics disappear, and the patient's consciousness increases (1). There is no medication to accelerate the process, and it is only a waiting process until the effects of the anesthetics diminish from the blood (2). This process depends on many factors such as the nature and length of surgery, anesthesia technique, the anesthetics used for induction and maintenance of anesthesia, the patient's age and physical status, and the coexistence of other diseases. Some uncommon reasons for delayed emergence include drug interactions, serotonin syndrome, central anticholinergic syndrome, psychiatric disorders, narcolepsy/sleep paralysis, and surgical complications (3). Time is an invaluable factor in operation rooms and costs 15-20 US dollars per minute (4). Different monoaminergic neurotransmitters such as noradrenaline, histamine, serotonin and the newly recognized population of dopaminergic neurons in the ventral periaqueductal gray matter all have their roles in wakefulness (5). Dopamine, norepinephrine, and histamine are monoaminergic neurotransmitters which cause awakening by nuclei in pons, midbrain and hypothalamus (6,7). Caffeine is a xanthine alkaloid which operates by blocking adenosine receptors in the brain. It passes through the brain-blood barrier freely, and its main effect in the brain is nonspecific antagonism of adenosine receptors. Caffeine molecule is structurally similar to adenosine and can occupy its receptors, acting as a competitive antagonist (8). Adenosine acts as an inhibitory neurotransmitter and decreases central nervous system's activity. Caffeine binds adenosine A1 and A2α receptors nonexclusively and its effect on increasing consciousness is related to A2α receptors block (9,10). Anatomic area for caffeine effect in the brain to increase consciousness is cortical areas of accumbens nucleus, and in spite of having A2α receptors, caffeine has no effect on other areas of basal nuclei (10). Likewise, it seems that caffeine, by indirectly activating the dopaminergic system, increases the activity of the ascending dopaminergic system and improves the level of consciousness (11,12). The caffeine's effect on improving consciousness, cognitive status, physical abilities, and exertion activities, especially in sleep-deprived individuals, has been studied (13-15). Animal studies have shown that caffeine has a significant effect in accelerating awakening from general anesthesia induced by isoflurane or propofol (16). The present study aimed to evaluate caffeine effect on speed and process of awakening from general anesthesia using Total Intravenous Anesthesia (TIVA) in human samples. Clinical importance of this study may lie in this fact that passive process of emergence from general anesthesia might be actively or partially reversed by using caffeine.

Materials and Methods

The protocol was registered at www.irct.ir (IRCT2016021725600N2). Following the approval by medical faculty research committee and ethics board of Urmia University of Medical Sciences (approval ID IR.UMSU.REC.1392.236) on 22 Feb 2014, fifty American Society of Anesthesiologists physical status I-II male and female patients aged at 20 to 50 years, scheduled for elective laparoscopic cholecystectomy, were enrolled in a double-blind placebo-controlled clinical trial. After obtaining informed written consent (Figure 1), using random allocation software, the patients were assigned to study and control groups with equal numbers. By using sealed, opaque envelopes, concealing was ensured and the envelopes were opened only after transferring the patients to the operation room and before induction of general anesthesia by an anesthesia nurse who was not involved in the research. Exclusion criteria included: age (older than 50 and younger than 20 years old); ASA physical status of higher than II; the use of opioid, caffeine or caffeine drinks 8 hours before anesthesia, history of psychologic or neurologic diseases, seizure or consumption of psychologic or antiepileptic drugs and history of liver or cardiac diseases. The patients were asked to fast considering solid foods and clear fluids, 8 and 3 hours before surgery, respectively. No premedication was administered the night prior to surgery. After an initial examination, a 20G IV cannula was placed in antecubital vein for infusion of IV anesthetics, muscle relaxant, opioid and neuromuscular blocking reverse drugs, and second 20G cannula on the dorsum of

