Original Article

Effect of Caffeine on the Acceleration of Emergence from General Anesthesia with Inhalation Anesthetics in Children Undergoing Inguinal Herniorrhaphy: A Randomized Clinical Trial

Soodabeh Emami, MD; Ashkan Panah, MD; Seyed Shaheen Hakimi, MD; Mohammad Ali Sahmeddini, MD

Anesthesiology and Critical Care Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Correspondence:
Ashkan Panah, MD;
Department of Anesthesiology, Namaazi Hospital, Zand Blvd., Postal code: 71348-44119, Shiraz, Iran
Tel: +98 71 32337636
Fax: +98 71 32318072
Email: panah@sums.ac.ir
Received: 10 August 2020
Revised: 14 December 2020
Accepted: 23 January 2021

What's Known

• In general, a number of studies have been performed on mice to investigate the effect of sleep-reversing drugs and accelerate emergence. Among them, caffeine citrate has responded positively with its inhibitory effect on the adenosine receptor in the central nervous system and the elevation of intracellular cyclic adenosine monophosphate.
• Despite the positive effects of caffeine on animal models, only one study was conducted on adults with acceptable results.

What's New

• Owing to the importance of anesthesia and its subsequent emergence in the pediatric population, we decided to conduct a study for the first time based on ethical and scientific principles.
• In children undergoing inguinal herniorrhaphy under general anesthesia, 10 mg/Kg of caffeine could not accelerate awakening after general anesthesia. However, caffeine did not increase the blood pressure and heart rate in the children, and there were no significant side effects.

Abstract

Background: Awakening following general anesthesia (GA) is one of the most important concerns of anesthesiologists in their daily work. Previous studies on adult humans found that caffeine could accelerate awakening after anesthesia. This study aimed to determine whether or not caffeine can accelerate awakening after anesthesia in children undergoing inguinal herniorrhaphy under GA.

Methods: In this randomized clinical trial, we enrolled 18 children undergoing inguinal herniorrhaphy under GA with inhaled anesthetics from June 2019 to September 2019 in the tertiary hospital affiliated with Shiraz University of Medical Sciences (Shiraz, Iran). These children were randomly allocated to two groups. In group A, the children received intravenous caffeine (10 mg/Kg) at the end of the surgery, and in group B, the children received intravenous normal saline at the end of the surgery. The primary outcome was laryngeal mask airway (LMA) removal time at the end of anesthesia. Intra-operative hemodynamic data and side effects such as nausea, vomiting, dysrhythmia, cyanosis, and seizures in the recovery room were recorded and compared between the two groups. We used the independent-samples t test, Fisher's exact test, and repeated measures ANOVA for analyzing the data. P values<0.05 were considered statistically significant.

Results: There were no significant differences in terms of demographic characteristics and hemodynamic data between the two groups. Furthermore, the time from the induction of anesthesia to laryngeal mask removal was 44.77±7.87 min in the placebo group and 44.55±10.68 min in the caffeine group. Therefore, there was no significant difference between the two groups (P=0.961).

Conclusion: In children undergoing inguinal herniorrhaphy under GA, 10 mg/Kg of caffeine could not accelerate awakening from GA. However, caffeine did not increase the blood pressure and heart rate in the children, and no significant side effects were observed.

Trial Registration Number: IRCT20190511043550N1.

Introduction

General anesthesia is a reversible coma induced by intravenous or inhaled prescription drugs.[1] In this process, the release of neurotransmitters from neurons and secretory cells is inhibited. If this inhibition is considered part of general anesthesia, then the drugs that induce the release of neurotransmitters can help awakening after anesthesia.[2] Awakening after general anesthesia is a stage of anesthesia, in which the patient regains full consciousness from the unconscious state and maintains it. However, awakening following general anesthesia is one of the most important concerns of anesthesiologists in their daily work.[3] Awakening following GA is unpredictable and depends on factors such as the duration and type of surgery, patient-related factors, and anesthetic drugs.[4, 5] At the end of anesthesia, the administration of anesthetics is ceased, but sometimes the residual effects of these drugs can lead to delayed awakening.[6, 7] Although awakening from GA is a passive event and depends on drug clearance, there are many pharmacological agents available for reversing the effects of some categories of drugs used during anesthesia, such as benzodiazepine, opioids, and muscle relaxants. Currently, there is no specific drug available for the reversal of the coma-like effect of anesthetic drugs.[8]

