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# Median Effective Dose of Intranasal Dexmedetomidine for Transthoracic Echocardiography in Children with Kawasaki Disease Who Have a History of Repeated Sedation

Authors' Contribution:

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Data Collection B

Statistical Analysis C

Data Interpretation D

Manuscript Preparation E

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**Background:** The aim of this study was to investigate the median effective dose (ED50) of intranasal dexmedetomidine for echocardiography in children with Kawasaki disease who had a history of repeated sedation.

**Material/Methods:** There were 73 pediatric Kawasaki disease patients aged 1 to 36 months enrolled in this study who had American Society of Anesthesiologists (ASA) I-II, were scheduled to undergo echocardiography under sedation. They were assigned to 2 groups (group A: age 1–18 months, and group B: age 19–36 months). Intranasal dexmedetomidine was administered before echocardiography. The dose of intranasal dexmedetomidine was determined with the up-down sequential allocation, and the initial dose was 2 µg/kg with an increment/decrement of 0.2 µg/kg. The ED50 of intranasal dexmedetomidine for sedation was determined with the up-and-down method of Dixon and Massey and probit regression. The time to effective sedation, time to regaining consciousness, vital signs, oxygen saturation, echocardiographic examination time, clinical side-effects, and characteristics of regaining consciousness were recorded and compared.

**Results:** The ED50 of intranasal dexmedetomidine for sedation was 2.184 µg/kg (95% CI, 1.587–2.785) in group A and 2.313 µg/kg (95% CI, 1.799–3.426) in group B. There were no significant differences in the time to sedation and time to regaining consciousness between groups. Additionally, change in hemodynamic and hypoxemia were not noted in both groups.

**Conclusions:** The ED50 of intranasal dexmedetomidine was determined in children with Kawasaki disease who had a history of repeated sedation to be appropriate for repeated-routine sedation of echocardiographic examination in pediatric patients. The ED50 of intranasal dexmedetomidine for echocardiography in this circumstance is similar to that in children receiving initial sedation.

**MeSH Keywords:** Administration, Intranasal • Dexmedetomidine • Hospitals, Pediatric

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## Background

In recent years, an increasing number of studies have focused on the influence of repeated anesthesia or sedation on the developing nervous system, but few studies have reported on the influence with regards to the pharmacodynamics. In infants, repeated or long-term general anesthesia might affect the brain development (<http://www.fda.gov/downloads/Drugs/DrugSafety/UCM533197.pdf>); and is closely related to the long-term attention deficit/hyperactivity disorder [1]. Dexmedetomidine possesses not only sedative activity, but neuroprotective effects and has little influence on respiration and circulation. In addition, the use of dexmedetomidine is convenient. Thus, it is increasingly used for sedation in children outside the operation room [2–5].

Kawasaki disease is now the most common cause of acquired heart disease in children in developed countries. The disease is markedly more prevalent in children in Japan and Asia, and predominantly affects children <5 years of age. The incidence has increased year by year. In China, the incidence was 30.3–71.9/100 000. However, the incidence of incomplete Kawasaki disease was 23.5%, and incidence of coronary artery diseases was as high as 15.9% [6–9]. The long-term prognosis is determined by the level of coronary artery involvement, and some patients are at risk for myocardial ischemia. Invasive angiography is not recommended during the acute illness stage. Besides, more than 80% of coronary artery involvement has been reported to occur within the first 10 days of illness onset. Thus, echocardiograms should be obtained at diagnosis at least within 1 to 2 weeks, and 4 to 6 weeks after treatment. Patients with aneurysm should have echocardiograms every 2 weeks, and at least once weekly in the first 45 days of illness, and then monthly until the third month after illness onset. Long-term follow-ups of echocardiograms were also needed. If a child is uncooperative, sedation is frequently needed [10,11]. Recently, most studies have focused on children who do not require much sedation. It is still unclear whether there is drug resistance after multiple uses of sedation. Thus, there is a need to conduct studies in this group of children, to explore the suitable dosage of sedation.

To our knowledge, few studies have been conducted to investigate the dose of dexmedetomidine after repeated sedation. This study aimed to investigate the median effective dose (ED50) of intranasal dexmedetomidine in children with a history of repeated sedation, which may provide evidence on the clinical use of dexmedetomidine in children.

