Behavioral and emotional effects of repeated general anesthesia in young children

Mohamed H. Bakri,
Eman A. Ismail,
Mohamed S. Ali,
Ghada O. Elsedfy[1],
Taher A. Sayed[2],
Ahmed Ibrahim[3]

Department of Anesthesia, Faculty of Medicine, Assiut University, [1]Department of Pediatric, Faculty of Medicine, Children's Hospital, Assiut University, Assiut, [2]Department of Psychiatry, Faculty of Medicine, Sohag University, Sohag, Egypt, [3]Department of Community Medicine, Faculty of Medicine, University of Western Kordofan, Sudan.

Address for correspondence:
Dr. M. H. Bakri,
Department of Anesthesia,
Faculty of Medicine, Assiut University,
Assiut 71515, Egypt.
E-mail: mhbakri@gmail.com

ABSTRACT

Background: Preclinical and clinical data suggest the possibility of neurotoxicity following exposure of young children to general anesthetics with subsequent behavioral disturbances. The aim of the study was to determine the overall effect of repeated general anesthesia on behavior and emotions of young children aged 1½-5 years old, compared to healthy children. **Materials and Methods:** Thirty-five children underwent repeated anesthesia and surgery were matched with the same number of healthy children who attended vaccination clinic, as a control group. Both groups were administered the child behavior checklist (CBCL) 1½-5 years and Diagnostic and Statistical Manual of Mental Disorders (DSM) oriented scale. Behavior data were collected through a semi-structured questionnaire. **Results:** The CBCL score revealed that children with repeated anesthesia were at risk to become anxious or depressed (relative risk [RR]; 95% confidence interval [CI] = 11 [1.5-80.7]), to have sleep (RR; 95% CI = 4.5 [1.1-19.4]), and attention problems (RR; 95% CI = 8 [1.1-60.6]). There was no difference in the risk between the two groups regarding emotionally reactive, somatic complaints, withdrawn problems, aggressive behavior, internalizing or externalizing problems. On DSM scale, children with repeated anesthesia were at risk to develop anxiety problems (RR; 95% CI = 3.7 [1.1-12.0]), and attention deficit/hyperactivity problems (RR; 95% CI = 3 [1.1-8.4]). There was no difference in the risk between the two groups regarding affective, pervasive developmental and oppositional defiant problems. **Conclusion:** Young children who undergone repeated surgical procedures under general anesthesia were at risk for subsequent behavioral and emotional disturbances. Proper perioperative pain management, social support, and avoidance of unpleasant surgical experiences could minimize these untoward consequences.

Key words: *Behavior, child, emotional disturbances, repeated anesthetics*

INTRODUCTION

Researchers questioned the safety of general anesthesia to the developing brain during early childhood,[1-5] because millions of children have surgery under general anesthesia all over the world each year. Many animal and human studies have been done trying to find an answer to this question. Indeed, there are accumulating preclinical and clinical data that suggest the possibility of pediatric neurotoxicity following exposure to general anesthesia.[1-4] Experimental studies in animals have shown that when the developing mammalian brain is exposed to a variety of commonly used anesthetic agents during the critical developmental periods, it can lead to neuronal apoptosis (programmed cell death) or neuro-degeneration.[6-9] Exposure of neonatal mice to inhaled sevoflurane could cause learning deficits and abnormal social behaviors similar to autism disorder.[6] Similarly; anesthesia with 3% sevoflurane for 2 h daily for 3 days induced cognitive impairment such as unusually poor mental function and elevated levels of brain inflammatory mediators in young but not in adult mice.[9]

Access this article online	
Quick Response Code:	Website: www.saudija.org
	DOI: 10.4103/1658-354X.152843

There are different groups of clinically-used general anesthetics that vary from intravenous (I.V.) anesthetics, such as benzodiazepines, barbiturates, ketamine, propofol, and etomidate; to inhaled anesthetics, such as halothane, isoflurane, sevoflurane, desflurane, and nitrous oxide. Although these compounds are chemically different, surprisingly, their mechanism of action to inhibit neuronal activity is very similar.[10,11] Various investigators developed new behavioral measurement modalities validated in several studies with good reliability, such as child behavior checklist (CBCL) for children 1½-5 years old.[12] The CBCL parental reports have been used to examine long-term behavior following childhood surgery under general anesthesia.[13] The aim of the present study was to determine the overall effect of repeated (two) exposure to general anesthesia on the behavior of young children aged 1½-5 years old, compared to a control group of healthy children who attended vaccination clinic and had no history of anesthesia.