Many studies have shown that drugs such as forskolin, theophylline, and caffeine, which raise the level of intracellular cyclic adenosine monophosphate (cAMP), release neurotransmitters, and therefore contribute to awakening from GA.[2, 9] Caffeine can accelerate the awakening after anesthesia in two ways. First, it raises the level of intracellular cAMP, and additionally, it can act as an adenosine receptor antagonist.[2, 10] According to the latest research, when adenosine binds its receptors in the central nervous system (CNS), it reduces the brain's activity and causes the patient to sleep.[10, 11] Furthermore, caffeine has been proven to have adverse effects on the cardiovascular and autonomic nervous systems, namely effects such as tachycardia, palpitation, and a rapid rise in blood pressure. The majority of these studies were performed on adult populations.[4] Caffeine also acts as a stimulant for the CNS.

However, the connection between caffeine and seizures is complex and unclear.[12]

In the literature, not only there has not been any comprehensive surveys regarding the impact of caffeine citrate use on the rate of awakening from GA in children, but also there have been no studies that consider the adverse effects of caffeine use. Therefore, we designed this study to survey the effect of caffeine on the rate of awakening from GA in children undergoing inguinal herniorrhaphy under GA.

Materials and Methods

Patients

This randomized, double-blind, parallel, clinical trial was conducted from June 2019 to September 2019 in the tertiary hospital affiliated with Shiraz University of Medical Sciences (Shiraz, Iran). The study protocol was approved by the Medical Ethics Committee of Shiraz University of Medical Sciences (Ethics committee reference number: IR.SUMS.MED. REC.1398.080). All the participants' parents provided their written informed consents before the study. This clinical trial was registered in the Iranian Registry of Clinical Trials (IRCT20190511043550N1).

The inclusion criteria of the study were: children ages 12 to 36 months, who were candidates for inguinal herniorrhaphy under GA, American Society of Anesthesiologists classification I (ASA I).[13] Exclusion criteria were: history of seizure, heart rate>150 beat/min, asthma, airway irritability, heart disease, hyperactivity, cerebrovascular diseases, obstructive sleep apnea, emergency surgeries, common cold, unsuccessful ventilation with laryngeal mask, need for a higher dose of remifentanil (exceeding 1 µg/Kg after induction) or any other medication during anesthesia, increased endtidal CO_2>40 mmHg, heart rate>150 beat/min at any time during the study, and administration of sevoflurane> hour.

The sample size was calculated based on a study conducted by Fong and colleagues, which showed a difference in the time of emergence between saline (16.5±3.9 min) and caffeine (9.6±5.1 min).[4] In our study, the sample size was 18 patients in both groups, with a power of 80% and an alpha coefficient of 0.05. Here, 18 children, who were for elective outpatient surgery, were randomly allocated to two groups (one receiving caffeine citrate and one placebo) using block randomization in blocks of size four (the list of randomized blocks was extracted from www.sealedenvelope.com).

Randomization was done by a nurse anesthetist, who was not involved in the study, in the pre-operative holding area. Moreover, she also prepared two sets of 20 ml syringes equaling in shape and size, labeled A or B. Syringes labeled A contained 10 mg/Kg caffeine citrate up to 20 ml, and syringes labeled B contained 20 ml normal saline.

Neither the two groups of patients nor the researchers were aware of the contents of either syringe sets. Therefore, the study was double-blinded.

