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ORIGINAL INVESTIGATION

Emergence delirium in children: a Brazilian survey☆

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Abstract
Background: Pediatric emergence delirium is characterized by a disturbance of a child's awareness during the early postoperative period that manifests as disorientation, altered attention and perception. The incidence of emergence delirium varies between 18% and 80% depending on risk factors and how it is measured. Reports from Canada, Germany, Italy, United Kingdom, and France demonstrated a wide range of preventive measures and definitions, indicating that there is a lack of clarity regarding emergence delirium. We aimed to assess the practices and beliefs among Brazilian anesthesiologists regarding emergence delirium.
Methods: A web-based survey was developed using REDCap®. A link and QR Code were sent by email to all Brazilian anesthesiologists associated with the Brazilian Society of Anesthesiology (SBA).
Results: We collected 671 completed questionnaires. The majority of respondents (97%) considered emergence delirium a relevant adverse event. Thirty-two percent of respondents reported routinely administrating medication to prevent emergence delirium, with clonidine (16%) and propofol (15%) being the most commonly prescribed medications. More than 70% of respondents reported a high level of patient and parent anxiety, a previous history of emergence delirium, and untreated pain as risk factors for emergence delirium. Regarding treatment, thirty-five percent of respondents reported using propofol, followed by midazolam (26%).

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Conclusion: Although most respondents considered emergence delirium a relevant adverse event, only one-third of them routinely applied preventive measures. Clonidine and propofol were the first choices for pharmacological prevention. For treatment, propofol and midazolam were the most commonly prescribed medications.

Introduction

Emergence delirium (ED) is characterized by a disturbance of a child's awareness during the early postoperative period. Children with ED are disoriented and present with alterations in consciousness, attention and perception, including hypersensitivity to stimuli and hyperactive motor behaviors.[1] This postoperative phenomenon is self-limited and generally lasts 15 to 30 minutes, however long-lasting postoperative cognitive changes after ED is not well defined in children.[2] Children with ED can harm themselves and their caregivers, leading to an increased likelihood of accidentally removing catheters, drains, or dressings as well as an increased workload for nurses and anesthesiologists in the postanesthesia care unit (PACU).[1,3] The incidence of ED varies between 18% and 80% depending on how ED is defined and depending on which scale is used for diagnosis.[4] Several scales were developed but not validated.[5,6] To date, the only validated scale is the Pediatric Anesthesia Emergence Delirium (PAED).[3]

Risk factors for ED include the type of surgical procedures (ear, nose, and throat surgery, and ophthalmology), clinical characteristics (preschool age), and anesthesia technique (inhalation anesthesia with sevoflurane and desflurane).[7] The ideal approach to ED is prevention; various medications have been shown to be effective, especially propofol and alfa-2 agonists.[8]

The definition, diagnosis, and management of ED varies in the literature. Reports from Canada,[9] Germany,[4] the UK,[10] Italy,[10] and France[11] describe various methods for ED risk stratification, diagnosis, prevention, and treatment among pediatric anesthesiologists. However, little is known about Brazilian anesthesiologists' experience with ED management. Therefore, we aimed to assess the practices and knowledge among Brazilian anesthesiologists regarding the diagnosis, prevention, and treatment of ED in children.

Methods

This study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[12] and the Checklist for Reporting Results of Internet E-surveys (CHERRIES)[13] guidelines.

After obtaining approval from the local IRB (Hospital das Clínicas, Faculdade de Medicina, Universidade de Sao Paulo. Research approval number: 3.158.799), a 37-item questionnaire was developed based on the publications of Rosen HD et al.[9] and Huett C et al.[4] The need for an informed consent form was waived by the IRB, as volunteering to respond to the survey was considered as consent.

The questionnaire was managed using the REDCap® electronic data capture tool hosted at Hospital das Clinicas, Faculdade de Medicina, Universidade de Sao Paulo.[14,15] A pilot study was performed with ten anesthesiologists to test the usability, content, and ease of completion. After the correction of technical functionalities, the questionnaire was transferred onto the software, and the final version was protected and could not be changed. A link and a QR Code were created to distribute the survey.