MATERIALS AND METHODS

The research proposal and data collection tools were approved by hospital research and Ethics Committee. Children undergoing repeated general anesthesia and surgery form the first group of the study (Group I). Group I was recruited out of those attending preanesthesia clinic for routinely preoperative assessment after the second anesthesia exposure, but before the third operation. Recruitment also included children coming to surgical outpatient clinic for postoperative follow-up after the second operation. Inclusion criteria included: Age ranged from 1½ to 5 years old, American Society of Anesthesiologists (ASA) I-II physical status, had a history of two general anesthesia and were free from acute or chronic illnesses. Of those approached; parents of the 35 children agreed to participate. The study group was matched with the same number of healthy children, who attended vaccination clinic, and had no history of anesthesia, as a control group (Group II). Orientation for parents about study objectives was carried out, before obtaining informed consent, with emphasis on the choice of nonparticipation. Participants' information confidentiality was maintained.

Data collection methods

Sociodemographic data were collected, including: Age in months, gender, residence, and weight via interview with parents, particularly mothers, in the two study groups. The interviews were carried out on the same day of attending the clinics by trained nurse under the supervision of the investigators. Parents accompanying the children were invited to complete a CBCL and DSM oriented scales, which are a group of self-rated questionnaire that survey a wide range of behavioral and cognitive difficulties encountered in children from 1½ to 5 years old.[12] The time of completion for the CBCL and DSM forms of the repeated anesthesia group was after the 2nd time of general anesthesia. As for the healthy control group, it was during the vaccination clinic visit.

Anesthetic management

The charts of patients in the anesthetized group were retrospectively reviewed for frequency and details of general anesthesia. All cases were done by the same anesthesia team over 3-4 years period, so the anesthetic management was almost the same. All children came from home to Day Surgery Unit and were discharged on the same day. All children were premedicated with oral midazolam 0.5 mg/kg 20-30 min before induction of anesthesia. Children were induced with sevoflurane 5-8% in 50% of O_2-N_2O, and then terminated when consciousness was lost, and I.V. access was obtained. Atropine was given in a dose of 10-20 mcg/kg to treat bradycardia. Both fentanyl and atracurium were given in a dose of 1 mcg/kg and 0.5 mg/kg, respectively, to facilitate endotracheal intubation. Children were maintained on pressure-controlled ventilation with an inspiratory pressure adjusted between 15 and 19 cm H_2O and respiratory rate adjusted to maintain normocapnia. Anesthesia was maintained with sevoflurane in 50% of O_2-N_2O mixture, and shots of fentanyl according to hemodynamics. At the end of surgery, sevoflurane was discontinued, and muscle relaxation was reversed with neostigmine in a dose of 50 mcg/kg combined with atropine 10-15 mcg/kg, and then awake extubation was carried out. One case (orchidopexy), from group II, suffered from extubation spasm which was managed immediately and successfully with positive pressure ventilation. Patients were sent to the recovery room for about 30-45 min, and then to their mothers in the postrecovery area. Children were discharged when they met discharge criteria and home readiness. For dental cases, the endotracheal tube was inserted nasally with throat pack which was removed before extubation.

Psychiatric measures

A semi-structured psychiatric interview based on CBCL 1½-5 and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision criteria for child and adolescent mental health was administered by all participants.[14]

The CBCL 1½-5 included 99 questions that describe specific kinds of behavioral, emotional, and social problems which characterize preschool children. There are also open-ended items for describing additional problems. The parents were asked to answer the questions with a three-point scale: 0 for not true of the child; 1 for somewhat or sometimes true, and 2 for very true or often true. The CBCL behavioral/emotional portion is divided into two broadband dimensions: Internalizing (emotional) and externalizing (behavioral), and those are divided into subscales. Items are scored on syndrome scales designated as emotionally reactive, anxious/depressed, somatic complaints, withdrawn, attention problems, aggressive behavior, and sleep problems. The scores for internalizing and externalizing problems were calculated according to the CBCL manuals. Open-ended questions requested information about illnesses and disabilities, what concerns the respondent most about the child and the best things about the child. The measures' internal consistency was found to be high, and test-retest reliability was observed to be acceptable. High scores mean great behavioral disturbances.[12]

Diagnostic and statistical manual of mental disorders oriented scale included assessment for five problems

