



## Neonatal anesthesia: how we manage our most vulnerable patients

Si Ra Bang

*Department of Anesthesiology and Pain Medicine, Seoul Paik Hospital, Inje University School of Medicine, Seoul, Korea*

Neonates undergoing surgery are at higher risk than older children for anesthesia-related adverse events. During the perioperative period, the maintenance of optimal hemodynamics in these patients is challenging and requires a thorough understanding of neonatal physiology and pharmacology. Data from animals and human cohort studies have shown relation of the currently used anesthetics may associate with neurotoxic brain injury that lead to later neurodevelopmental impairment in the developing brain. In this review, the unique neonatal physiologic and pharmacologic features and anesthesia-related neurotoxicity will be discussed.

**Key Words:** Anesthetics, Neurotoxicity syndromes, Newborn infant, Parental consent.

### Introduction

During the 1980s, the management of high-risk neonates improved because specialized incubators and mechanical ventilation became available in Korea [1]. In the 1990s, the introduction of artificial pulmonary surfactant to reduce neonatal respiratory distress syndrome [2] and high-frequency ventilators for the significant improvements of intensive neonatal care were associated with a significant decrease in mortality of premature infants. The ratio of the neonatal mortality rate (NMR) in rela-

tion to the infant mortality rate (IMR) was 66.7% in 1993 and dropped to 53.1% in 2009; however, approximately half of the IMR still consists of the NMR, demonstrating the important contribution of neonatal mortality to the IMR in Korea and the need for meticulous perinatal management [3].

The combination of major surgery and anesthesia in infants with very low birth weights is independently associated with an increased risk of mortality or the neurodevelopmental impairment of survivors that is greater than 50% [4]. Thus, there is clearly a need to improve the survival rate and decrease the morbidity of neonatal surgical patients. However, anesthetizing neonates continues to be very difficult even for the skilled anesthesiologist, as there is little clinical evidence supporting current guidelines for neonatal anesthesia. Because neonates have dynamic physiologies and feel pain in response to noxious stimuli, both the prevention of physiologic stress from surgical stimulation and the control of neonatal cardiovascular responses to anesthesia are crucial.

In this review, the unique neonatal physiologic and pharmacologic features and anesthetic implications will be addressed. Further, we will discuss anesthetic-induced neurotoxicity, and associated trials, and how we can provide support to the parents of our vulnerable patients.

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Corresponding author: Si Ra Bang, M.D., Ph.D.  
Department of Anesthesiology and Pain Medicine, Seoul Paik Hospital, Inje University School of Medicine, 9, Mareunnae-ro, Jung-gu, Seoul 04551, Korea  
Tel: 82-2-2270-0093, Fax: 82-2-2270-0094  
E-mail: sira1045@naver.com  
ORCID: <http://orcid.org/0000-0002-3290-0199>

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The following risks are associated with neonatal anesthesia:

- Prematurity
- Presence of congenital lesions or syndromes
- Disease processes particular to neonates including necrotizing enterocolitis (NEC) and patent ductus arteriosus (PDA)
- Narrow margin for error regarding drug administration and dilution, difficulty of correct placement of endotracheal tube

## Physiology

Neonates including preterm and term infants are at a higher risk of anesthesia-related adverse events than older children, which can be explained by the unique respiratory and cardiovascular physiology of this vulnerable patient group.

### Respiratory physiology

Although it begins early in gestation, the respiratory control system of neonates including central respiratory rhythmogenesis and central and peripheral chemoreception is immature, and development continues for weeks or months after birth [5]; also, the respiratory response to hypoxia and hypercapnia is decreased in neonates [6]. Apnea of prematurity occurs in babies born before 34 weeks [7]-apnea may persist after term gestation in those babies born before 28 weeks [8]. Chronic apnea and intermittent hypoxemia produce free radicals and are associated long-term adverse outcomes [9].

### Anatomic airway differences

The anatomic dead space of infants (early infancy > 3 ml/kg vs. adults 2.2 ml/kg) in relation to their larger head size is much greater compared with adults [10]; furthermore, the epiglottis of neonates is narrower, larger, and in a superior position compared with adults [11]. Infants are obligate nasal breathers due to the low airway resistance through their nasal passage. The upper respiratory tract of neonates is compliant so that dynamic collapse is more common. The breathing of infants is more severely impacted when their relatively smaller airway diameters are narrowed by secretions in the endotracheal tube [6].