A cover letter explaining the objectives of the study along and the link or QR Code for the study were emailed to a list of all anesthesiologists associated with the Brazilian Society of Anesthesiology (SBA). Two reminders were sent, including one in the beginning of April 2019 and one in May 2019. Data were automatically stored and protected in REDCap®.

Considering that there are 24,000 anesthesiologists in Brazil, a sample size of 648 anesthesiologists was required to obtain a 99% confidence interval and 5% margin of error for this study.[16] Data stored in the REDCap® were downloaded to a .csv (coma-separated values) file, and only completed questionnaires were analyzed. Statistical analysis was performed using STATA® 15.1. Data are presented as frequencies.

Results

The link and QR Code for the questionnaire was available from April to June 2019 and was opened 863 times. We collected 671 completed questionnaires.

Characteristics of participants and hospitals

The data in Table 1 demonstrates that the majority of respondents (53%) worked in tertiary hospitals, and only 11% worked in pediatric hospitals. Regarding experience in anesthesia practice, 36 respondents were practicing anesthesia for more than 15 years and 35% were practicing for less than five years.

Incidence of emergence delirium

The majority of respondents (97%) considered ED a relevant adverse event in their clinical practice. When asked about how much ED affects the quality of anesthesia, 29% and 39% answered ''a lot'' and ''too much'', respectively. Thirty-five percent of respondents reported an increase in the work of nurses in the PACU to treat ED at least once a week, and 24% of respondents were called to the PACU to treat ED at least once a week. On the other hand, the majority of respondents (45%) were never called to the PACU to treat ED.

Table 1 Characteristics of participants, hospital structures, and clinical practice.

Characteristic	N (%)
Type of hospital	
Tertiary	353 (53)
Secondary	101 (15)
University	121 (18)
Outpatient clinic	18 (3)
Pediatric	76 (11)
Years practicing anesthesia since end of residency program	
Less than 5	235 (35)
6-10	130 (20)
11-15	60 (9)
More than 15	243 (36)
Pediatric cases per day	
Less than 5	324 (48)
5-10	199 (29)
11-15	51 (8)
16-20	24 (4)
More than 20	70 (11)
Pediatric cases per week	
Less than 5	433 (65)
5-10	176 (26)
11-15	38 (6)
16-20	4 (1)
More than 20	17 (2)
Pediatric surgical and diagnostic specialties anesthesiologists mostly work with	
Pediatric general surgery	525 (78)
ENT	488 (73)
Radiology	363 (54)
Orthopedic	351 (52)
Endoscopic	299 (45)
Trauma and emergency	242 (36)
Urology	217 (32)
Neurosurgery	216 (32)
Ophthalmology	180 (27)
Dentist	157 (23)
Plastic surgery	108 (16)
Cardiac surgery	89 (13)

ENT, ear, nose, and throat.

Characteristics of practice regarding premedication, induction, maintenance, and recovery of general anesthesia

Forty-eight percent of respondents reported using premedication routinely. Midazolam was the most commonly used medication (95%), and it was mostly administered orally (88%). A few respondents reported using another class of premedication, such as clonidine (2%) or dexmedetomidine (1%). Few respondents reported using intramuscular administration for premedication (1%).

When asked about anesthesia induction, the majority of respondents (86%) preferred inhalation induction. Regarding anesthesia maintenance, 59% reported a preference for inhalation with sevoflurane or balanced anesthesia (35%). Only a few respondents (4%) reported using intravenous anesthesia for maintenance in pediatric anesthesia.

Regarding anesthesia recovery, the majority of respondents (84%) reported that children recovered in a general PACU, and only 11% reported that children recovered in a ''quiet and nice pediatric PACU''. Eighty-three percent and 61% of respondents reported that nurse technicians and registered nurses worked in the PACU, respectively. Thirty-seven percent and 2% reported that general physician anesthesiologists and pediatric anesthesiologists worked in the PACU, respectively.

Parental presence was allowed in the PACU for the majority of respondents (77%), and only 9% reported that parents could wait for their children to awaken in the operating room.

Table 2 Potential risk factors for emergence delirium.