Affective, anxiety, pervasive developmental, attention deficit/hyperactivity, and oppositional defiant problems. As in the CBCL questionnaire, parents were asked to answer the questions with a three-point scale: 0 for not true of the child; 1 for somewhat or sometimes true, and 2 for very true or often true. Furthermore, high scores mean great suffering. The Arabic version of the CBCL and DSM tests were given to Arab participants and the reliability and validity for the Arab children was proven and standardized.[14]

Statistical analysis

All data variables were coded, entered, and analyzed using the Statistical Package for Social Science (SPSS) version 17.0 (SPSS Inc., Chicago, Illinois, USA). The study hypothesis was that repeated anesthesia is a risk factor for the development of psycho-behavioral problems in children aged 1½-5 years old. To answer this question, data were transformed from quantitative data to qualitative data using CBCL 1½-5 and DSM oriented scales. The cut point of behavioral and emotional problems divided into dichotomous outcomes of (<65) and (≥65) for normal range and clinical significance, respectively. Descriptive statistics was performed in terms of mean, standard deviation, or percentages. *t*-test and Chi-squared test were performed to assess differences between study groups; statistical significant level was set at $P < 0.05$. For comparing the outcomes between the two groups, the relative risk (RR) and 95% confidence interval (CI) were reported.

RESULTS

The total study population was 70 children; of them, 35 were the study group who had a history of two general anesthesia. The control group included 35 healthy children attending vaccination clinic and had no history of anesthesia. All children in both study and control group were matched for age which is the main measure according to the CBCL age classification for development of behavioral problems. Table 1 shows demographic data for both study groups. There were no statistically significant differences in age, weight, gender, or residence between the study and control groups.

Table 1: Demographic data for both study groups

Variable	Repeated anesthesia (*n* = 35)	Healthy control (*n* = 35)	*P*
Age (months)			
Mean±SD	38.3±10.7	39.8±15.9	0.6
Weight (kg)			
Mean±SD	14.1±1.5	14.6±2.6	0.3
Gender *n* (%)			
Male	17 (48.6)	20 (57.1)	0.6
Female	18 (51.4)	15 (42.9)	
Residence *n* (%)			
Rural	13 (37.1)	10 (28.6)	0.6
Urban	22 (62.9)	25 (71.4)	

No significant differences between the two study groups; SD: Standard deviation

Children in repeated anesthesia group were undergone different surgical procedures under general anesthesia at different times (arthrogram and Hip spica cast for Developmental Dysplasia of the Hip, polydactyly, syndactyly, cleft lip, burn graft, circumcision, orchidopexy, penile hypospadia, hernia, and dental rehabilitation). The mean anesthesia time was 87 ± 39 min. All were ASA I-II physical status. Table 2 shows the CBCL score that revealed children with repeated anesthesia were at risk to become anxious or depressed (RR; 95% CI = 11 [1.5-80.7]), to have sleep problems (RR; 95% CI = 4.5 [1.1-19.4]), and attention problems (RR; 95% CI = 8 [1.1-60.6]) when compared to control group. However, there was no difference in the risk between the two groups regarding emotionally reactive, somatic complaints, withdrawn problems, aggressive behavior, internalizing or externalizing problems.

Table 3 shows the DSM score that revealed children with repeated anesthesia were at risk to develop anxiety problems (RR; 95% CI = 3.7 [1.1-12.0]), and attention deficit/hyperactivity problems (RR; 95% CI = 3 [1.1-8.4]). However, there was no difference in the risk between the two study groups regarding affective, pervasive developmental and oppositional defiant problems.

DISCUSSION

The possibility of anesthesia-induced neurotoxicity during exposure of young children to general anesthetics led researchers to question the safety of anesthesia during early childhood. The present study highlighted the overall effect of repeated general anesthesia on the behavior of preschool children aged 1½-5 years old. We found that children with repeated general anesthesia are at risk for subsequent behavioral and emotional changes compared

Table 2: Comparative analysis of behavioral problems among repeated anesthesia and control groups using CBCL 1½-5 scale

