

MINI-REVIEW

The importance of maintaining normal perioperative physiological parameters in children during anaesthesia

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Abstract

Every year, millions of neonates, infants and young children need general anesthesia for a variety of procedures. As pediatric anesthesia remains at high risk of perioperative morbidity and mortality, attention has been directed towards the anesthesia training and the anesthetics safety. We are now reassured about the relatively safeness of the anesthetic drugs, but the safest intraoperative conduct has still to be determined. In the absence of clear evidence, it appears logical to prevent perturbations of the child “baseline”, by avoiding preoperative distress, maintaining normal intraoperative parameters and preventing postoperative discomfort. Recently, ten “N” principles (no fear/awareness, normovolemia, normotension, normal heart rate, normoxemia, normocapnia, normonatremia, normoglycemia, normotermia and no pain/nausea/vomiting/emergence delirium) have been proposed as the base of a safer anesthesia care. The current paper aims to summarize the current evidence behind the “10-Ns” rational and to help guide anesthesiologists in their practice.

Keywords

Safetots; Pediatric anesthesia; Pediatric homeostasis

1. Introduction

Children undergoing general anesthesia have an increased risk for morbidity and mortality compared to adults [1], especially in the hands of occasional pediatric anesthesiologists [2]. Respiratory complications and cardiovascular instability are the most common perioperative severe critical events [3] and can be avoided by adequate training and exposure [1–3]. The focus of safety in pediatric anesthesia has now shifted from the quest for the safest anesthetic agent to the known and established risk: the conduct of anesthesia [1–4]. Along with providing extra training in pediatrics [5], an overarching framework for critical elements in clinical anesthesia, “10-Ns”, has been developed (<http://www.safetots.org>) [1] (Fig. 1). This paper reviews these elements to help everyday pediatric anesthesia practitioners.

2. No fear, no awareness

Preoperative anxiety and intraoperative awareness are well known but yet underestimated anesthesia related complications. Pre-operative anxiety affects 50% to 75% of the children undergoing surgery. Long lasting maladaptive behaviors such as nightmares, separation anxiety, eating problems and increased fear of doctors can persist in 19% of the children for 6 months and in 6% for one year postoperatively [6]. Several pharmacological [7, 8] and non-pharmacological [8–10] interventions have investigated to decrease children anx-

ety, including virtual reality [11]. Age appropriate psychological and educational preparation, parenteral presence, and premedication have shown to be effective in reducing anxiety preoperatively [6, 7, 9, 12] (Table 1).

Intraoperative awareness is estimated to be as high as 1.2% in children, which is 6 times more frequent than in adults [13]. The real incidence is, however, unknown, as children may confound real and imaginary events, may perceive the recall experiences less distressful than adults, or may be unable to communicate their experience. To date, there are no data on awareness in patients < 3 years of age [13]. Contrary to adults, long term consequences are also unclear [14].

Determining the adequate depth of anesthesia in children is not easy. In fact, raw electroencephalography (EEG) analysis is a very good technique to monitor the depth of anesthesia, however, interpreting the EEG requires expertise [15]. On the contrary, the Bispectral index (BIS), a processed EEG widely used in adults, does not have a linear correlation with the concentrations of sevoflurane in children, varies with age (higher in younger children) and poorly predicts the level of consciousness in children less than 3 years old [15, 16]. It is also affected by medications such as ketamine and nitrous oxide, commonly used in pediatric anesthesia [16]. Several alternatives are currently under investigation [17], but data in children are still limited.