Eligible patients received pre-medication with oral midazolam (0.5 mg/Kg; Caspian Tamin Pharmaceutical Co., Iran) and were monitored by the anesthesia staff 20 min prior to the study. Then, the children entered the operating room with their mothers under the supervision of an anesthesiologist, where they underwent standard monitoring and their vital signs were recorded. For vein cannula insertion, mask induction with sevoflurane anesthetic (Baxter, USA), 6% to 8%, was used with 50% oxygen and 50% nitrous oxide (Shomal Co., Iran). At the same time, as the children's level of consciousness decreased, the percentage of the sevoflurane gas was reduced to 3% to 4%. Then, an intravenous catheter (SUPA, Iran) was inserted, and when we made sure it was working properly, all patients received Ringer's solution (Samen Pharmaceutical Co., Iran) for maintenance fluid therapy. Propofol (Aram Kimia Caspian Co., Iran) was used at 1 mg/Kg and a bolus of remifentanil (Norman Co., Spain) at 1 µg/Kg.

After two minutes, the sevoflurane was turned off and a suitable-size laryngeal mask was placed. Sevoflurane was monitored by a gas analyzer with a minimum alveolar concentration (MAC) of 1%, as well as 50% oxygen and 50% nitrous oxide, which were used to maintain the anesthesia. Monitoring of age-adjusted minimum alveolar concentration of exhaled anesthetic was performed using an infrared analyzer (Drager Primus, Germany); End-tidal CO_2 was maintained between 30 and 40 mmHg, and the heart rate and blood pressure were recorded every five minutes on the anesthesia chart. Continuous monitoring of vital signs was carried out with a gas analyzer during anesthesia. If we assessed the depth of anesthesia to be insufficient during surgery (increased respiration rate, heart rate, or blood pressure, pain, or surgical stimulation), remifentanil would be administered at a rate of 1 µg/Kg and recorded. Sevoflurane was discontinued at the time of surgery, when the skin was sutured by the surgeon, and 20 cc syringes containing 10 mg/Kg of caffeine citrate (Chemidarou Co., Iran) diluted with distilled water were administered to the patients in the intervention group. In the control group, 20 cc of distilled water was administered in 20 cc syringes. Injections were performed according to a randomization chart, and the syringes were labeled A or B by the anesthesia personnel,

who were unaware of the type of drug. When wound dressing was applied, the nitrous oxide gas was turned off and oxygen was continued up to 100%. Then, the anesthesiologist would wait for the child's spontaneous respiration.

The primary outcome was the Laryngeal Mask Airway (LMA) removal time. The criteria for laryngeal mask removal included the spontaneous eye-opening, purposeful movement of the extremities without any physical stimulation, and response to verbal commands.[14]

Secondary outcomes were: heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) during the perioperative period, complications such as nausea and vomiting, dysrhythmia, cyanosis, and seizures in the recovery room.

HR, SBP, and DBP were recorded five times in double-blinded conditions by the anesthesia staff as follows: at the onset of anesthesia and before induction with sevoflurane (T1); at the start of surgery (T2); at the time of the injection of caffeine citrate or placebo (T3); five minutes after the injection of caffeine citrate or placebo (T4); 30 minutes after caffeine citrate or placebo injection in the recovery room (T5).

After ensuring the child's vital signs were stable, we would transfer them to the recovery room. Then, the exit time from the operation room and the discharge time from the recovery room were recorded. The patients were monitored by expert staff for possible complications, such as nausea and vomiting, dysrhythmia, cyanosis, and seizures in the recovery room.

The criteria for discharge from the recovery room included a score of nine or higher in the post-anesthetic discharge scoring system chart.[14]

The recorded times included: a) from the injection of caffeine citrate or placebo to LMA removal time (T1), b) the time the child exited the operating room (T2), and c) the time of discharge from the recovery room (T3).

Data Analysis

In this study, the continuous variables were expressed by mean±SD. The categorical variables were expressed as numbers and percentages. The differences between groups were examined by the independent-samples *t* test. Furthermore, Fisher's exact test and the Mann-Whitney U test were used to test the differences in the categorical variables. We used repeated-measures ANOVA to analyze the data in the groups during the time. Since the interaction between time and group was not significant, we were able to report the overall effect during the time. Data were analyzed

using SPSS Statistics 21.0 (SPSS Inc, Chicago, IL, USA) and P values<0.05 were considered statistically significant.