## Material and Methods

### Patients

This was a single-blinded, prospective study, approved by the Institutional Review Board of Shanghai Children's Medical Centre (SCMCIRB-K2017069). It was registered at the Chinese Clinical Trial Registry (ChiCTR-1800015038). Before experiments, all instruments were adjusted [12]. A total of 76 children with Kawasaki disease who were scheduled for daytime echocardiography were recruited into the present study, and informed consent was obtained from their guardians before study. In addition, the guardians were also informed of the potential adverse effects of sedation and precautions during monitoring. According to the age, the study patients were divided into group A (age 1–18 months; n=38) and group B (age 19–36 months; n=38). Inclusion criteria were as follows: children aged 1–36 months, both males and females were eligible; the ASA grade was I–II; children received echocardiography under sedation more than 3 times within the prior 6 months and no adverse effects of sedation were present. Exclusion criteria were as follows: 1) children had a history of cardiac conduction system disease; 2) children were treated with digoxin, alpha-adrenergic, or beta-adrenergic agonist or antagonist, anti-arrhythmic medications, or vasodilators within 48 hours; 3) children were allergic to or had contraindications to any of the drugs used in this study; 4) children were diagnosed with severe coarctation of the aorta (risk of exaggerated vasoconstriction); 5) children had concomitant heart failure, pneumonia, and fever. The consort flow diagram is shown in Figure 1.

### Anesthesia

All the children received food and water deprivation for 2 hours before examination. Children were transferred into the sedation room with the presence of their parents. They were examined in a single-blinded manner by the anesthetists and the ASA grade was determined. Moreover, the heart rate, non-invasive blood pressure (BP), and blood oxygen saturation (SpO<sub>2</sub>) were recorded as baseline. Dexmedetomidine (Aibeining; Jiangsu Hengrui Medicine Co., Ltd., China) was administered intranasally. In the first child, dexmedetomidine was administered at 2 µg/kg. The dose of dexmedetomidine in the following child was then reduced by 0.2 µg/kg if sedation was successful or increased by 0.2 µg/kg if sedation failed. If sedation failed, phenobarbital sodium was then administered at 5 mg/kg for rescued sedation, examination continued, and then the observation was defined as failure. Dexmedetomidine at a half dose was administered in each side of the nose, the wing of nose was pressed twice after administration and the child was asked to lie in bed or in hands of parents in a supine position for at least 2 minutes, under the guardianship of parents. The heart rate, BP, and SpO<sub>2</sub> were monitored continuously during

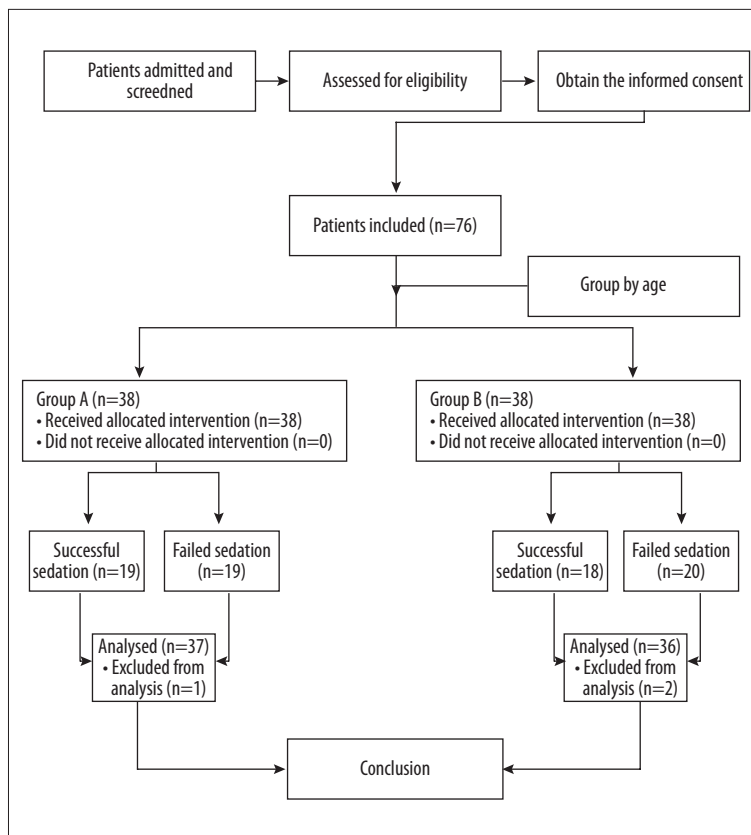


Figure 1. The consort flow diagram.