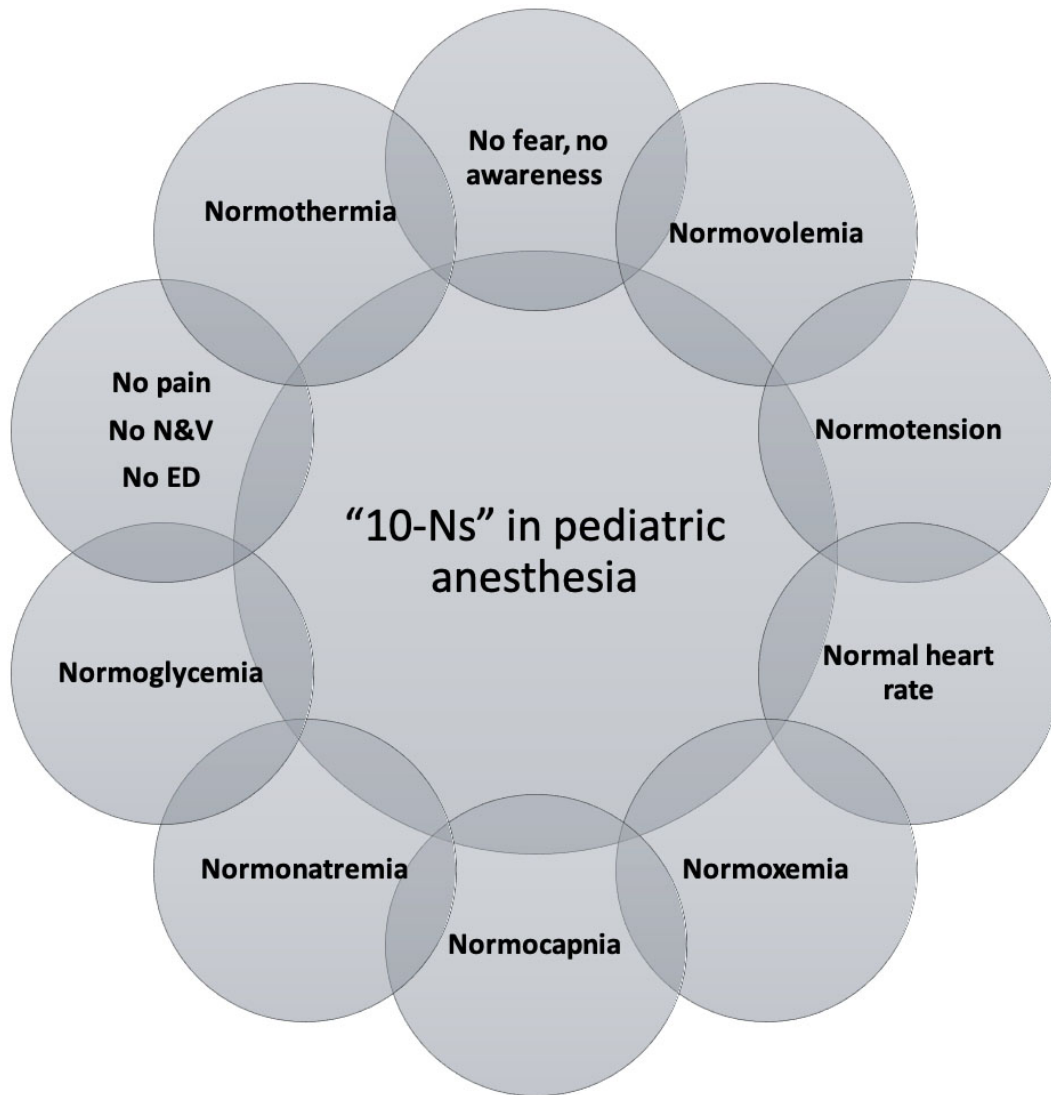


FIGURE 1. 10-N concept of pediatric anesthesia. Adapted from www.safetots.org.

TABLE 1. Risk factors and proposed interventions and measure to reduce preoperative anxiety.

Risk factors for preoperative anxiety	Non-pharmacological intervention	Pharmacological intervention
Age (1-5 years)	Parental presence during induction	Benzodiazepines (Midazolam, Diazepam)
High baseline anxiety	Pre-operative preparation programs	Ketamine
Children with passive coping style (ex. avoidance, violence)	Audiovisual (AV) interventions (videos, multi-faceted programs, interactive games, virtual reality music and Internet programs)	α_2 -adrenergic agonists (Dexmedetomidine, Clonidine)
Attention deficit hyperactivity disorder (ADHD)	Clowns or clown doctors	Opioid (morphine)
Previous medical and surgical encounters	Quiet environment	Chloral hydrate
Parental anxiety	Hypnosis	
	Parental acupuncture	
	Childlife specialists	

3. Normovolemia

Perioperative fasting times should be as short as possible to prevent patient discomfort, dehydration, post-induction hypotension, ketoacidosis and a catabolic state [18, 19].