the same limb for Ringer's lactate solution infusion. Patients' baseline vital signs including systolic and diastolic blood pressure, heart rate, respiratory rate, and depth of anesthesia using Bispectral Index (BIS) monitor (Datascope, Passport 2) were monitored and recorded before induction of anesthesia. 3 *ml/kg* of Ringer's lactate solution was infused for each of the patients15 minutes before induction of anesthesia. The patients received15 *μg/kg* IV midazolam and 2 *μg/kg* fentanyl as premedications at the beginning of anesthesia. Anesthesia was induced with 2-2.5 *mg/kg* of propofol as anesthetic and 0.6 *mg/k*g atracurium. The airway was managed by tracheal intubation using cuffed endotracheal tube. To maintain anesthesia, 100% oxygen, propofol (100-150 *μg/kg/min*), and remifentanil (0.1-0.5 *μg/kg/min*) infusion was initiated. Nitrous oxide was not used. By adjusting the propofol infusion rate during surgery, BIS values were maintained between 40 and 60 (preferably 45 and 55). Systolic blood pressures were kept between ± 30% of baseline by adjusting remifentanil infusion rate. Fifteen minutes before termination of surgery, control group patients received 500 *m*l of normal saline solution as placebo and 500 *mg* caffeine citrate (*Caffeine* Citrate 10 *mg/ml* Solution for Injection) in 500 *ml* normal saline solution was infused to the patients in the study group. Both the researcher and the patients were blind to the content of the infusion solution. At the end of the surgery and after the surgical site dressing, propofol and remifentanil infusion stopped. Anesthesia duration time was defined as the time interval between inductions of anesthesia until holding infusion of anesthetics (propofol and remifentanil), and total infusion doses were measured and recorded. Residual neuromuscular block was reversed with IV neostigminand atropine 0.04 and 0.02 *mg/kg*, respectively. Then the suctioning of mouth and throat secretions was performed and extubation was completed. The time it took for BIS values to increase from 60 to 80, eyes opening with verbal command, and tracheal extubation were measured and recorded using a chronometer.

In our study, the definition of awakening from anesthesia was the time interval between BIS = 60 following the anesthetic infusion holding to a clinical state with Aldrete's recovery score ≥ 9 (17). To assess the cognitive recovery, we used 'Short Orientation Memory Concentration Test' (SOMCT) 30 minutes after the tracheal extubation (18). This gives a 0-28 score with higher scores over 20 being 'normal'. During patients' monitoring in the recovery unit, in addition to vital signs, postoperative complications including nausea, vomiting, agitation, and shivering were monitored and managed correspondingly. Pain intensity was also measured with the Visual Analog Scale (VAS), and the patients with pain VAS more than 4 were managed with 1 *μg/kg* fentanyl in the recovery unit.

Sample size

With regard to clinical trials related to intravenous caffeine effect on postdural puncture headache, 50 male and female patients scheduled for elective laparoscopic cholecystectomy, were enrolled and randomly allocated to the study and control groups with equal number of patients utilizing random allocation software (19).

Statitical analysis

Patients' demographic information, hemodynamic variables including systolic and diastolic pressures, pulse rate, and respiratory rate were monitored and recorded using Datascope, Passport 2 monitors. BIS values (Aspect Medical Systems A-2000™ BIS® Monitoring System); the time interval for BIS to increase from 60 to 80, the time for the patient to open eyes, tracheal extubation, and achieving Aldrete's score ≥ 9 were measured in seconds during awakening patients from general anesthesia and recorded in computer. SOMCT scores based on patients' answers to 6 previously planned questions were also evaluated and recorded. Quantitative variables with normal and abnormal distributions were analyzed using Independent Sample T Test and Mann-Whitney U-Test, respectively. Qualitative variables with normal and abnormal distributions were analyzed with Chi-2 and Fisher's Exact Tests, respectively. Any p value less than 0.05 was considered statistically significant.

Results

Demographic data including mean weight, gender distribution, operation time, and basic hemodynamic variables were comparable in both groups. (Table 1).