Risk factor	Yes (%)
Untreated postoperative pain	93
High level of patient anxiety	80
High level of parental anxiety	78
Previous history of ED	72
Preschool age	57
Use of sevoflurane	57
ENT or ophthalmology surgery	49
Rapid emergence	42
Developmental delay	37
Short duration of anesthesia	12

ED, emergence delirium; ENT, ear, nose, and throat.

Risk factors

More than 70% of respondents reported that a high level of patient anxiety, a high level of parental anxiety, a previous history of ED, and untreated pain were risk factors for ED. The other potential risk factors for ED are listed in Table 2. When asked if they discussed the potential risk factors with parents during the preanesthetic visit, the majority of respondents (54%) answered ''no''. Forty-four percent of respondents reported that a PACU with considerable noise could influence the occurrence of ED.

Isoflurane and desflurane were considered risk factors by 55% and 52% of respondents, respectively. Midazolam was either considered to be a risk factor for ED (36%) or a protective factor against ED (34%). The majority of respondents (62%) reported that the presence of parents during induction protects against ED.

Sixty-five percent of respondents reported that when a child is agitated in the induction, she/he will awake agitated, and 47% reported that if a child is calm during induction, she/he will awaken calm.

Evaluation and diagnosis

Sixty-one percent of respondents reported that they routinely evaluated their patients regarding ED. However, only a few (5%, 20 respondents) routinely assessed patients with a specific scale; most of them (14 respondents) reported using the PAED scale.

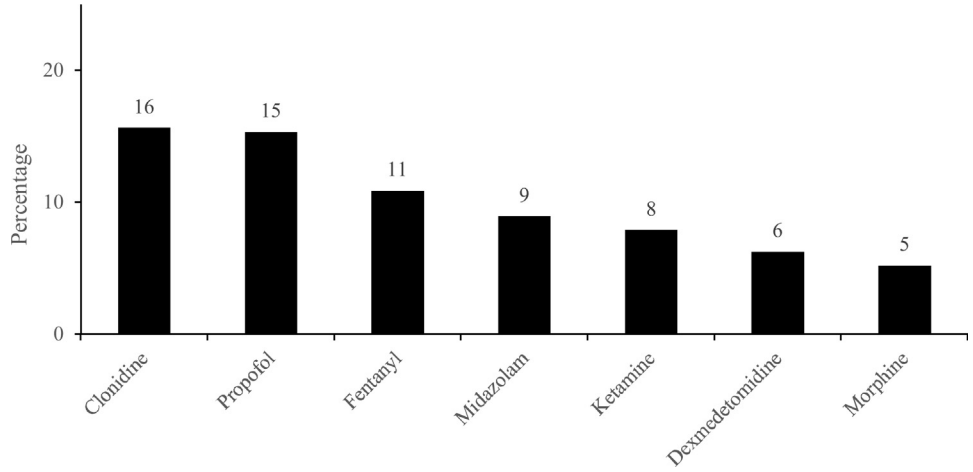

Figure 1 Frequency of preferences for preanesthetic or intraoperative anesthetic drugs to prevent emergence delirium.

Prevention

Thirty-two percent of respondents reported routinely administrating medication to prevent ED before or during anesthesia. The most commonly used drugs are displayed in Figure 1.

Fourteen percent of respondents reported using total intravenous anesthesia (TIVA) to prevent ED.

Treatment

Participants were asked about when they treated a child with ED, and the majority reported providing treatment when the patients were agitated and did not recognize the environment or their parents (77%) or when the children displayed vigorous and potentially harmful agitation (84%). Few respondents (5%) reported providing routine treatment in accordance with hospital protocols.

After ruling out postoperative pain and other causes of agitation, thirty-five percent of respondents reported using propofol, followed by midazolam (26%) and dexmedetomidine (6%) to treat ED. A small number of respondents (4%) reported using fentanyl to treat ED. When asked about the effectiveness of the treatment, 89% reported that a single dose is usually effective.

Discussion

This survey assessed the beliefs and practices among Brazilian anesthesiologists regarding ED. Although the majority of anesthesiologists considered ED a relevant adverse event, only 32% routinely applied preventive measures. Propofol and clonidine were the most commonly used drugs to prevent ED, and propofol and midazolam were the most frequently used drugs to treat ED.