In children, guidelines recommend the administration of water or sugar-containing clear fluids up one hour before surgery [20]. However, fasting times are often exceeded in

the clinical practice. Avoidance of prolonged fasting may be particular challenging in infants, who preferentially drink milk that must be administered no later than four to six hours before surgery [20].

According to the Association of the Scientific Medical Societies in Germany, fluid maintenance should employ balance isotonic solutions instead of Ringer Lactate or 0.9% saline [18]. In fact, Ringer Lactate is mildly hypotonic compared to plasma

TABLE 2. Prevention of post-operative nausea and vomiting.

Risk Factors for POV & PONV	Risk stratification factors	Prophylaxis Rx	Extra rescue medication if needed in PACU	
Age \geq 3 years	Low risk: No risk factors	One anti-emetic (5-HT3 antagonist or dexamethasone)	5 Metoclopramide or Dimenhydrinate Promethazine	
History of POV/ PONV/motion sickness		Medium risk: 1-2 risk factors	Two anti-emetics (5-HT3 antagonist and dexamethasone)	Droperidol Aprepitant
Family history of POV/ PONV			High risk: \geq 3 risk factors	Two anti-emetic (5-HT3 antagonist and dexamethasone) and consider TIVA
Sex: Post-pubertal female				
Surgery \geq 30 minutes				
Volatile anesthetics				
Anticholinesterases				
Long-acting opioids				
Strabismus surgery Adenotonsillectomy Otoplasty				

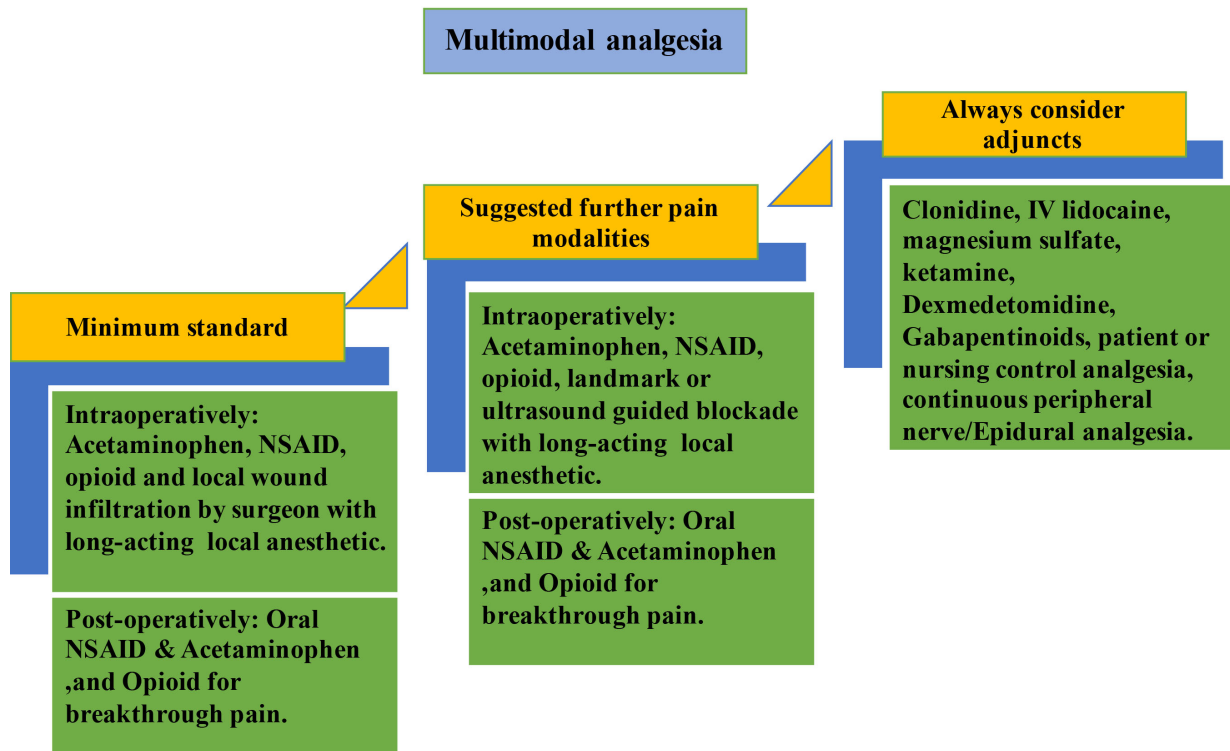


FIGURE 2. Approach to perioperative pain management.

and 0.9% saline carries the risk of hyperchloremic metabolic acidosis [18, 19].