Reduced pulmonary alveoli elastic recoil and high closing volume make it difficult to maintain the functional residual capacity (FRC) of neonates. Infants have the following properties to increase and maintain FRC: First, the post-inspiratory activity of the intercostal and diaphragmatic muscles (self-recruitment maneuver); second, high respiratory rates with short expiratory times (auto-positive end-expiratory pressure [PEEP] or dynamic hyperinflation); and lastly, laryngeal adduction in expiration to increase expiratory airway resistance (functional PEEP) [12].

## Ventilation

The mechanical ventilation of neonatal patients is an uncertain practice because small changes in tidal volume can induce unintentional hyperventilation or hypoventilation, leading to lung injury. Traditional mechanical ventilators of the anesthetic field were unable to deliver small tidal volumes (20 ml for most ventilators), so most pediatric anesthesiologists prefer pressure-controlled ventilation rather than volume-controlled ventilation [13]. However, modern anesthesia ventilators have been developed to deliver actual tidal volumes, thereby avoiding volutrauma and atelectrauma. These volume-targeted modes of ventilation can reduce the potential of ventilator-induced lung injury [14].

A lung-protective ventilation strategy is needed for neonatal patients, particularly for extremely pre-term infants ( $\leq 28$  weeks of gestational age), as their structurally and biochemically immature lungs are highly susceptible to injury from positive-pressure ventilation [15]. The major goals of lung-protective strategy are to avoid atelectrauma, limit tidal volume to prevent alveolar over-distension, and minimize oxygen toxicity by improving V/Q matching [16]. The lung-protective strategy includes PEEP to avoid atelectasis, a smaller tidal volume, and a recruitment maneuver as needed [13]. PEEP, however, is relatively contraindicated in infants with hypertension, volume depletion, and bronchopleural fistula. There are only a few comparative studies regarding ventilator parameter guidelines for mechanical ventilation during neonatal anesthesia. Therefore, further controlled trials are needed.

Mild hypercapnia (PaCO<sub>2</sub> 45–55 mmHg) is respiratory care strategy that is used to reduce the potential of lung injury. Also, in very low birth weight infants, permissive hypercapnia is an effective and safe ventilator strategy to decrease pulmonary complications associated with mechanical ventilation [17]. In preterm infants at risk of intraventricular hemorrhage of brain, both hypocapnia (PaCO<sub>2</sub> < 39 mmHg) and hypercapnia (PaCO<sub>2</sub> > 60 mmHg) as well as magnitude fluctuations in PaCO<sub>2</sub> should be avoided during the first 4 days of life [18].

### Optimal oxygen saturation target

Excess oxygen can be harmful to neonates, as it can result in conditions such as retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), injury to the developing brain, and DNA damage that can lead to childhood cancer [19]; however, in a recent meta-analysis, no significant differences in mortality, BPD, ROP, and neurodevelopmental outcomes were found between restricted (SpO<sub>2</sub> 85 to 89%) and liberal (SpO<sub>2</sub> 91 to 95%) oxygen group [20]. The optimal level of oxygen guidelines to reduce risk of ROP while also improving the outcome and devel-

opment of preterm infants is still unclear. A recent review suggests that wider and intermediate SpO<sub>2</sub> targets, such as 87–94% or 88–94%, are safe for vulnerable patients [21].

## Cardiovascular Physiology

### Infants blood pressure and hypotension

During the perioperative period, it is very challenging for anesthesiologists to maintain optimal hemodynamics in preterm neonates. Yet, among pediatric anesthesiologists, there is no agreement regarding the definition of hypotension, its treatment during neonatal anesthesia, or even the optimal measurement site [22].

The blood pressure (BP) of neonates increases on the first day after birth. In preterm infants, BP similarly increases over the first week [23]. Ex-premature infants generally have a higher BP than term babies, and this elevation may be explained by the stressful condition of extrauterine life. Also, the BP of full-term infants increases until 6 weeks of age. In neonates older than 36 hours, the average mean arterial pressure (MAP) is 53.0 mmHg with a standard deviation of 7.3 mmHg [24].

In a survey of pediatric anesthesiologists, the majority reported the use of systolic BP as a measurement parameter, with a 20–30% decline from baseline interpreted as significant intraoperative hypotension [25]. However, in neonatal anesthesia, hypotension is usually defined using MAP. In preterm neonates, the MAP is roughly related to the gestational age in weeks and is considered the minimum acceptable BP in this population [26]-neonatologists usually regard 30 mmHg MAP as the lowest limit of their patients [22].