Variable	Repeated anesthesia (*n* = 35)	Control group (*n* = 35)	RR, 95% CI
Emotionally reactive			
Normal range (<65)	32 (91.4)	34 (97.1)	3 (0.3-27.5)
Clinical significance (≥65)	3 (8.6)	1 (2.9)	
Anxious/depressed			
Normal range (<65)	24 (68.6)	34 (97.1)	11 (1.5-80.7)
Clinical significance (≥65)	11 (31.4)	1 (2.9)	
Somatic complaints			
Normal range (<65)	33 (94.3)	34 (97.1)	2 (0.2-21.1)
Clinical significance (≥65)	2 (5.7)	1 (2.9)	
Withdrawn			
Normal range (<65)	32 (91.4)	34 (97.1)	3 (0.3-27.5)
Clinical significance (≥65)	3 (8.6)	1 (2.9)	
Sleep problems			
Normal range (<65)	26 (74.3)	33 (94.3)	4.5 (1.1-19.4)
Clinical significance (≥65)	9 (25.7)	2 (5.7)	
Attention problems			
Normal range (<65)	27 (77.1)	34 (97.1)	8 (1.1-60.6)
Clinical significance (≥65)	8 (22.9)	1 (2.9)	
Aggressive behavior			
Normal range (<65)	29 (82.9)	33 (94.3)	3 (0.6-13.9)
Clinical significance (≥65)	6 (17.1)	2 (5.7)	
Internalizing			
Normal range (<65)	29 (82.9)	34 (97.1)	6 (0.7-47.3)
Clinical significance (≥65)	6 (17.1)	1 (2.9)	
Externalizing			
Normal range (<65)	30 (85.7)	33 (94.3)	2.5 (0.5-12.0)
Clinical significance (≥65)	5 (14.3)	2 (5.7)	

RR: Relative risk; CI: Confidence interval; CBCL: Child behavior checklist

Table 3: Comparative analysis of behavioral problems among repeated anesthesia and control groups using DSM oriented scale

Variable	Repeated anesthesia (*n* = 35)	Control group (*n* = 35)	RR, 95% CI
Affective problems			
Normal range (<65)	27 (77.1)	33 (94.3)	4 (0.9-17.5)
Clinical significance (≥65)	8 (22.9)	2 (5.7)	
Anxiety problems			
Normal range (<65)	24 (68.6)	32 (91.4)	3.7 (1.1-12.0)
Clinical significance (≥65)	11 (31.4)	3 (8.6)	
Pervasive developmental problems			
Normal range (<65)	32 (91.4)	34 (97.1)	3 (0.3-27.5)
Clinical significance (≥65)	3 (8.6)	1 (2.9)	
Attention deficit/hyperactivity problems			
Normal range (<65)	23 (65.7)	31 (88.6)	3 (1.1-8.4)
Clinical significance (≥65)	12 (34.3)	4 (11.4)	
Oppositional defiant problems			
Normal range (<65)	30 (85.7)	32 (91.4)	1.7 (0.4-6.5)
Clinical significance (≥65)	5 (14.3)	3 (8.6)	

RR: Relative risk; CI: Confidence interval; DSM: Diagnostic and Statistical manual of mental disorders

to healthy children of the same age who were not exposed to general anesthesia. We do not suggest a cause-effect relationship, but rather an association between repeated anesthesia and behavioral consequences.

The effects of repeated postnatal anesthesia in humans have been examined in different studies.[1-4] Ing *et al.* found that young children who were exposed to general anesthesia before the age of three had a higher RR of language and abstract reasoning deficits at an age of 10 years when compared to unexposed children.[4] DiMaggio *et al.* reported that children below 3 years of age who underwent surgery for hernia repair under general anesthesia had the chance for subsequent developmental or behavioral disorder more than twice as likely as children who did not have hernia repair (i.e., who were not exposed to general anesthesia).[2] Stargatt *et al.* observed that anesthesia in young children can lead to prolonged behavioral abnormalities such as sleep disturbance, attention seeking, crying, and temper tantrums, which occurred in up to 50% of children early after anesthesia.[15] Kain *et al.* postulated that these symptoms have been repeatedly associated with a younger patient age, the severity of postoperative pain, and with the lack of sedation during induction of anesthesia.[16]

The findings of the present work go along with Wilder *et al.* study which revealed that two or more exposures to general anesthesia before the age of four were associated with an increased risk of attention problems, cognitive impairment, and learning disabilities (LD).[1] Moreover, they found that a single exposure to anesthesia was not associated with LD and that the risk for LD increased with increasing duration of exposure to anesthesia. However, they could not determine whether anesthesia itself may contribute to attention problems and LD or whether the need for anesthesia is a marker for other unidentified factors that contribute to attention problems and LD.[1] Further analysis done by Flick *et al.* who reported that children who had two or more exposure to general anesthesia, before the age of 2 years, was a significant independent risk factor for subsequent development of LD after adjustment for other factors that associated with LD.[3] They also confirmed that a single exposure to general anesthesia was not associated with an increase in LD.[3] For the same previous cohort, Sprung *et al.* examined the association between the incidence of attention-deficit/hyperactivity disorder (ADHD) and the exposure to general anesthesia. They found that children who were exposed to repeated general anesthesia before the age of two were at increased risk for the later development of ADHD.[17]