Children have the same fluid composition as adults, but a larger extracellular compartment (i.e., 40% in neonates compared to 20% in adults) [19]. Therefore, in case of large amount fluid administered, the fluid osmolality and composition are pivotal in maintaining intravascular homeostasis [18, 19].

In presence of hemodynamic instability, boluses of 10-20 mL/kg followed by vasoactive agent are usually recommended, although there is no unanimous agreement [21]. In the presence of hypovolemia poorly responsive to crystalloids, 5-10 mL/kg of colloids (albumin, gelatins, hydroxyethyl starch - HES) may be considered. It must be taken into account, however, that colloids carry important side effects, such as anaphylactic reactions, kidney injury, coagulopathy and worsening of edema [18, 19]. In neonatal intensive care, albumin

failed to provide any advantage over crystalloids during fluid resuscitation [22], but it may preserve the glycocalyx better than semisynthetic colloids [23]. In Europe, HES solutions are contraindicated in critically ill patients [19]. Nevertheless, gelatine and third generation HES (HES 130) may be safely administered to children with normal renal function [19]. If colloids are employed, gelatins and HES may be used in balanced solutions to maintain the acid-base homeostasis [18].

4. Normotension

Variations of the blood pressure above and below the normal limits can determine organ hypoperfusion or hyperemia, particularly in the brain [24, 25]. In children, the safe blood pressure limits are still unknown [24, 25]. In general, hypotension is defined as blood pressure below the 5-10% percentile for age [21, 25]. However, it is unknown whether critical organ

perfusion is guaranteed at lower blood pressure levels under general anesthesia compared to awake conditions. A large cohort study showed that the lowest mean blood pressure in ASA 1 and 2 children under general anesthesia for non-cardiac surgeries was 17-22 mmHg lower than in awake children [26].

As a general rule, it is recommended that the mean arterial blood pressure should be kept above the infant's gestational age (in weeks) and never below 30 mmHg [25]. Beyond this age and until 6 months, the mean blood pressure should be within 20% of the baseline and never below 45 mmHg [21]. For older children, a mean blood pressure within 20% of the baseline and above 60 mmHg may be acceptable [27]. Finally, the non-invasive blood pressure of the legs is often lower than the pressure in the arm. Alternative non-invasive hemodynamic monitors commonly underestimate the systolic blood pressure [28].

5. Normal heart rate

Neonates have a heart rate dependent cardiac output. The maintenance of an appropriate age-based heart rate and contractility is pivotal to balance the maximum cardiac output and the myocardial oxygen consumption.

In children, the parasympathetic activity is impaired at birth, increases rapidly during the first year of life and then more slowly until late childhood [29].

During surgery, the autonomic system may be affected, and hypotension associated tachycardia may not always be present [30].

6. Normoxemia

Hypoxia is the most common intraoperative complication in children [31]. Nevertheless, oxygen saturation should be maintained $\leq 95\%$ in preterm neonates, as hyperoxia is a well-known risk for chronic lung disease, retinopathy of prematurity and brain injury [21]. In older children, an oxygen saturation above 95% is generally accepted [21]. It must be noted, however, that a large, single centre, retrospective study found that a high partial arterial oxygen concentration (partial arterial oxygen > 350 mmHg, or > 250 mmHg in sicker children) at the time of the intensive care admission was an independent risk factor for increased mortality [32]. Until further studies clarify these findings, anesthesiologists may need to titrate the delivered amount of oxygen, as inadvertent intraoperative hyperoxia (partial arterial oxygen > 200 mmHg) is common [33].

7. Normocapnia

For every mmHg of partial arterial carbon dioxide (CO_2) change, there is directly proportional change in cerebral blood flow of approximately 3% [4]. High partial arterial carbon dioxide increases cardiac index by 1-1.5% for every mmHg, and shifts the hemoglobin dissociation to the right [34]. Moderate hypercapnia causes cerebral vasodilation and may lead to IVH and neurological injury [35], may increase the lower limit of cerebral blood flow autoregulation enhancing the detrimental effect of hypotensive episodes [4], and cause myocardial

depression [36].