### Managements of low blood pressure

During anesthesia, target BP is estimated using the preoperative normative BP, whereas all hemodynamic parameters must be checked to monitor adequate organ perfusion [22]. It is difficult to detect the relationship between BP and inadequate tissue perfusion. Evidence of the benefit of treating low BP with inotropics and fluids does not exist, but overtreatment in extremely low birth weight infants is more likely to delay their motor development, cause hearing loss, and result in death [27].

In neonatal anesthesia, anesthesiologists use treatments including fluid administration, inotropic agents, chronotropic agents, and vasoactive agents for hypotension. The neonatal heart, however, has a limited capacity for an increased preload, so excessive fluid replacement can cause heart failure [28]. Bradycardia is the main neonatal cardiac problem, but when inotropic agents or chronotropic agents should be administered is not

easily determined; therefore, anesthesiologists treat bradycardia with adrenalin, as it comprises both inotropic and chronotropic properties. In addition, the myocardium is sensitive to catecholamines and their overuse can lead to myocardial damage [28]. BP is not a single reliable predictor of neurologic brain injury in neonates, but fluctuations in the MAP in those who are immature and have pressure-passive cerebral vascular circulation are correlated with intraventricular hemorrhage [29]. Thus, the maintenance of adequate hemodynamics should be accompanied by a thorough understanding of neonatal physiology.

### Transitional circulation

Neonates have a dynamic circulation that can convert to the fetal circulation at any time. In the first week after birth, neonatal pulmonary circulation is sensitive to hypoxia, hypercarbia, asphyxia, acidosis, hypothermia, hypo- or hyperglycemia, hypocalcemia, and sepsis, all of which may cause an increase in pulmonary vascular resistance and thus a re-opening of transitional circulation shunts, leading to persistent pulmonary hypertension of the neonate (PPHN) [30]. During the perioperative period, the presence of any of these factors may likewise induce a shift to the transitional circulation. The monitoring of preductal (on the right arm) and postductal (on either leg) oxygen saturation levels may allow the detection of a reversion to a transitional circulation, the preductal saturation show higher saturation than postductal values [30]. Pulmonary hypertension is one of the major risk factors for the morbidity and mortality related to neonatal anesthesia. Adequate respiratory control and the prevention of right ventricular dysfunction are essential to avoid PPHN [31].

### Coagulation and transfusion

Normal hemoglobin (Hb) levels of neonates are in the range of 14–20 g/dl. Preoperative transfusion and subsequent management require Hb levels < 9 g/dl in term infants and < 7 g/dl in preterm infants [32]. The use of blood products collected within 7 days and their slow administration (< 1 ml/kg/min) are recommended to prevent the transfusion-related complications of hypocalcemia and hyperkalemia.

The coagulation system of healthy neonates is functional and does not show tendency of abnormal bleeding and thrombosis [33]. Severe coagulopathic bleeding in neonates occurs during heart surgery [33], while severe sepsis such as NEC represents thrombocytopenia [34]. Perioperative platelet transfusion should be considered in neonatal patients with NEC who have platelet counts of < 50,000 /mm<sup>3</sup>.

## Pharmacology

### Off-label drug use

The use of many of the medications in clinical neonatal practice is off-label because clinical trials for neonates are difficult to perform. In a review of neonatal drug labeling and exposure, only a minority (< 5%) of the drugs used in hospitalized neonates had been approved by the Food and Drug Administration (FDA) [35]. Among them, only three anesthetic drugs (remifentanyl, rocuronium, and sevoflurane) had updated labeling for neonates, but none included premature infants born at 23–29 weeks [36]. Further clinical research should be conducted on the anesthetic agents that are usually used.

### Pharmacokinetics and pharmacodynamics

Growth and maturation are major issues that influence drug action in pediatric patients. The absorption, distribution and clearance of drugs change abruptly during the infant period [37]. The neonatal liver and kidneys are immature and develop over the first 2 years of life [37]. The glomerular filtration rate (GFR) at 25 weeks is only 10% of the mature value, and for babies born at term it is 35% of the asymptotic adult value. At 1 year, the GFR in neonates born at term is 90% and at 2 years it is 98% [38]. Postconceptional age, rather than postnatal age, would be a better biological marker of maturation. In addition, the volume of distribution is affected because total body water and extracellular fluid are increased in neonates. This volume of distribution may be increased or decreased according to body composition, plasma protein bindings, regional blood flow, and blood-brain-barrier permeability [37].