the examination. Abnormality was defined if heart rate or blood pressure was lower or higher than 120% of normal values, and hypoxia was defined if SpO<sub>2</sub> was lower than 92%. At 5 minutes after dexmedetomidine administration, the Ramsay scale was employed to assess the depth of sedation. Successful sedation was defined if the Ramsay score was higher than 5 and the child could receive echocardiography in a sleepy state; sedation failure was defined if the Ramsay score was lower than 5 at 40 minutes after dexmedetomidine administration, or the child woke up during echocardiography or the echocardiography could not be done due to body movement. Then, further sedation was needed. Time to sedation was defined as the time from drug administration to the onset of satisfactory sedation. The time to effective sedation (from drug administration to the time of the Ramsay score  $\geq 5$ ), the time to echocardiography and time to regaining consciousness (from drug administration to the time of modified Aldrete score  $\geq 9$ ) were recorded. In addition, the adverse effects, such as nausea, vomiting, bradycardia, tachycardia, abnormal blood pressure, hypoxia, irritability during regaining consciousness, bleeding, inflammation, delayed regaining consciousness (time from end of echocardiography to regaining consciousness longer than 2 hours), respiratory depression and respiratory tract obstruction were also recorded. After examination, patients stayed in the post-anesthesia care unit for monitoring. When the modified Aldrete score was  $\geq 9$  and no adverse effects were observed,

the patient was discharged and the acceptance on the sedation was evaluated by the clinician and the guardians.

### Statistical analysis

Statistical analysis was performed with SPSS version 20.0 and EXCEL software. Quantitative data were subjected to testing of normal distribution with Kolmogorov-Smirnov test. Quantitative data with normal distribution were expressed as mean  $\pm$  standard deviation and were compared with one-way analysis of variance when the homogeneity of variance was present. Data with abnormal distribution or heterogeneity of variance were compared with Kruskal-Wallis test. Qualitative data were analyzed with Pearson chi-square test or Fisher exact test. A value of  $P < 0.05$  was considered statistically significant.

ED50 and 95% confidence interval (CI) were estimated from the up-and-down sequences, using the method of probit regression. The dosage of ED50 was determined from the mid-points of all independent pairs of patients who involve a crossover from failure to success according to the study conducted. Group A had 37 patients and group B had 36 patients who were enrolled until  $\geq 10$  crossovers were obtained.

**Table 1.** Demographic characteristics of children at baseline.

Group	Gender (Male/Female)	Age (year)	Height (cm)	Weight (kg)	Body surface area (m <sup>2</sup> )
Group A	22/15	1.32±0.51 <sup>#</sup>	85.5±5.3 <sup>#</sup>	12.5±4.9 <sup>#</sup>	0.51±0.12 <sup>#</sup>
Group B	21/15	2.21±0.47	101.6±6.5	15.37±3.6	0.68±0.14

Data are presented as mean ±SD, except for gender which is expressed as frequency. <sup>#</sup> <0.05. The difference in age between groups has no clinical significance because these children were divided according to the age. Group A: age 1–18 months, and group B: age 19–36 months.

**Table 2.** Demographic data and baseline scores after intranasal dexmedetomidine sedation.

	Before sedation		During sedation		During regaining consciousness	
	Group A	Group B	Group A	Group B	Group A	Group B
HR (/min)	107±13	109±17	105±15	109±12	110±16	118±17
SpO <sub>2</sub>	96.6±2.6	96.8±2.1	97.1±1.2	97.3±2.5	96.4±2.2	96.2±1.5
SBP (mmHg)	78.5±13.5	79±17.6	81±13.3	82±14.8	85±13.2	83±16.3
DBP (mmHg)	45.4±11.4	50±11.2	49±10.6	51±11.5	47±12.7	52±13.9

Data are presented as mean ±SD. SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; SpO<sub>2</sub> – oxygen saturation. Group A: age 1–18 months, and group B: age 19–36 months.