Severe, prolonged hypocapnia induces brain injuries such as cerebral ischemia, hemorrhage, periventricular leukomalacia [4]. Therefore, partial arterial carbon dioxide pressures should be maintained within normal limits [4, 27], and mild hypo or hypercapnia should be reserved to selected cases [27]. Finally, very low birth weight infants and those with severe lung disease may have inaccurate correlation between end-tidal CO_2 and arterial CO_2 with high difference as high as 20 mmHg [4].

8. Normonatremia

For over half century, the ideal maintenance fluid has been considered mildly hypotonic [37]. In the last decades, however, it has become evident that up to 31% of postsurgical patients are hyponatremic, and surgery is independent risk factor for hospital-acquired hyponatremia [37]. On the contrary, perioperative hypernatremia is uncommon, although extreme premature neonates may be at risk of an excessive sodium load even with 0.2% sodium solutions [38].

Hyponatremia leads to encephalopathy, cerebral edema, and respiratory insufficiency, particularly in neonates [18]. On the contrary, isotonic fluids containing normal sodium concentration decrease the risk of perioperative hyponatremia [18]. Contrary to Ringer lactate and 0.9% saline, a balanced isotonic solution with 1% of glucose guarantees a sufficient provision of glucose, bicarbonate, chloride and a close to normal in-vivo osmolarity [19]. Balanced isotonic-glucose 1% solutions have demonstrated to reduce the risk of hyperchloremic metabolic acidosis comparing to 0.9% saline and are recommended for fluid resuscitation in Europe [18].

It must bear in mind that in infants < 32 weeks, even mild hypernatremia (< 150 mmol/L) can have neurodevelopmental sequelae [39].

9. Normoglycemia

After a transient decrease in the first few hours after birth, glucose stabilizes within normal range. However, neonates remain at high risk of hypoglycemia due to their metabolic rate, which is 2-3 times higher than adults [4].

Although transient mild to moderate hypoglycemia may not lead to neurocognitive injury, low plasma glucose concentrations are associated with neurological signs that range from irritability and poor feeding to seizures and ultimately death. Hypoglycemia may become particularly deleterious in the presence of hypotension [4].

Hyperglycemia is also an independent factor for prolonged length of stay and postoperative complications [40, 41]. Hyperglycemia (> 6.1 mmol/L) and severe hyperglycemia (> 11.1 mmol/L) were reported in up to 93% and 27% of patients admitted to the pediatric intensive care unit (PICU) after major abdominal, thoracic [40] and cardiac [41] surgeries.

In order to maintain the intraoperative glucose levels within normal limit, a background infusion of 1-2.5% glucose at 10 mL/kg/h is recommended [18]. In healthy preschool children, 1% glucose appears to be sufficient to provide stable sodium and glucose level and avoid acid-base derangement, whereas

patients with comorbidities (i.e., prematurity, parenteral nutrition, liver disease) will likely require higher concentrations [18]. Young age (particularly neonates), weight for age < 5th percentile, ASA status \geq III, the presence of gastric or jejunal tube, poor feeding, and abdominal surgery remain the most important risk factors for intraoperative hypoglycemia [42].

Given the lack of commercial, glucose-based balance solutions in North America, the American Academy of Pediatric recommends isotonic solution such as 5% dextrose-0.9% saline with KCl as fluid maintenance [43]. It must be noted, however, that in the presence of high perioperative levels of anti-diuretic hormone, hyponatremia can develop with 5% dextrose-0.9% saline infusion, once the glucose is reabsorbed and the excess of sodium is excreted [37].

10. Normothermia

Both perioperative hypo- and hyperthermia can be harmful in children and should be avoided [44, 45].

Normal body temperature is 36.0 °C to 37.9 °C rectally, 34.7 °C to 37.3 °C axillary and 35.7 °C to 37.5 °C tympanic [46]. Hypothermia is defined as a core body temperature < 36.5 °C, or a skin temperature < 36.0 °C [45, 47]. Severe hypothermia occurs when the core and skin temperatures are < 32.0 °C and < 31.5 °C [45, 47], respectively.