The pharmacodynamics of infants are more prone to alteration and variability than adults. Age is one of the main contributors to pharmacodynamics change [39]. The minimal alveolar concentration of almost all of the anesthetic vapors is lower in neonates than those in infants [40]. Both changes in brain regional blood flow and the number of  $\gamma$ -aminobutyric acid type A (GABA<sub>A</sub>) receptors contribute to the altered drug responses [41]. Measurements of anesthetic pharmacodynamics outcomes are represented by electroencephalogram results of the depth of anesthesia (e.g., bispectral index) and the degrees of neuromuscular blockade, but the availability of monitoring for the neonatal population is poor.

As previously mentioned, off-label drug use is common and evidence-based usage is limited in neonates. Anesthesiologists must bear in mind that neonates are not “small adults” and the mirroring of adult concepts for pharmacotherapy is not appropriate [42]. Drug-substitution and drug-dosage errors are more common in pediatric patients than adult patients; also, narrow

margins of error in drug delivery and dilution aggravate the problem [30]. After the administration of opioids, which can induce respiratory depression, the line should be flushed to prevent adverse effects in the postoperative care unit or, after outpatient surgery, prior to patient discharge.

## Anesthetic Induced Neurotoxicity

Animal studies have demonstrated the neurotoxic effects of anesthetics in the developing brain [43–45]. Not only neonatal rodents but also mammals including piglets and primates are represented anesthetic-induced neuronal injury [46–49]. These animal research studies revealed anesthetic induced neurotoxicity by various mechanisms. The neuronal apoptosis is led by a suppression of neurotrophic synaptic signal [50] via both the intrinsic and extrinsic pathways [51]. The intrinsic pathway involves internal cell signals resulting in the release of proapoptotic proteins [52]. The extrinsic pathway is stimulated by death receptors such as the tumor necrosis factor receptor families [53]. In addition, the affected animals showed abnormal attention, memory and learning disabilities, and behavioral changes. The translation of animal research to humans, however, is problematic. The anesthetic management of animals involves greater clinical anesthetic drug doses and potency, and a longer duration of exposure, and these are three major risk factors that affect neonatal anesthetic-induced neurodegeneration. The animal studies lack the presence of surgical stress. In addition, there are differences in monitoring and management between animals and humans [54].

### Retrospective and prospective human study

The large number of animal research studies led us to perform a retrospective human cohort study to investigate the neurodevelopmental effects of anesthetics. However, as mentioned above, these accumulated anesthetic-induced diverse injuries have limited ability to translate to human. The limitations are as described different adequate dose, period of vulnerable developmental period and interpretation of neurodevelopmental outcomes and the managements of physiological responses during surgery and effect of surgery itself.

Wilder et al. reported a retrospective study of a birth cohort of children born between 1976 and 1982 [55,56]. There were no differences regarding later learning disabilities for children exposed to anesthetics prior to birth [55]. Using the same cohort, Wilder et al. [56] studied 593 children who received surgery and general anesthetics before the age of 4 years. Learning differences were not found for those children who had a single exposure of general anesthetic [56]. DiMaggio and colleagues' birth case-control [57] and siblings [58] studies found increased

developmental and behavioral delays or disorders for those infants who underwent anesthesia during surgery. Bartels et al. [59] studied 1,143 monozygotic twin pairs using the Netherlands Twin Registry, and found that early (before 3 years) anesthetic exposure was associated with significantly reduced educational achievement; however, no effects regarding a causal relationship between anesthesia administration and later learning-related outcomes were observed among the monozygotic twins [59]. In the meta-analysis of Wang et al. [60], there was an elevated risk of later neurodevelopmental impairments in association with surgery/anesthesia performed in patients younger than 4 years of age. Interestingly, the authors found that the frequency of surgery/anesthesia exposure was a more important risk factor than patient age at exposure.