**Table 3.** Time to effective sedation, time to echocardiography, and time to regaining consciousness.

	Time to effective sedation (min)	Time to echocardiography (min)	Time to regaining consciousness (min)	Acceptance of guardian (n)	Acceptance of clinician (n)
Group A	14±3	18±4	49±13	36	37
Group B	14±4	17±3	51±12	35	36

Group A: age 1–18 months, and group B: age 19–36 months.

## Results

### General data

A total of 76 children were recruited, but 3 were lost to follow-up (group A: n=1; group B: n=2) because they did not stay in the post-anesthesia care unit after examination and thus could not be accurately evaluated. Therefore, 73 children were included in our final analysis (group A: n=37; group B: n=36). The demographic characteristics of these children at baseline are shown in Table 1. Hemodynamics parameters were monitored continuously, and no significant differences were observed among different time points in a specific group and between groups (Table 2). This suggests that the hemodynamics remain stable in these children during examination.

### Efficacy of sedation

Time to effective sedation, time to echocardiography, and time to regaining consciousness were compared between groups (Table 3). Results showed the time to effective sedation was about 14 minutes in both groups; the time to echocardiography was about 17 minutes in both groups; the time to regaining consciousness was about 50 minutes in both groups. Significant differences were not observed in the time to effective sedation, time to echocardiography, and time to regaining consciousness between the 2 groups ( $P>0.05$ ). As shown in Table 3, these children can regain consciousness within 30 minutes after examination.

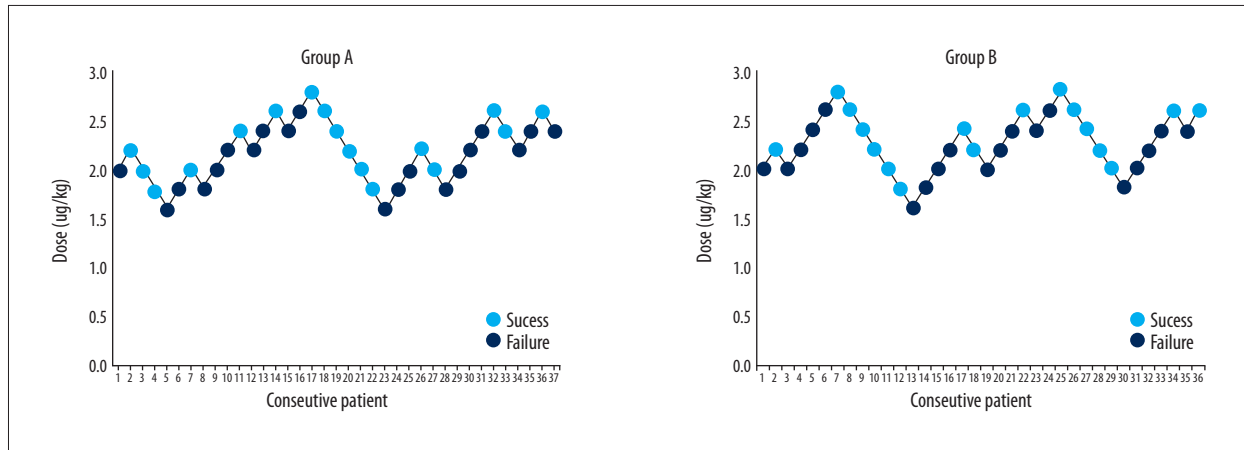
### Adverse effects

The adverse effects are shown in Table 4. Severe adverse effects were not observed in any group, including respiratory depression and abnormalities in BP and SpO<sub>2</sub>. Analysis showed

**Table 4.** Adverse effects in two groups.

	Group A	Group B
Adverse effects (n)	1	2
No adverse effects (n)	36	34

Adverse effects were found in 1 child of group A (reduced heart rate) and 2 children of group B (reduced heart rate: n=1; nausea: n=1). Special treatments were not administered in these children, but monitoring was done. They recovered smoothly before discharging. Group A: age 1–18 months, and group B: age 19–36 months.