Results

Among the 31 eligible children scheduled for inguinal herniorrhaphy under GA in our hospital between June 2019 and September 2019, 13 children were excluded, and finally, 18 patients completed the study (figure 1). A total of 18 patients were selected as subjects in this study and were divided into the two groups of Placebo and Caffeine.

There were no significant differences between the two groups regarding demographic variables (table 1).

Figure 2 (A, B, and C) shows the mean±SD of DBP, SBP, HR at the induction time (T1), surgery incision time (T2), drug or placebo injection time (T3), five minutes after injection (T4), and 30 minutes after injection (T5). According to the repeated measures ANOVA, there were no statistically significant differences between the groups in any of the variables at any timestamp (P>0.05).

Regarding the primary outcome, the time from the induction of anesthesia to laryngeal mask removal was 44.77±7.87 min in the placebo group and 44.55±10.68 min in the caffeine group. Therefore, there was no significant difference between the two groups in this regard (P=0.961).

Table 2 shows the time interval between caffeine citrate or placebo injection and LMA removal (a), leaving the operating room (b), and recovery room clearance conditions (c). Here, none of the comparative data of the two groups were statistically significant (P=0.467, P=0. 893, and P=0.179, respectively).

Complications due to caffeine citrate or placebo, such as nausea and vomiting, dysrhythmia, cyanosis, and seizures, were not observed in either group in the recovery room.
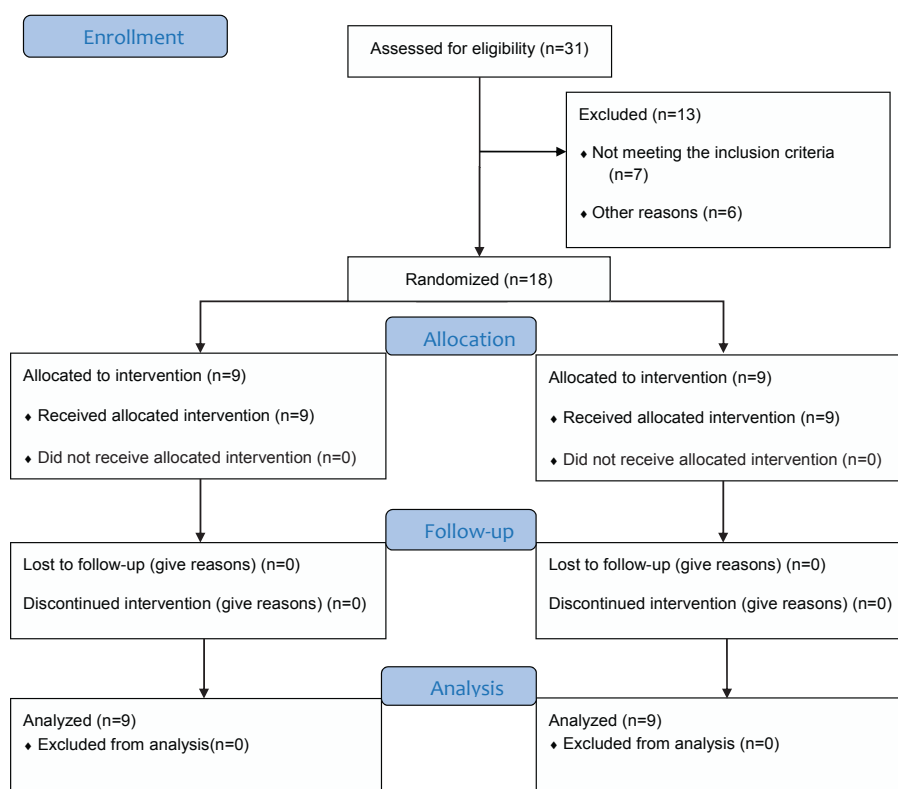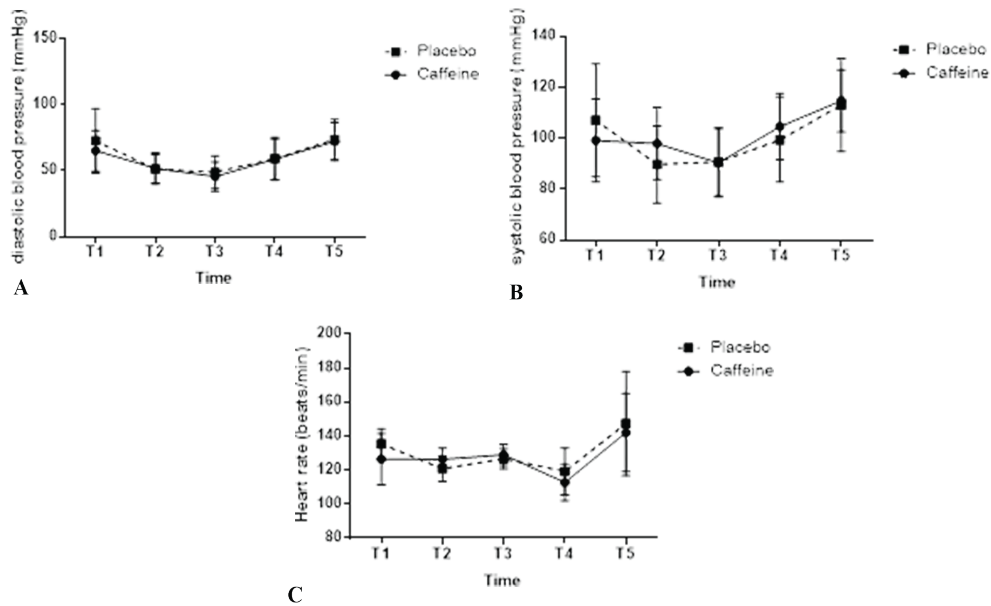