Several meta-analyses have demonstrated that inhalation anesthetics, especially sevoflurane and desflurane, are linked to ED.[8,17,18] The majority of respondents reported using inhalation anesthesia for the induction and maintenance of anesthesia, similar to the German study, which found that 61% of the respondents used sevoflurane for anesthesia maintenance.[4] More than a half of respondents considered sevoflurane as a risk factor for ED. Considering this information, it appears that Brazilian anesthesiologists are not always focused on the prevention of ED.

Only 14% of anesthesiologists considered TIVA as an anesthetic technique for ED prevention. This finding is different from the German and Canadian studies, which found that 60% and 38% of respondents used TIVA for ED prevention, respectively.[4,9] This difference may highlight the difficulty or lack of experience with the use of TIVA in children among Brazilian anesthesiologists.

One-third of respondents reported using pharmacological strategies to prevent ED. This compares with almost half of respondents from the Canadian study who reported using pharmacological strategies to prevent ED.[9] Clonidine and propofol were considered the first choice for prevention among Brazilian anesthesiologists. This was similar to the French study, which found that clonidine was the first choice, and to the Canadian and German studies that reported propofol as the first choice for prevention.[4,9,11] Previous studies have shown that propofol and alfa-2 agonists are effective in preventing ED.[8,19]

Many studies have shown that dexmedetomidine can be used as a proper pharmacological prevention.[8,20,21] Our study showed that few anesthesiologists used dexmedetomidine, similar to the Canadian and German studies; respondents in the French study did not consider dexmedetomidine.[4,9,11] Dexmedetomidine is relatively new for pediatric anesthesia and has not yet been approved for anesthesia procedures. The U.S. Food and Drug Administration has only approved dexmedetomidine for sedation, predominantly in intensive care units.[22] Being an off-label drug for anesthesia could explain the relatively low use of dexmedetomidine for ED prevention.

More than 96% of respondents reported ED as a relevant adverse event; however, only 5% reported using specific tools to measure ED. Fourteen respondents reported using the PAED scale, which is the only validated scale for assessing ED.[3] Although the majority considered ED a relevant adverse event, almost half of respondents reported that they were never called to the PACU to access or treat ED. One reason could be that the PAED scale is validated only in English,

making this scale more difficult to apply among Portuguese speakers. The translation and transcultural validation of the PAED scale is necessary to improve the quality of ED diagnosis in Brazil.

Untreated postoperative pain was considered a risk factor for more than 90% of respondents. This was in contrast with the German and Canadian studies, in which untreated pain was not stated as a risk factor, although an Italian survey showed that pain was considered a risk factor for ED.[4,9,10] Somaini et al.[1] conducted a prospective study and concluded that it is difficult to differentiate between ED and pain using observational scales such as the PAED scale. Locatelli et al.[23] also reported that the first three items of the PAED scale (eye contact, purposeful action, awareness of the surroundings) presented a higher correlation to ED compared to the PAED items that were more correlated with pain (restlessness and inconsolability). It is important to point out that pain, hypoxia, hypercapnia, anxiety, pre-existing behavior characteristics, among others, are causes of agitation, but not delirium.

When a clinician is evaluating an agitated child, pain should be ruled out or treated if it is present. Non-surgical, diagnostic procedures under general anesthesia in children also have a high incidence of ED. Costi et al.[19] showed that the transition to propofol in sevoflurane-based anesthesia could reduce the incidence and severity of ED in children undergoing magnetic resonance imaging (MRI) under general anesthesia. Several meta-analyses[24–26] have compared pharmacological strategies to prevent ED in children undergoing MRI and highlighted that procedures under general anesthesia without noxious stimulus can still lead to ED.