**Figure 2.** Up-and-down sequential allocation analysis of intranasal dexmedetomidine in 2 groups. Up-and-down sequential allocation analysis of intranasal dexmedetomidine was done in children receiving sedation for echocardiography in 2 groups. The dose increment/decrement was 0.2 µg/kg. The calculated ED50 was 2.184 µg/kg for group A and 2.313 µg/kg for group B. Group A: age 1–18 months, and group B: age 19–36 months.

**Table 5.** Dose-response to intranasal dexmedetomidine in two groups.

	Group A (n=37)		Group B (n=36)	
Dixon and Massey				
ED50 (µg/kg)	2.151	(2.076–2.229)	2.247	(2.148–2.350)
Probit regression				
ED50 (µg/kg)	2.184	(1.587–2.785)	2.313	(1.799–3.426)
ED95 (µg/kg)	3.214	(2.689–12.59)	3.304	(2.771–19.224)

Data are ED50 or ED95 with 95% CI. ED50=50% effective dose; ED95=95% effective dose. Group A: age 1–18 months, and group B: age 19–36 months.

there was no significant difference in the incidence of adverse effects between the 2 groups. The incidence of adverse effects was about 3% in each group. Thus, the medical staff for anesthesia and sedation should emphasize monitoring during examination and explain potential risks to the guardians.

#### Dose – response to intranasal dexmedetomidine

Results showed the ED50 was 2.184 µg/kg in group A and 2.313 µg/kg in group B. The actual response curve and drug dose are shown in Figure 2. The ED50 in group A was slightly

lower than in group B, and a difference was also observed in 95% CI. However, these differences had no clinical significance. The range of 95% CI for ED95 was large, but had no clinical significance, and the dose of the upper limit was out of the safe range (Table 5).

#### Discussion

In clinical practice, anesthesia and/or sedation is often conducted in patients with a history of repeated anesthesia and/



or sedation. According to our previous experience, these patients might be considered as being tolerant to these drugs and thus anesthetics and/or sedatives at a higher dose might be required. To our knowledge, there is no consensus on the dose of anesthetics and/or sedatives for patients with a history of repeated anesthesia and/or sedation.

Kawasaki disease is an acute febrile, systemic vasculitic syndrome of an unknown etiology that primarily occurs in children younger than 5 years of age and has the prevalence of 2.34/100 000 to 54.22/100 000 [13]. Long-term follow-up by echocardiography is required for these children. Long lasting immobilization is needed during the echocardiography, but children younger than 3 years of age are usually unable to cooperate with the examination. Under this condition, complete sedation is required for echocardiography. Children with Kawasaki disease were recruited into this study. In 2016, the FDA reported that repeated exposure to drugs such as phenobarbital, benzodiazepines, or ketamine might affect the brain development of children younger than 3 years of age. Of note, clinical sedation is usually performed with chloral hydrate, phenobarbital, benzodiazepines, ketamine, or dexmedetomidine. Therefore, for children with risk for repeated exposure to these drugs, it is necessary to investigate the optimal dose of these drugs and choose optimal drugs for sedation.

Chloral hydrate is irritating, and most children refuse to receive medication with chloral hydrate. Moreover, chloral hydrate has the risks for tumorigenesis and genotoxicity [14]. Dexmedetomidine is a highly selective  $\alpha_2$  adrenergic receptor agonist and acts on the receptors in the locus caeruleus of the brain to exert sedative and anti-anxiety effects without evidence respiratory suppression. After sedation, dexmedetomidine may also induce physiological sleep, and rapid regaining of consciousness may be achieved. After separation from parents and anesthesia induction, children seem to be calm, cooperative, and are easy to communicate with, and the parents' acceptance also increases. Preclinical studies have shown that anesthetics for general anesthesia (including NMDA antagonists and GABA agonists) might affect the early neuroanatomy and relevant functions [15], but dexmedetomidine displays neuroprotective effects in animals and humans and can inhibit neuronal apoptosis in a dose dependent manner [16–20]. The intranasal use of dexmedetomidine has some advantages. It avoids first-pass hepatic metabolism and can be rapidly delivered to the brain through the olfactory mucosa, which directly contacts with the central nervous system; the rate of absorption and blood concentration are markedly higher than an oral route. Thus, in this study, dexmedetomidine was intranasally administered.