Figure 1: The CONSORT diagram shows the allocation process throughout the trial

Table 1: Demographics of the two study groups				
Variables		**Caffeine (N=9)**	**Placebo (N=9)**	**P value**
Age (Month) (Mean±SD)		27.22±7.46	22.22±6.44	0.148*
Sex	Male	9	6	0.206#
	Female	9	12	
Weight (Kg) (Mean±SD)		11.89±2.15	11.55±1.01	0.679*

*Independent-samples *t* test for mean±SD; #Fisher's exact test; N: Number of patients

Figure 2: The Mean±SD of systolic blood pressure, diastolic blood pressure, and heart rate (A, B, and C) are shown during the induction time (T1), surgery incision time (T2), drug or placebo injection time (T3), five minutes after injection (T4), and 30 minutes after injection (T5).

Table 2: Time interval between caffeine citrate or placebo injection and LMA removal, leaving the operating room, and recovery room clearance conditions

Variables time(min)	Caffeine (N=18)	Placebo (N=18)	P value*
IN. LMA removal (a)	10(9.5-13)	9(7-13)	0.467
IN.OR leaving (b)	15(13-16)	14(12.5-18)	0.893
IN.RR clearance conditions(c)	29(24.5-38.5)	35(30-47)	0.179

IN: Injection, LMA: Laryngeal Mask Airway, OR: Operating room, RR: Recovery Room *Mann-Whitney U test. N: Number of patients

Discussion

According to the findings of our study, caffeine administration had no effect on awakening from GA in children, who underwent inguinal herniorrhaphy under GA. Furthermore, we did not find any hemodynamic changes such as tachycardia or hypertension in children who received caffeine to accelerate awakening from GA.

Caffeine is an adenosine receptor antagonist, which is nowadays used as a psychoactive compound. It accelerates awakening by blocking the adenosine A receptors in the brain.[11] Moreover, by inhibiting the phosphodiesterase enzyme, caffeine elevates intracellular cAMP. In the study by Fong and colleagues on adult rats, caffeine dramatically accelerated recovery from anesthesia by ~60%.[2]