Brazilian anesthesiologists also considered a high level of child/parental anxiety and preschool age to be risk factors for ED. The Canadian study showed that preschool age was the most prevalent risk factor reported, followed by a previous history of ED.[9] The German study reported a previous history of ED and preoperative anxiety as the most common risk factors.[4] A survey from the UK and Italy also found that preoperative anxiety was a risk factor among respondents.[10] A previous history of ED was considered a risk factor for more than 70% of Brazilian respondents, similar to the Canadian and German survey.[4,9] The European Society of Anaesthesiology evidence-based and consensus-based guidelines on postoperative delirium state that the risk of recurrence of ED is unclear.[2] However, compared to the elderly, long-lasting cognitive changes studies after ED in children are scarce.[2] On the other hand, strong evidence showed that single exposures during a short period to general anesthetics were not related to long-term cognitive outcomes in the pediatric population.[27–29]

The use of midazolam as pharmacological prevention for ED is controversial. Surveys of anesthesiologists from the UK and Italy demonstrated that the majority of Italian respondents reported using midazolam as the first choice for the prevention and treatment of ED.[10] In contrast, few UK anesthesiologists used midazolam as the first choice. The Brazilian survey also demonstrated conflicting results, with one-third of respondents considering midazolam as a risk factor and one-third considering midazolam to be useful as a pharmacological prevention strategy.

The best approach to ED is prevention, with the majority of clinical trials related to pharmacological or nonpharmacological strategies. Regarding ED treatment, Brazilian anesthesiologists reported using propofol as the first choice, very similar to the Canadian,[9] German,[4] British,[10] and French[11] surveys.

One of the nonpharmacological treatment options is parental presence in the PACU. The majority of Brazilian anesthesiologists reported that parents are allowed to wait for their children to awake in the PACU. This was also reported in the French, British, and Italian studies.[10,11] Additionally, Brazilian respondents considered the parental presence during the induction a preventive measure, in contrast with Canadian anesthesiologists, who did not find parental presence to be protective against ED.[9]

This study has limitations inherent to all web-based survey reports. The questionnaire was sent to all Brazilian anesthesiologists associated with the Brazilian Society of Anesthesiology (SBA). A lack of information about how many anesthesiologists received the email made it impossible to determine the response rate. We analyzed only the completed questionnaires, so we did not analyze partially completed questionnaires. Another limitation, very similar to the German study,[4] is that approximately only 5% of Brazilian respondents reported using the PAED scale for ED diagnosis. The absence of an adequate tool to measure ED could jeopardize proper treatment, prevent anesthesiologists from knowing the true incidence of ED, and inhibit the application of preventive measures. Additionally, the PAED scale has not been translated and cross-validated for Brazilian Portuguese, which makes its use even more difficult.

In conclusion, this study assessed the beliefs and practices among Brazilian anesthesiologists regarding ED. Although most respondents considered ED as a relevant adverse event, only one-third routinely applied preventive measures. Clonidine and propofol were the first choices for pharmacological prevention, and propofol was the first choice for pharmacological treatment. Untreated pain was considered the leading risk factor. This finding indicated that Brazilian anesthesiologists also have difficulty differentiating postoperative pain and ED, likely due to a lack of appropriate tools to measure postoperative pain and ED.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bjane.2020.12.029.