However, Kalkman *et al.* observed a trend of long-term attention problems and cognitive impairment with even a single early exposure to general anesthesia, contrary to the previous studies, which have shown that cognitive deficits occurred only in relation to two or more anesthesia exposures.[13] Hudson and Hemmings explained that neuro-developmental factors in the young brain may predispose young children to general anesthesia toxicity. They postulated that the effect of early exposure to general anesthetics on neurogenesis and synaptogenesis may impair neurocognitive function.[18] Kain *et al.* claimed that increased preoperative anxiety in children was associated with increased postoperative pain, analgesic consumption, anxiety, and sleeping problems. However, they mentioned that most of these outcomes did not extend beyond the first 3 postoperative days.[19] Indeed, children who were sedated with midazolam before surgery showed a significantly lower incidence of postoperative maladaptive behavioral changes.[20] Contrary to our results and the studies mentioned above, Kayaalp *et al.* reported that repeated general anesthesia does not seem to disturb the child's psychological health further, when proper perioperative management are undertaken, such as; the use of proper premedication, effective postoperative pain control, having good rapport with children, and performing surgery and anesthesia on an outpatient basis where possible.[21] Fan *et al.* have another opinion that sevoflurane-based general anesthesia does not have significant adverse effects on the attention and other cognitive function on children between the ages of 4 and 7 years when evaluated at 1-month and 6 months after exposure to general anesthesia.[22]

To control the potential confounding factors and overcome the shortcomings of observational studies, two large-scale clinical studies are currently underway to examine the effect of general anesthesia on child behavior. The Pediatric Anesthesia and Neuro-Developmental Assessment (PANDA) study is a large-scale, multisite, ambi-directional sibling-matched cohort study in the USA. It will examine the neuro-developmental effects of exposure to general anesthesia during inguinal hernia surgery before 36 months of age. The second study is the General Anesthesia Study (GAS), which will compare the neuro-developmental outcome between two anesthetic techniques; general sevoflurane anesthesia versus regional anesthesia, in infants undergoing inguinal hernia repair. Hopefully, the results of both studies will provide clear conclusions about the neuro-developmental effects of general anesthesia on young children. Until we have answers from the PANDA and GAS studies, the current data do not support significant changes in practice other than recommendations, such as delay truly elective surgery, good preoperative sedation, effective perioperative pain control, maintenance of hemodynamic stability, avoidance of hypoxia, use of appropriate doses of anesthetic agents, minimizing duration of anesthesia exposure, and considering the use of regional anesthetic techniques where possible. Finally, the advice given by Davidson is "When discussing the issues with parents we need to be cautious not to cause undue alarm, but we must also not be too quick to dismiss any concern."[23]

Study limitations

The main limitation of the present study was a small sample size that cannot detect the precise effect of repeated anesthesia on the behavioral and emotional outcomes. Furthermore, we were unable to study the effect of postoperative pain management and the impact of the surgical procedures on the children's caregivers that could affect the children outcomes. Residual confounding factors are additional problems that could only be solved in prospective randomized studies. We think that this is the first application of the Arabic version of CBCL and DSM scores in this particular age group of children who undergone repeated anesthesia. It provides researchers with an additional insight into the neuro-behavioral effects of repeated anesthesia by using a simple questionnaire.

CONCLUSION

Young children who had undergone repeated surgical procedures under general anesthesia were at risk for subsequent behavioral and emotional disturbances. Proper perioperative pain management, social support, and avoidance of unpleasant surgical experiences could minimize these untoward consequences. The CBCL and DSM are time and cost-efficient tools to assess various behavioral and emotional disorders in early childhood.

ACKNOWLEDGMENTS

This research was carried out without funding.

REFERENCES

1. Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, Mickelson C, *et al*. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology 2009;110:796-804.
2. DiMaggio C, Sun LS, Kakavouli A, Byrne MW, Li G. A retrospective cohort study of the association of anesthesia and hernia repair surgery with behavioral and developmental disorders in young children. J Neurosurg Anesthesiol 2009;21:286-91.
3. Flick RP, Katusic SK, Colligan RC, Wilder RT, Voigt RG, Olson MD, *et al*. Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. Pediatrics 2011;128:e1053-61.
4. Ing C, DiMaggio C, Whitehouse A, Hegarty MK, Brady J, von Ungern-Sternberg BS, *et al*. Long-term differences in language and cognitive function after childhood exposure to anesthesia. Pediatrics 2012;130:e476-85.