But there was a significant age difference between two groups (p = 0.008), table 2 shows the time interval from BIS = 60 to different stages of awakening from anesthesia measured in seconds. They included time from BIS value of 60 to eyes opening with verbal command, tracheal extubation, Aldrete's score ≥ 9 and reaching BIS value of 80. The time measured in seconds from BIS = 60 (end of surgical dressing and stopping infusions) to Aldrete's score ≥ 9 is defined as the time patients can be discharged from recovery

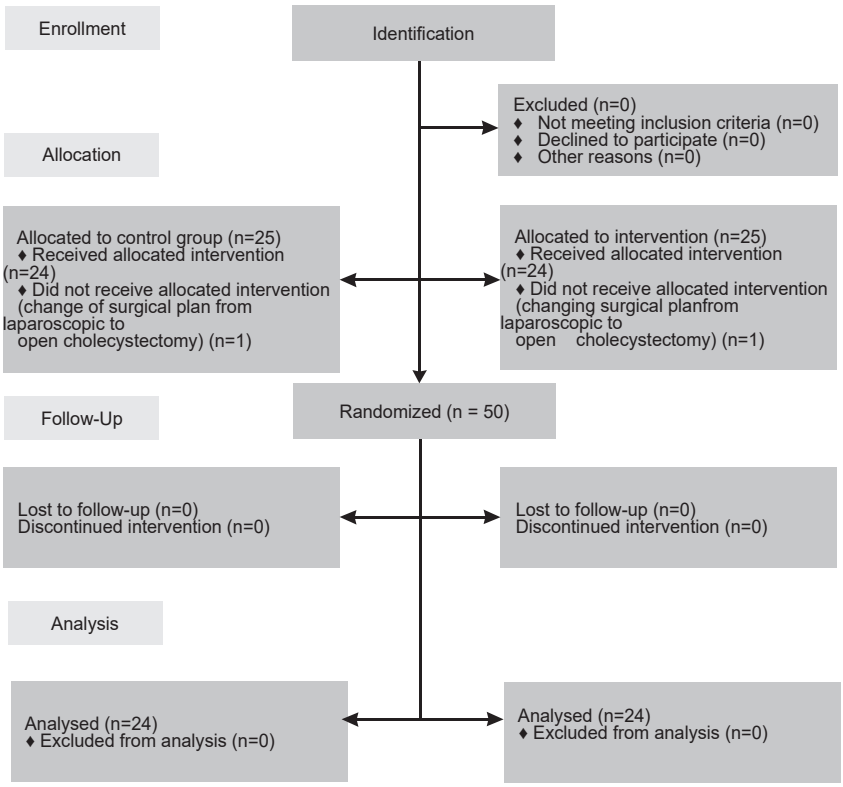

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

Table 1. Demographic data

Characteristics	Control	Study	p-value†
Age(y)	38.67 ± 8.31	32.42 ± 8.34	0.013*
ht(*kg*)	76.38 ± 11.95	74.25 ± 12.82	0.555*
Gender(male/female)	15/9	18/6	0.349‡
Surgery time(min)	53.75 ± 11.16	54.58 ± 9.55	0.614*
Propofol induction dose(*μg kg*-1)	2.54 ± 9.55	2.51 ± 0.07	0.438*
Baseline hemodynamics			
Systolic blood pressure(*mmHg*)	142.29 ± 14.82	133.75 ± 16.25	0.063*
Heart rate(b/min)	76.88 ± 11.82	79.88 ± 10.84	0.364*

Data are presented as mean (SD) or absolute numbers.
* T. Test
†. Fisher's Exact Test
‡. Kruskal-Willis Test

Table 2. Comparison of time to BIS = 60 to different stages of awaking from general anesthesia

	Control	Study	p-value†
Time from BIS*=60 to BIS=80(Sec)	505.21 ± 110.19	255.42 ± 87.88	<0.0001
Time from BIS=60 to eyes opening(sec)	572 ± 121.12	292.5 ± 97.99	<0.0001
Time from BIS=60 to tracheal extubation(sec)	611.67 ± 132.84	316.67 ± 100.32	<0.0001
Time from BIS=60 to Aldrete score >8(min)	15.29±3.22	9.83±1.99	<0.0001

*. Bispectral Index
†. T Test
Values are presented as mean (SD)

Table 3. Time decrease from BIS* = 60 in different stages of awaking from general

	Percentage of time decrease (%)
Time from BIS* = 60 increases to BIS = 80(Sec)	49.44
Time to BIS = 60 to eyes opening (sec)	48.87
Time to BIS = 60 to tracheal extubation (sec)	48.23
Time to BIS=60 to Aldrete score >8 (min)	35.71

Anesthesia in study group compared to control.
*. Bispectral index

Table 4. Short orientation memory concentration (SOMCT) score 30 minutes after endotracheal extubation in study and control group