In infants and neonates, unintentional hypothermia is common (9-48%) [48, 49]. Passive and active warming techniques are effective in preventing hypothermia [45]. Common passive and active warming techniques used to maintain normal temperature perioperatively includes pre-warming of the operating room, forced-air warmer, fluid warmer, plastic cover, head cover, warming mattress, and airway heating and humidification [45, 50, 51]. For preterm neonates < 29 weeks, radiant warmer, overhead heat lamps, vinyl bags, thermal mattresses, pre-warmed transport incubator and in particular polyethylene wraps have been demonstrated to be effective [45, 51]. However, those interventions must be employed judiciously as they can also cause hyperthermia ($T > 37.5$ °C) [45, 48], as reported in 9% of neonates admitted to the intensive care unit after surgery [48].

Hypothermia is associated with multiple complications including respiratory distress syndrome, metabolic derangements, major brain injury, bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, coagulopathy, increased oxygen consumption, cardiac events, increase surgical wound infection, hospital length of stay [44, 45] and, in addition, altered drug pharmacokinetics and pharmacodynamics [44].

In infants, the thermoregulation mechanism is impaired particularly in the first 2 weeks of life [52]. The brown adipose tissue metabolism is the main route of heating until 6-12 months of age. Preterms < 30 weeks of gestational age have no brown fat thermogenesis and remain at higher risk of hypothermia [53]. After induction, temperature drops dramatically in the first 10 minutes and continues for at least 60 minutes. Major risk factors are neonates, infants, low operating room temperature (< 23 °C) and major surgery [54]. The American Society of Anesthesiologists strongly recommends monitoring patient core temperature during cases of general anesthesia and

neuraxial anesthesia lasting more than 30 minutes and to use of active and passive patient warming techniques to target a core temperature 36-37 °C [55].

11. No pain, no emergence delirium, no nausea and vomiting

Pain associated with surgical stress delays postoperative ambulation and hospital discharge, promotes the development of chronic postoperative pain and increases morbidity and mortality [56]. Pain has been also associated with cognitive disturbances [57], increases cancer recurrence [58], impaired brain development [59] and immune system [60]. Despite the advancement in analgesics and pain control modalities, severe postoperative pain is present in up to 40% of patients [56]. Extensive pain management guidelines have been recently published by the pain committee of the European Society for Paediatric Anaesthesiology [61]. Multimodal or balanced analgesia is a strategy used to treat acute pain with several medications that target different receptors to reduce the risk of adverse effects associates to monotherapy, especially opioids [62]. The minimum multimodal analgesia [61, 62] (Fig. 2) should be achievable by all anesthesia providers even in institutions with limited resources and expertise. Neuraxial, regional analgesia, patient or nursing controlled analgesia are recommended when equipment, resources and expertise are available. Adjuvants should be considered whenever available.

Emergence Delirium (ED) is an anesthesia related complication and affects around 25% children undergoing surgery [63]. ED is associated with significant adverse events including injury to the patient and personnel, damage to incision sites, exacerbated parental anxiety, and increased nursing requirements, further resulting in an increased burden and cost to the healthcare system [64]. Once ED occurs, supplemental sedative and/or analgesic medications may be necessary, which delays patient discharge [65]. Children showing ED after anaesthesia are seven times more likely to have new-onset separation anxiety, apathy, eating and sleeping problems [66].

The risk postoperative nausea and vomiting (PONV) in children ranges from 9% to 70% and should be prevented, as part of the wide spreading ERAS recommendations [67]. Clear pediatric guidelines have been recently published [67] (Table 2).

Anti-emetic prophylaxis should be directed by patient's risk stratification for nausea and vomiting. It is recommended to use anti-emetic from different classes if rescue medications are needed postoperatively. Along with common medications such as dexamethasone and ondansetron, therapies such as liberal fluid administration (30 mL/kg), lidocaine (1.5 mg/kg followed by 2 mg/kg/h), or α_2 agonists and non-pharmacological therapies (i.e., acupuncture) may also be considered [67].

12. Conclusions

Despite the advancements in drug safety and monitoring, pediatric anesthesia remains a specialty at high morbidity risk and low error tolerance.

Anesthesiologists who practice pediatric anesthesia should

aim to maintain patient homeostasis at all time during the perioperative period.

The 10-N principles provide clinical goals for a safe anesthesia conduct and should be integrated in pediatric training and daily practice.

AUTHOR CONTRIBUTIONS

IAA was responsible for manuscript preparation and reference selection. GB was responsible for literature review and manuscript editing.

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CONFLICT OF INTEREST

No conflict of interest to declare.

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