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EDITORIAL

The cutting edge of neonatal anesthesia: the tide of history is changing

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As reviewed by Drs. Yu and Liu in the previous issue of *Journal of Anesthesia* [1], focus on the safety of neonatal anesthesia has been from the aspect of long-term neurobehavioral outcomes. Neonatal anesthesia can be challenging even for experienced pediatric anesthesiologists if the baby was born prematurely or had co-morbidities. Epidemiological data suggest that the incidence of life-threatening critical events in the perioperative period is consistently higher in the neonatal population. Their small body size and the prematurity of vital organ systems cause the safety margin to be small in perioperative management. The anesthesia equipment may not be exclusively designed for small babies, and not all anesthesiologists have appropriate training and experience in neonatal anesthesia. Some modern monitoring systems are not applicable for the neonate, and basic vital signs are still the mainstay of patient monitoring. Information regarding the rational use of anesthesia-related medication for the neonatal population is often sparse. In addition, there seems to be substantial individual pharmacokinetic and pharmacodynamic variability among neonatal patients. Clinical trials exploring better management are often difficult for a number of practical and ethical reasons. Thus, although the progress of neonatal anesthesia has been somewhat slow, we are currently witnessing a landmark event in the history of neonatal anesthesia.

Until the 1980s, the "Liverpool technique" had been the common anesthesia method for neonates. The Liverpool technique for neonatal anesthesia consists fundamentally of light general anesthesia and a muscle relaxant, typically with nitrous oxide and with *D*-tubocurarine (curare). At that time, neonates were believed not to feel pain because of their immature sensory nervous system. Pain treatment for neonates was considered to be unnecessary or even contraindicated. By reason of their immature cardiovascular and respiratory systems, neonates were assumed to be too sensitive to the depressant effects of anesthetics. However, in the 1980s, with the development of neurophysiological research in the neonatal population, accumulating evidence showed that neonates do feel pain and consistently respond to noxious stimuli. A seminal study by Anand et al. in 1987 [2] showed that withholding opioids in invasive neonatal surgery results in an exaggerated stress response and adversely affects the surgical outcome. Since then, anesthesiologists have been aware that analgesia is an essential component of neonatal anesthesia. However, clinical application of analgesia for neonatal surgery has been inconsistent among practitioners, even though there has been a growing body of evidence supporting the importance of analgesia during surgery. Analgesia using regional anesthesia is not always feasible for small patients, and the use of opioids, including fentanyl or morphine, was generally limited to patients who were originally planned to be on the ventilator. As a result, hypnotic-based anesthesia, such as sevoflurane, has been a popular approach to anesthetize neonatal patients.

In recent years, we have been facing newly emerging problems concerning the neurotoxic effects of anesthetics on the developing brain. More than 50 animal studies indicate that varieties of anesthetics, including volatile anesthetics, thiopental, propofol, benzodiazepines, and ketamine, cause neuronal apoptosis under specific conditions. Some animal studies clearly demonstrated long-term neurobehavioral impairment following neonatal exposure to anesthetics. Although experimental evidence

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from animal studies seems to be robust, there is controversy as to whether the findings using juvenile animal models would be applicable to human babies. Because the intrinsic limitations of animal research make it difficult to translate animal data to human subjects, human data are necessary for clinical decision making. To date, various retrospective cohort studies have been reported, and the available epidemiological data seem to be equivocal in terms of the long-term cognitive outcome following anesthetic exposure early in life. Prospective clinical studies are being conducted to determine adverse neurocognitive outcomes caused by early exposure to anesthetics, and the results from these studies will be reported in the next few years.

The robust and consistent animal data make it difficult to completely dismiss the possible cause–effect relationship between neonatal exposure to anesthetics and neuroapoptosis in the developing human brain. On the other hand, long-term neurobehavioral adverse effects caused by anesthetics may be subtle in human subjects, even if that is the case. Thousands of neonates have been anesthetized using a variety of anesthetics, and until recently, the long-term neurocognitive adverse reactions attributed solely to anesthetics were not recognized. Neonatal surgery is usually urgent in nature, and withholding surgery is impractical and may impede the chance of the best possible surgical care. Surgical treatment without appropriate anesthesia is unethical, and it also results in long-term adverse sequelae. Neonatal pain induced by surgery is also known to induce prolonged behavioral effects in animals and humans [3]. Thus, the benefit of anesthetics overweighs the possible small risks of subsequent neurobehavioral derangement by anesthetics.