Previously, the study by Fong and colleagues indicated that caffeine can accelerate awakening from anesthesia in rats.[2] In that study, they showed that caffeine is effective even at deep levels of anesthesia. They also

showed that caffeine operates by both elevating the intracellular cAMP levels and blocking the adenosine receptors. This complicated pharmacology makes caffeine especially effective in the acceleration of awakening from anesthesia.[2] Furthermore, in another recent study, Fong and colleagues demonstrated the ability of caffeine to accelerate awakening from GA in adult human volunteers.[4] The recovery of consciousness was significantly faster, when subjects were treated with caffeine rather than a placebo.[4] In contrast with the studies of Fong and colleagues, the findings of our study showed that caffeine did not have any effect on the rate of awaking after anesthesia.[2, 4]

In children, caffeine is used clinically to treat neonatal apnea.[15] However, the caffeine dosage used to treat neonatal apnea is higher than the dose used in this study. Since this study was the first to survey the effect of caffeine on awakening rate following GA, we designed our study and the caffeine dosage in accordance with the study by Fong and colleagues on adults.[4] Furthermore, the dose requirements of nearly all drugs used in

anesthesia vary for adults and children. Hence, there may be a need for higher drug dosage. This difference may be due to pharmacokinetics and pharmacodynamics differences between the children and adults.[16] Therefore, although caffeine could not accelerate awakening from GA in our study, in contrast with the findings of Fong and colleagues, caffeine may induce faster awakening from anesthesia in adults.[4] Thereby, probably if we had used a higher caffeine dose in our study, we may have been able to accelerate awakening from GA and find the same results as Fong and colleagues.[4]

According to our study findings, caffeine administration in children did not increase their blood pressure or heart rate, and these findings were in line with the results reported by Fong and colleagues regarding hemodynamic changes following caffeine administration.[4] Furthermore, in our study, we did not find any complications such as nausea and vomiting, dysrhythmia, cyanosis, and seizures in the caffeine group during the study. Therefore, according to these findings, caffeine is a safe drug to use in children.

This study had certain limitations. First, we should have used higher caffeine doses to better evaluate the effect of caffeine on emergence in children following GA. Secondly, we should have surveyed the effect of caffeine on awakening in children following a long duration of surgery and anesthesia, because anesthesiologists are more concerned about delayed awakening after long durations of anesthesia, and in such a condition, maybe the accelerating effect of caffeine on awakening from GA would become more prominent. In future studies, these limitations should be taken into consideration.

Conclusion

According to the findings of our study, caffeine administration (10 mg/Kg) did not accelerate awakening from GA in children, who underwent inguinal herniorrhaphy under GA. However, we did not find any hemodynamic changes, such as tachycardia or hypertension in children who received caffeine for the acceleration of emergence from GA. Furthermore, in our study, we did not find any complications with caffeine either. Therefore, caffeine (10 mg/Kg) is a safe drug to use in children.

Acknowledgment

Authors' Contribution

S.E: study conception, proposal writing, Acquisition of data, drafting the manuscript; A.P: study conception, proposal writing, drafting and revising the manuscript; S.Sh.H: study design, acquisition and analysis of data, drafting the manuscript; M.A.A: proposal preparation, analysis of data and drafting and revising the manuscript; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

References

1   Solt K, Cotten JF, Cimenser A, Wong KF, Chemali JJ, Brown EN. Methylphenidate actively induces emergence from general anesthesia. Anesthesiology. 2011;115:791-803. doi: 10.1097/ALN.0b013e31822e92e5. PubMed PMID: 21934407; PubMed Central PMCID: PMCPMC3178041.

2   Fong R, Khokhar S, Chowdhury AN, Xie KG, Wong JH, Fox AP, et al. Caffeine accelerates recovery from general anesthesia via multiple pathways. J Neurophysiol. 2017;118:1591-7. doi: 10.1152/jn.00393.2017. PubMed PMID: 28659466; PubMed Central PMCID: PMCPMC5596131.

3   Cascella M, Bimonte S, Di Napoli R. Delayed Emergence from Anesthesia: What We Know and How We Act. Local Reg Anesth. 2020;13:195-206. doi: 10.2147/LRA.S230728. PubMed PMID: 33177867; PubMed Central PMCID: PMCPMC7652217.