	Control group	Study group	P-value
Median	24	26	0.008*
Mean	23.83	25.58	0.006**

*. Median Test (k samples)
**. Mann-Whitney Test

room to surgical ward. This period was 5.46 minutes shorter in study group compared to the control group. This means that patients in study group can be discharged to surgical ward 5-6 minutes earlier than the patients in control group. Decreases in awakening time in study group compared to the control group are presented in table 3. Thirty minutes following the extubation, both groups were compared based on SOMCT score. The comparison showed that SOMCT score was higher in the study group than the control group (the median score 26 *vs*. 24, respectively, range 6, p value = 0.005) (Table 4). During maintenance of anesthesia, propofol and remifentanil total infusion doses were more in study group than control 17.59 and 26.32%, respectively) which was statistically significant (Table 3). No postoperative complication was noted. Shivering was comparable in both groups (one in each group). Two patients of study group

and four patients of control group had nausea, but regarding the statistical analysis with Fishers' Exact Test, no significant difference was shown (p value = 0.666).

Discussion

To the best of our knowledge, this is the first human study evaluating IV caffeine effect on awakening from general anesthesia. The results of the present study suggest the administration of intravenous caffeine at the end of surgery can accelerate awakening from general anesthesia using TIVA technique and improves the level of the consciousness and conceptual status during recovery. At present, general anesthesia is induced by different IV anesthetics, but there is no method or drug available for reversal of their effects (except for opioids and benzodiazepines) which may occur due to our limited knowledge considering the molecular function of anesthetics' effect. Based on some animal studies, one of the proposed mechanisms to reverse general anesthesia is to increase the cholinergic activity (20). In these studies, some drugs have been directly injected into the brain. Aiming to reverse anesthesia, neostigmine as a cholinesterase enzyme inhibitor showing cholinergic activity has been studied in some human clinical studies previously. Some researchers could show that physostigmine decreased post anesthesia somnolence (21). Due to the caffeine's variable effects on IV anesthetics including propofol and sevoflurane and also its side effects, its clinical use was limited in anesthesia (22). Different studies suggest that inhibition of neurotransmitters release probably has an important role in the induction of general anesthesia (23). Regarding this theory, drugs which can prevent such inhibitory effect may affect awakening. Indeed, it is known that the increasing intracellular cAMP can accelerate neurotransmitters' release (24). Among intracellular cAMP increasing drugs, theophylline, a phosphodiesterase inhibitor has been administered for treatment of asthma, newborn apnea, and chronic pulmonary diseases (25). Recently, Wang *et al* in a laboratory study showed that theophylline can completely reverse isoflurane-induced neurotransmitters' inhibition and significantly accelerate recovery from anesthesia in rats (16). On the other hand, they found out that caffeine is more effective among other drugs in this field. In addition to phosphodiesterase inhibition and increasing intracellular cAMP, caffeine blocks adenosine receptors (26). Adenosine acts as an inhibitory neurotransmitter and decreases central nervous system activity. Caffeine unselectively binds A1 and A2α adenosine receptors and its effect on improving the level of consciousness is associated with A2α receptors block (26). Many other studies have shown the role of dopaminergic neural transmission in increasing the level of consciousness and regulating awakening and sleeping circles. However, the molecular mechanisms of this process are not completely perceived (27). It seems that caffeine by the indirectly activating dopaminergic system can increase the activity of ascending arousal pathways and improve the level of consciousness (28). In addition to daily consumption, caffeine is the most commonly used psychoactive drug which is classified by the United States Food and Drug Administration (FDA) as the Generally Recognized Safe Drug (GRAS) (20). A great number of studies have represented the effect of caffeine in improving conceptual functions, level of consciousness, and physical activities following sleep deprivation (8-11, 13-15). In clinical anesthesia, studies regarding caffeine are mostly connected to its effect on post-dural puncture headache following spinal anesthesia, apnea of newborns, and post-dural puncture headache (19,29,30). Based on our research, we believe that the present study is the first clinical trial aiming to evaluate caffeine effect on awakening from general anesthesia in humans. As mentioned previously, the findings of the present study show that caffeine significantly fastens recovery from general anesthesia and increases patients' cognitive ability during the recovery period. Wang *et al* study demonstrated that IV caffeine shortens the reversal of general anesthesia with propofol besides accelerating recovery from general anesthesia with isoflurane in rats. Our study has shown similar results, confirming the same findings. A 48% decrease in recovery speed indexes in the study group than the control group show recovery acceleration in our study. One of the Khalil *et al* findings considering caffeine effect on decreasing airway complication after general anesthesia was the decrease in recovery stay time in patients receiving