Nonetheless, many retrospective studies have not been able to provide clear evidence that commonly used anesthetics affect brain development. Thus, prospective studies are currently being conducted. The Pediatric Anesthesia Neurodevelopmental Assessment research network, a multi-institutional study carried out by Columbia University investigators, is assessing pediatric anesthetic neurotoxicity among patients under the age of 3 years who have been scheduled for inguinal hernia repair. To reduce genetic and environmental confounders, the assessment is being conducted in sibling pairs [61]. The General Anesthesia Study is a randomized controlled trial of more than 700 neonates that compares the use of general vs. spinal anesthesia for hernia surgery. The trial will prospectively involve infants of a post-conceptual age less than 60 weeks, and will be conducted by investigators at both The Royal Children's Hospital Melbourne in Australia and Boston Children's Hospital in the United States [61]. The aim of the trial is to evaluate whether general anesthesia and awake regional anesthesia have similar effects on cognitive function at 2 years and 5 years of age. Enrollment for the trial has been completed, but the final analyses have not been conducted. The Mayo Anesthesia Safety in Kids study compared children exposed to no anesthesia, one anesthetic, or multiple anesthetics before the age of 3 years [52].

## Pain and neurodevelopment

During maturation, nerve tracts are myelinated up to the thalamic level at 30 weeks and the afferent neurons of the thalamus project axons that migrate into the neocortex. Synaptic connections of the thalamocortical tracts may occur at 24 weeks of gestational age [62]. Even preterm neonates feel pain, which elicits a stress response that can lead to metabolic acidosis, hypoglycemia or hyperglycemia, and electrolyte imbalances, all of which are associated with increased morbidity and mortality [63]. Painful stimuli can be neurotoxic to the neonatal brain, whereas adequate analgesia can prevent associated injury.

## Recommendations for parents

According to a survey, parents are the most anxious regarding surgery and anesthesia when the child is under 1 year of age and when it is his or her first surgery [64]. The extrapolation of animal data for humans in this context needs to be undertaken with great caution. Therefore, communication between caregivers and parents should be clear, objective and emphatic way.

Strategies for Mitigation of Anesthesia-Related Neurotoxicity in Tots (SmartTots), established by the FDA and the International Anesthesia Research Society, seeks to close scientific and clinical gaps in knowledge regarding the safe use of anesthetics and sedatives in children. In June 2014, the International Anesthesia Research Society and SmartTots convened a group of experts to consider the emerging evidence from animal and human studies and to revise the 2012 statement of these organizations. A revised statement on the use of anesthetic and sedative drugs in infants, toddlers, and preschool children was drafted by SmartTots and included the following (<http://www.smarttots.org/resources/consensus.html>): "Parents and caregivers should discuss the risks, benefits, and timing of surgery and procedures requiring anesthetics and sedative drugs. Surgeries and procedures requiring anesthetic and sedative drugs that could reasonably be delayed should possibly be postponed because of the potential risk to the developing brain of infants, toddlers, and preschool children. When surgeries and procedures are required using current standard of care anesthetics, consider participating in a study to help identify better anesthetic and sedative practices and/or drugs that have the least effect on the developing brain."

In Europe, for safe anesthesia conduct in pediatric patients, the Safe Anesthesia For Every Tot initiative was founded to address perioperative risk in young children, and to provide safe pediatric anesthesia guidance [65]. Also in Korea, it should be initiated the nationwide collaboration of parents, organization, researchers and health care providers to conduct safe anesthesia for our vulnerable patients. All currently used anesthetics are associated with neuronal apoptosis and later maladaptive behavior in animals that were exposed during the critical neurodevelopment of maximal synaptogenesis [61]. However, appropriate pain relief should be provided to very young patients, which necessitates the use of anesthesia. Thus, particularly in infants, procedures requiring general anesthesia should be limited to the essential ones and the duration of the anesthesia should be as brief as possible.

## Conclusion

To ensure optimal neurocognitive outcomes for our vulnerable patients, effective collaboration is required between anesthesiologists, pediatric surgeons, and neonatal intensive care

unit providers. The risk of harm to the neurocognitive development of most neonatal surgery patients is already high because of prematurity, congenital anomaly, and ischemic injury during early life [66]. Our duty as care providers in the detection and treatment of correctable neurocognitive adverse risk factors, such as perioperative low BP and hypocapnia, is to proceed with extreme caution. Animal studies have shown that almost all clinically used anesthetics are associated with neuronal apopto-

sis and later maladaptive behavior when exposure occurs during the critical neurodevelopment period; however, neurotoxic effects in humans have not been proven. We believe that, in neonates, a single and short duration of anesthetic exposure to reduce painful stress during surgery is safe but should be accompanied by the meticulous management of these most vulnerable patients.

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