Regardless of prospective clinical study results, a better solution is required to manage our fragile patients. Because many hypnotic agents, i.e., medications causing loss of consciousness, are shown to induce neuroapoptosis in premature animal models, the use of hypnotics, including volatile anesthetics and benzodiazepines, has been questioned in neonatal anesthesia. The classic triad of general anesthesia comprises unconsciousness, analgesia, and immobility. In modern balanced anesthesia, unconsciousness is induced by hypnotics, analgesia is provided by opioids or by regional anesthesia, and immobility is assured by muscle relaxants. In recent years, intraoperative awareness is a major issue in the adult anesthesia world and in pediatric patients as well, but not all surgical patients need to be completely unconscious during surgery. For example, most adult patients will tolerate lower limb surgery with effective neuraxial anesthesia while they are fully awake. The same situation may happen in infant inguinal surgery with spinal anesthesia. The point is to make patients free of distress, not simply render them unconscious. Simple unconsciousness with immobility, typically employed when using the classical Liverpool technique, would not be our ideal goal. Anand's [2] study clearly showed that simple hypnosis might not be enough to blunt a stress response and might result in an adverse outcome in neonatal surgical patients.

Opioids are considered to be relatively benign in terms of anesthetic-induced apoptosis in the developing brain [4]. In infant cardiac surgery, a high-dose fentanyl technique has been used for years as a primary anesthetic. Previous reports indicate that large doses of fentanyl in infant cardiac surgery results in stable hemodynamics and blunts the stress response caused by deep hypothermic cardiopulmonary bypass. The study by Gruber et al. suggests that adding midazolam (i.e., hypnotics) does not provide an additional benefit for hemodynamic stability and blunts the stress response if the plasma fentanyl concentration is kept around 10 ng/ml [5]. Higher-dose fentanyl anesthesia for neonates would be appealing in that the use of hypnotics could be avoided in neonatal anesthesia. However, the pitfalls of a high-dose fentanyl technique include difficulty with extubation immediately after surgery in consequence of the residual fentanyl effects. Currently, remifentanil, which is a newer, ultra-short-acting opioid, is another potentially useful choice if the neonatal patients are to be extubated at the end of surgery. The pharmacokinetics of remifentanil seem to be predictable even in neonates [6]. Limited pharmacokinetic data in the neonatal population may provide a useful dosing guide for remifentanil. The potency of remifentanil, a μ-opioid agonist, is known to be roughly equal to that of fentanyl, and it is thus necessary to keep the remifentanil concentration above 10 ng/ml to use it as a primary anesthetic for neonates. Because the clearance of remifentanil in younger infants is reported to be approximately twice that of the adult value, a double maintenance dose per body mass is necessary for small infants, assuming the target plasma remifentanil concentration is the same as adults [7]. Our anecdotal experiences in past years suggest that even sick neonates will reasonably tolerate higher doses of remifentanil in terms of hemodynamic stability. Emergence from high-dose remifentanil anesthesia seems to be within a predictable range in neonatal patients, as reported in previous studies [6]. Patients receiving μ-opioid receptor agonists may occasionally exhibit muscle rigidity at higher doses, which may result in difficult positive pressure ventilation, and intense muscle relaxation would be required for high-dose opioid anesthesia. Sugammadex has almost eliminated the risk of residual paralysis after rocuronium use, and anesthesiologists no longer need to rely on volatile anesthetics for intraoperative immobility.

The choice of anesthetics is not the only modifiable factor to minimize neuronal adverse outcomes in the operating room. More evidence about neonatal cerebral

physiology is becoming available, and it reveals that autoregulation of cerebral blood flow in neonates might not be sufficiently developed to maintain cerebral blood flow when systemic hypotension occurs. Systemic hypotension should be avoided as much as possible to prevent hypoxic damage to the vulnerable nervous system. Deep anesthesia using volatile agents may be disadvantageous in this regard. Hypocapnia is another potentially detrimental factor to reduce cerebral blood flow. In the neonatal intensive care unit, pediatricians have been focusing on minimizing ventilator-induced lung injury, and the safety and the efficacy of permissive hypercapnia have been evaluated. Although the significance of protective lung ventilation strategies in the operating room needs further evaluation, mild hypercapnia, per se, seems to result in no clinically significant adverse effects in the neonatal population [8]. Considering that there are multiple factors to decrease cerebral blood flow during surgery and anesthesia, mild hypercapnia for augmenting cerebral blood flow would be a prudent choice in intraoperative ventilation management.

The developing nervous system is found to be more vulnerable to nonphysiological conditions than previously thought. The trend in neonatal anesthesia is now changing from hypnotic-based anesthesia to opioid-based anesthesia to minimize the risk of neuroapoptosis. Until further prospective clinical evidence on anesthetic-induced long-term neurocognitive adverse effects is available, anesthesia providers taking care of neonates should closely monitor the latest findings from animal laboratory and human epidemiological studies. Surgical neonates are considered to be a group that is potentially at high risk for later neurocognitive dysfunction. We are responsible for providing the best possible anesthesia care to protect the future of our patients.

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