References

1. Somaini M, Sahillioğlu E, Marzorati C, Lovisari F, Engelhardt T, Ingelmo PM. Emergence delirium, pain or both? A challenge for clinicians. Paediatr Anaesth. 2015;25:524–9.
2. Aldecoa C, Bettelli G, Bilotta F, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. Eur J Anaesthesiol. 2017;34:192–214.
3. Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. Anesthesiology. 2004;100:1138–45.
4. Huett C, Baehner T, Erdfelder F, et al. Prevention and therapy of pediatric emergence delirium: a national survey. Paediatr Drugs. 2017;19:147–53.
5. Watcha MF, Ramirez-Ruiz M, White PF, Jones MB, Lagueruela RG, Terkonda RP. Perioperative effects of oral ketorolac and acetaminophen in children undergoing bilateral myringotomy. Can J Anaesth. 1992;39:649–54.
6. Cravero J, Surgenor S, Whalen K. Emergence agitation in paediatric patients after sevoflurane anaesthesia and no surgery: a comparison with halothane. Paediatr Anaesth. 2000;10:419–24.
7. Dahmani S, Delivet H, Hilly J. Emergence delirium in children: an update. Curr Opin Anaesthesiol. 2014;27:309–15.
8. Costi D, Cyna AM, Ahmed S, et al. Effects of sevoflurane versus other general anaesthesia on emergence agitation in children. Cochrane Database Syst Rev. 2014:CD007084.
9. Rosen HD, Mervitz D, Cravero JP. Pediatric emergence delirium: Canadian Pediatric Anesthesiologists' experience. Paediatr Anaesth. 2016;26:207–12.
10. Almenrader N, Galante D, Engelhardt T. Emergence agitation: is there a European consensus? Br J Anaesth. 2014;113:515–6.
11. Sintzel S, Bourdaud N, Evain JN. Current practice regarding pediatric emergence delirium in France: a survey of the ADARPEF. Paediatr Anaesth. 2020;30:624–5.
12. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med. 2007;4:e296.
13. Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). J Med Internet Res. 2004;6:e34.
14. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research el.ectronic data capture (REDCap) — a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377–81.
15. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
16. Scheffer M. Demografia Médica no Brasil 2018; 2018. Available from http://www.flip3d.com.br/web/pub/cfm/index10/?numero=15&edicao=4278#page/110. (accessed 04 de novembro 2020).
17. Lim BG, Lee IO, Ahn H, et al. Comparison of the incidence of emergence agitation and emergence times between desflurane and sevoflurane anesthesia in children: a systematic review and meta-analysis. Medicine (Baltimore). 2016;95:e4927.
18. Dahmani S, Stany I, Brasher C, et al. Pharmacological prevention of sevoflurane- and desflurane-related emergence agitation in children: a meta-analysis of published studies. Br J Anaesth. 2010;104:216–23.
19. Costi D, Ellwood J, Wallace A, Ahmed S, Waring L, Cyna A. Transition to propofol after sevoflurane anesthesia to prevent emergence agitation: a randomized controlled trial. Paediatr Anaesth. 2015;25:517–23.
20. Pickard A, Davies P, Birnie K, Beringer R. Systematic review and meta-analysis of the effect of intraoperative α_2-adrenergic agonists on postoperative behaviour in children. Br J Anaesth. 2014;112:982–90.
21. Tsiotou AG, Malisiova A, Kouptsova E, Mavri M, Anagnostopoulou M, Kalliardou E. Dexmedetomidine for the reduction of emergence delirium in children undergoing tonsillectomy with propofol anesthesia: a double-blind, randomized study. Paediatr Anaesth. 2018;28:632–8.
22. Pollock M, Wong J, Camilli S, Gill R, Jones SC, Chai G. Pediatric postmarketing pharmacovigilance and drug utilization. Review. 2016. Available from https://www.fda.gov/media/97355/download
23. Locatelli BG, Ingelmo PM, Emre S, et al. Emergence delirium in children: a comparison of sevoflurane and desflurane anesthesia using the Paediatric Anesthesia Emergence Delirium scale. Paediatr Anaesth. 2013;23:301–8.
24. Tang Y, Meng J, Zhang X, Li J, Zhou Q. Comparison of dexmedetomidine with propofol as sedatives for pediatric patients undergoing magnetic resonance imaging: a meta-analysis of randomized controlled trials with trial sequential analysis. Exp Ther Med. 2019;18:1775–85.
25. Zhou Q, Shen L, Zhang X, Li J, Tang Y. Dexmedetomidine versus propofol on the sedation of pediatric patients during magnetic resonance imaging (MRI) scanning: a meta-analysis of current studies. Oncotarget. 2017;8:102468–73.
26. Fang H, Yang L, Wang X, Zhu H. Clinical efficacy of dexmedetomidine versus propofol in children undergoing magnetic resonance imaging: a meta-analysis. Int J Clin Exp Med. 2015;8:11881–9.
27. Sun LS, Li G, Miller TL, et al. Association between a single general anesthesia exposure before age 36 months and neurocognitive outcomes in later childhood. JAMA. 2016;315:2312–20.
28. McCann ME, de Graaff JC, Dorris L, et al. Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): an international, multicentre, randomised, controlled equivalence trial. Lancet. 2019;393:664–77.
29. Vutskits L, Culley DJ. GAS, PANDA, and MASK: no evidence of clinical anesthetic neurotoxicity! Anesthesiology. 2019;131:762–4.