In pharmacological research, sequential design is common, especially using the Dixon and Mood's up-and-down method [21,22] and the biased coin design [23,24]; with the use of continual reassessment method less common [25–27]. These methods

have been applied in oncological and pharmacological studies. In the up-and-down method, the sample size required is small, and usually 20 to 40 participants and 6 crossovers are sufficient, the method is classic and simple, and investigators can estimate the minimum dose that provides a 50% probability of favorable response (ED50) [22]. Therefore, in this study, an up-and-down method was employed to investigate the ED50 of intranasal dexmedetomidine in children with Kawasaki disease who had repeated exposure to sedation. There were 37 children in group A and 36 in group B; the number of crossover was higher than that recommended by Dixon (group A:  $n=15$ ; group B:  $n=12$ ). This suggests that the accuracy and sample size meet the requirements and thus our results are more convincing and closer to reality compared to those from studies with small sample sizes [28,29]. Of note, ED50 is a pharmacological concept, and refers to the dose of a drug at a specific relative probability. Thus, it might not reflect the actual dose of the drug, and is only indicative. The up-and-down method has the inherent limitation of any sequential approach: that the dose of a drug used in a former patient determines the dose of the drug used in a following patient.

Our results showed that the ED50 and ED95 of dexmedetomidine in children with repeated exposure to sedation were consistent with previously reports [30–33] (2–3  $\mu\text{g}/\text{kg}$ ). This implies that repeated sedation has little influence on the dose of sedatives. In clinical practice anesthesia, it should not be voluntary to increase the dose of drugs and the dose of drugs used should be determined according to clinical conditions. Our study revealed that the regaining consciousness was smooth after dexmedetomidine treatment, and clinicians, nurses, and parents had a high level of acceptance, the time of sleeping was controllable, and the patient could be aroused if necessary. Sedation with this drug was easy, simple, convenient, safe, and rapid with little respiratory suppression, and thus echocardiography can be successful performed at one time.

In this study, probit regression was used to calculate ED50. Our results showed the incidence of adverse effects was comparable between the 2 groups (both about 3%) although there was a 10% difference in ED50 between the groups (slightly higher in group B); alteration of hemodynamics and respiratory suppression ( $\text{SpO}_2$  reduction) were not observed. Thus, specific treatments were not administered in these children, but the children received continuous monitoring for the prevention of accidents. The difference in ED50 was 0.13  $\mu\text{g}/\text{kg}$  between the 2 groups, which might be ascribed to the large drug distribution volume, relative insufficient metabolic enzyme activity in young children, and low drug clearance in young children (drug clearance in neonates and 1-year old children is about 42.2% and 84.5% of that in adults, respectively) [34–36]. Thus, the dose of dexmedetomidine was larger in group B. Moreover, in group B, the blood brain barrier is mature and complete, and

thus the dose of drug administered is higher. Actually, the dose of drug between the 2 groups was not significant. Results of this study were different from those of Qing et al., due to a more exquisite grouping in the Qing et al. study; thus, it could reveal the need of dosage increase with the increasing age. However, children were mainly between 2 to 3 years old in this study, thus the pharmacodynamics were not significantly different between the 2 groups [37]. Besides, in the Qing et al. study, patients who were diagnosed with left-to-right shunt congenital heart disease were often accompanied with increased pulmonary blood flow even pulmonary arterial hypertension. More drugs were blocked in the lung, and some drugs were in a futile cycle of systemic and pulmonary circulation. Thus, a higher dosage of drug was needed.

There were limitations in our study. First, the pre-operative sleep status was not classified, and the prior sleep status (sleep deprivation) might affect the efficacy of sedation in the following day. Second, the drugs used in prior sedation were not further classified.

This study aimed to investigate the ED50 of intranasal dexmedetomidine in children with repeated exposure to sedation.

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## Conclusions

Taken together, this study for the first time reports the ED50 of intranasal dexmedetomidine in children with Kawasaki disease who had repeated exposure to sedation. Our results indicated that prior repeated exposure to sedation had little influence on the dose of drugs used for next sedation. Thus, clinicians should be cautious in the use of sedation and the dose of sedatives should be individualized. Besides the anesthesia and/or sedation induced alterations to hemodynamics, clinicians should also pay attention to the neurotoxicity of these drugs and the cumulative influence of repeated exposure to these drugs on the developing brain.

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