5. Sanders RD, Hassell J, Davidson AJ, Robertson NJ, Ma D. Impact of anesthetics and surgery on neurodevelopment: An update. Br J Anesth 2013;110 Suppl 1:i53-72.
6. Satomoto M, Satoh Y, Terui K, Miyao H, Takishima K, Ito M, *et al*. Neonatal exposure to sevoflurane induces abnormal social behaviors and deficits in fear conditioning in mice. Anesthesiology 2009;110:628-37.
7. Loepke AW. Developmental neurotoxicity of sedatives and anesthetics: A concern for neonatal and pediatric critical care medicine? Pediatr Crit Care Med 2010;11:217-26.
8. Zhu C, Gao J, Karlsson N, Li Q, Zhang Y, Huang Z, *et al*. Isoflurane anesthesia induced persistent, progressive memory impairment, caused a loss of neural stem cells, and reduced neurogenesis in young, but not adult, rodents. J Cereb Blood Flow Metab 2010;30:1017-30.
9. Shen X, Dong Y, Xu Z, Wang H, Miao C, Soriano SG, *et al*. Selective anesthesia-induced neuroinflammation in developing mouse brain and cognitive impairment. Anesthesiology 2013;118:502-15.
10. Campagna JA, Miller KW, Forman SA. Mechanisms of actions of inhaled anesthetics. N Engl J Med 2003;348:2110-24.
11. Loepke AW, Soriano SG. An assessment of the effects of general anesthetics on developing brain structure and neurocognitive function. Anesth Analg 2008;106:1681-707.
12. Achenbach TM, Rescorla LA. Manual for the Achenbach System of Empirically Based Assessment (ASEBA): Preschool Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2000.
13. Kalkman CJ, Peelen L, Moons KG, Veenhuizen M, Bruens M, Sinnema G, *et al*. Behavior and development in children and age at the time of first anesthetic exposure. Anesthesiology 2009;110:805-12.
14. American Psychiatric Association. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Text Revision. Washington, DC: American Psychiatric Press; 2000.
15. Stargatt R, Davidson AJ, Huang GH, Czarnecki C, Gibson MA, Stewart SA, *et al*. A cohort study of the incidence and risk factors for negative behavior changes in children after general anesthesia. Paediatr Anesth 2006;16:846-59.
16. Kain ZN, Caldwell-Andrews AA, Maranets I, McClain B, Gaal D, Mayes LC, *et al*. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. Anesth Analg 2004;99:1648-54.
17. Sprung J, Flick RP, Katusic SK, Colligan RC, Barbaresi WJ, Bojanic K, *et al*. Attention-deficit/hyperactivity disorder after early exposure to procedures requiring general anesthesia. Mayo Clin Proc 2012;87:120-9.
18. Hudson AE, Hemmings HC Jr. Are anesthetics toxic to the brain? Br J Anesth 2011;107:30-7.
19. Kain ZN, Mayes LC, Caldwell-Andrews AA, Karas DE, McClain BC. Preoperative anxiety, postoperative pain, and behavioral recovery in young children undergoing surgery. Pediatrics 2006;118:651-8.
20. Kain ZN, Mayes LC, Wang SM, Hofstadter MB. Postoperative behavioral outcomes in children: Effects of sedative premedication. Anesthesiology 1999;90:758-65.
21. Kayaalp L, Bozkurt P, Odabasi G, Dogangun B, Cavusoglu P, Bolat N, *et al*. Psychological effects of repeated general anesthesia in children. Paediatr Anesth 2006;16:822-7.
22. Fan Q, Cai Y, Chen K, Li W. Prognostic study of sevoflurane-based general anesthesia on cognitive function in children. J Anesth 2013;27:493-9.
23. Davidson AJ. Anesthesia and neurotoxicity to the developing brain: The clinical relevance. Paediatr Anesth 2011;21:716-21.

How to cite this article: Bakri MH, Ismail EA, Ali MS, Elsedfy GO, Sayed TA, Ibrahim A. Behavioral and emotional effects of repeated general anesthesia in young children. Saudi J Anaesth 2015;9:161-6.

Source of Support: Nil, **Conflict of Interest:** None declared.