4   Fong R, Wang L, Zacny JP, Khokhar S, Apfelbaum JL, Fox AP, et al. Caffeine Accelerates Emergence from Isoflurane Anesthesia in Humans: A Randomized, Double-blind, Crossover Study. Anesthesiology. 2018;129:912-20. doi: 10.1097/ALN.0000000000002367. PubMed PMID: 30044241; PubMed Central PMCID: PMCPMC6191316.

5   Yang A, Palmer AA, de Wit H. Genetics of caffeine consumption and responses to caffeine. Psychopharmacology (Berl). 2010;211:245-57. doi: 10.1007/s00213-010-1900-1.

PubMed PMID: 20532872; PubMed Central PMCID: PMCPMC4242593.

6 Son Y. Molecular mechanisms of general anesthesia. Korean J Anesthesiol. 2010;59:3-8. doi: 10.4097/kjae.2010.59.1.3. PubMed PMID: 20651990; PubMed Central PMCID: PMCPMC2908224.

7 Thomas E, Martin F, Pollard B. Delayed recovery of consciousness after general anaesthesia. BJA Educ. 2020;20:173-9. doi: 10.1016/j.bjae.2020.01.007. PubMed PMID: 33456947; PubMed Central PMCID: PMCPMC7807841.

8 Chemali JJ, Van Dort CJ, Brown EN, Solt K. Active emergence from propofol general anesthesia is induced by methylphenidate. Anesthesiology. 2012;116:998-1005. doi: 10.1097/ALN.0b013e3182518bfc. PubMed PMID: 22446983; PubMed Central PMCID: PMCPMC3339625.

9 Fox AP, Wagner KR, Towle VL, Xie KG, Xie Z. Caffeine reverses the unconsciousness produced by light anesthesia in the continued presence of isoflurane in rats. PLoS One. 2020;15:e0241818. doi: 10.1371/journal.pone.0241818. PubMed PMID: 33152041; PubMed Central PMCID: PMCPMC7643991.

10 Ferre S. An update on the mechanisms of the psychostimulant effects of caffeine. J Neurochem. 2008;105:1067-79. doi: 10.1111/j.1471-4159.2007.05196.x. PubMed PMID: 18088379.

11 Lazarus M, Shen HY, Cherasse Y, Qu WM, Huang ZL, Bass CE, et al. Arousal effect of caffeine depends on adenosine A2A receptors in the shell of the nucleus accumbens. J Neurosci. 2011;31:10067-75. doi: 10.1523/JNEUROSCI.6730-10.2011. PubMed PMID: 21734299; PubMed Central PMCID: PMCPMC3153505.

12 van Koert RR, Bauer PR, Schuitema I, Sander JW, Visser GH. Caffeine and seizures: A systematic review and quantitative analysis. Epilepsy Behav. 2018;80:37-47. doi: 10.1016/j.yebeh.2017.11.003. PubMed PMID: 29414557.

13 Daabiss M. American Society of Anaesthesiologists physical status classification. Indian J Anaesth. 2011;55:111-5. doi: 10.4103/0019-5049.79879. PubMed PMID: 21712864; PubMed Central PMCID: PMCPMC3106380.

14 Moncel JB, Nardi N, Wodey E, Pouvreau A, Ecoffey C. Evaluation of the pediatric post anesthesia discharge scoring system in an ambulatory surgery unit. Paediatr Anaesth. 2015;25:636-41. doi: 10.1111/pan.12612. PubMed PMID: 25581378.

15 Moschino L, Zivanovic S, Hartley C, Trevisanuto D, Baraldi E, Roehr CC. Caffeine in preterm infants: where are we in 2020? ERJ Open Res. 2020;6. doi: 10.1183/23120541.00330-2019. PubMed PMID: 32154294; PubMed Central PMCID: PMCPMC7049734.

16 Sumpter A, Anderson BJ. Pediatric pharmacology in the first year of life. Curr Opin Anaesthesiol. 2009;22:469-75. doi: 10.1097/aco.0b013e32832bc7ff. PubMed PMID: 19593898.