caffeine (31). However, they failed to find a significant difference. Using multiple objective and relatively precise indexes in our study, we could show that not only faster awakening but also the level of consciousness in recovery period in patients receiving caffeine has significantly increased in the study group compared to the control. One of the indexes we measured was the time elapsed from BIS = 60 (end of surgery) to achieving Aldrete's score ≥ 9 (post-anesthesia recovery score). These indexes were 15 and 9.83 minutes in study and control groups, respectively, which is statistically significant (35.71% decrease, p value < 0.0001). In Khalil *et al*'s study, the time elapsed in PACU was compared between study and control groups, showing 45 and 54 minutes, respectively (16.7% decrease), which was not statistically significant. We believe that the accurate and precise measurements in our study can explain this result. As mentioned earlier, the caffeine effect on accelerating awakening from general anesthesia is related to intracellular increase of cAMP and adenosine receptors block in which the effect of the intracellular cAMP is probably more significant (16). One of the recovery indexes we used is SOMT test, which was applied for evaluation of patients' cognitive level 30 minutes after the tracheal extubation. The comparison of results showed that the study group patients had higher cognitive status than the control group's (mean score 25.58 *vs.* 23.83, respectively). The findings of this study can also be used in the studies regarding caffeine effect on the level of consciousness, physical strength, and accuracy of decision making in sleep-deprived conditions (8,9, 11,13,14). One of the interesting findings of the present study is the significant increase in propofol and remifentanil maintenance infusion dose in patients receiving caffeine. We think that caffeine mediated adenosine receptor block and intracellular increase of cAMP, and subsequently, inhibitory impact on the anesthesia process can be the probable explanation. In other words, any drug that increases intracellular cAMP or blocks adenosine receptors may cause resistance against anesthesia. The patients' hemodynamic changes were not investigated during anesthesia since they are the reflection of patient's pain and anesthesia depth, and thus, by adjusting remifentanil infusion rate, we kept systolic blood pressure in the range of ±30% of basic. Therefore, we assumed that higher hemodynamics including systolic blood pressure in the study group needed increased remifentanil dose to keep the hemodynamics in the aforementioned range. In line with Wand *et al*, we believe that increased intracellular cAMP by exciting cardiac muscle and increasing muscular strength, stabilizes or even increases blood pressure (16). Although the increasing propofol (17.6%) and remifentanil (26.3%) doses in the study group is significant, compared to accelerating recovery, the increase was less significant. Prevalence of nausea and vomiting was comparable between two groups which can be due to the antiemetic effect of propofol anesthesia; however, comparing these postoperative complications was not the main goal of our study. This finding is not comparable with some studies suggesting caffeine increase nausea rate (29). We utilized TIVA by using propofol which has an antiemetic effect and may explain this difference. Going through scant studies published on using caffeine for accelerating emergence from anesthesia, the recommendation to use in every patient is neither scientific nor safe. After larger clinical trials validated its safety and efficacy, caffeine may be utilized in certain group of patients who are prone to prolonged emergence from anesthesia. For now, considering caffeine as a reversal agent for general anesthesia is too early.

Conclusion

The present study showed that the administration of IV caffeine can significantly accelerate emergence from TIVA and improve cognition and consciousness level during the recovery period. Further studies are required regarding caffeine effects including its effect on general anesthesia with volatile anesthetics. It is also suggested that different doses of caffeine and postoperative hemodynamic changes and com-plications be studied in the future researches.

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Conflict of Interest

The authors declare that they have no competing interest.

Ethical approval

Ethics board of Urmia University of Medical Sciences approval ID: IR.UMSU.REC.1392.236

TRIAL REGISTRATION: Iranian Registry of Clinical Trials (IRCT2016021725600N2), (www.irct.ir).

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