

Bogumiła Wołoszczuk-Gębicka

WHY IS NEONATAL ANAESTHESIA SUCH A CHALLENGE?

CZY ZNIECZULANIE NOWORODKA JEST ŁATWE?

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Abstract

Approximately 1.5 million neonates receive general anaesthesia each year for surgical procedures. Providing anaesthesia to neonates is not easy. Surgical procedures are often difficult and extensive, and the physiology of neonates makes respiratory and cardiovascular problems more frequent and life-threatening.

The paper covers the changing concepts in neonatal anaesthesia, including recent studies that indicate that anaesthetic exposure could cause neuronal apoptosis in the developing brain. This could potentially influence the long-term developmental outcome, especially in infants requiring multiple surgical procedures. Respiratory and cardiovascular critical events, age-related differences of the pharmacokinetics of the drugs used for anaesthesia, as well as technical problems are also covered.

Key words: anaesthesia, general; anaesthesia, recovery period; anaesthetic effects, anaesthetics; neurotoxicity, infant; newborn

Streszczenie

Okolo 1,5 miliona noworodków znieczulanych jest co roku do zabiegów operacyjnych. Znieczulenie noworodka nie należy do łatwych. Zabiegi operacyjne, wykonywane u noworodków z powodu wad wrodzonych są często trudne i rozległe, a odrębności fizjologiczne noworodka powodują, że zarówno oddechowe, jak i krążeniowe problemy są znacznie bardziej nasilone.

W artykule omówiono zmieniające się koncepcje w znieczuleniu noworodków, a także najnowsze badania, w których wykazano, że ekspozycja na anestetyki może powodować apoptozę neuronów w rozwijającym się mózgu. Może to mieć wpływ na rozwój dziecka, zwłaszcza, jeśli konieczne było wykonanie kilku zabiegów w okresie niemowlęcym.

Omówiono również „zdarzenie krytyczne”, zarówno krążeniowe, jak oddechowe, związane z wiekiem odrębności farmakokinetyki leków używanych podczas znieczulenia oraz problemy techniczne.

Słowa kluczowe: znieczulenie, ogólne; znieczulenie, okres pooperacyjny; anestetyk, działanie; anestetyk, neurotoksyczność; noworodek

Each year approximately 1.5 million neonates require anaesthesia and/or sedation for surgery and painful procedures. According to the Polish Registry of Congenital Malformations, congenital malformations occur in 2-4% of the newborn babies. Given that approximately 350.000 infants are born each year in Poland, 7.000-15.000 of them may require surgery. Many newborn infants do so shortly after birth: 30% of newborns suffer from congenital heart defects, a vast majority of those with congenital

malformations concern the gastrointestinal (GI) tract; there are also cases of meningomyelocele, congenital hydrocephalus, bladder exstrophy and many other, less common congenital defects. They often require multistage surgery, therefore the number of anaesthesias performed in infancy is even higher.

Prematurely born infants present for surgery and anaesthesia with their specific health problems, like retinopathy of prematurity, or necrotizing enterocolitis.

Providing anaesthesia to neonates is not easy. Anaesthesia-related morbidity and mortality is higher in infants than in adults, and higher in younger children compared to older ones. In particular, airway complications are more likely to occur in very young infants. The critical event rate is highest in infants <2 kg b.w. [1]. Such events are related to the congenital malformation itself and its complications, age-related physiology, as well as technical problems. In order to provide safe anaesthesia, the anaesthesia team must understand all of them.

HISTORY

Dr Gordon Jackson Rees, a consultant anaesthetist at the Alder Hey Hospital in Liverpool, became a pioneer of paediatric anaesthesia. Together with Professor Cecil Gray, they proposed and introduced the revolutionary concept of the "triad of anaesthesia" using different specific agents to produce a desired effect, which was subsequently adapted for children (Liverpool technique). Jackson Rees introduced a routine of "heavy" premedication with atropine and opioids (with or without phenothiazines), intravenous induction, the routine employment of muscle relaxants and the use of endotracheal intubation and controlled ventilation by means of simple adaptation of the Ayre's T-piece with an addition of an open-ended bag, and the high frequency of respiration [2]. This technique was associated with great improvement in the results of infants undergoing surgery, and soon it became known in other countries, Poland included, since Dr Jackson Rees visited Poland, and shared his expertise with anaesthesiologists in paediatric hospitals in Warsaw.

A few decades later, the Liverpool technique, described in 5 steps: intubate, paralyse, give nitrous oxide, hyperventilate, and operate [3], became criticised. With the important development of more complicated operations in a variety of surgical fields, the practice of operating on neonates with minimal anaesthesia or analgesia had to change.

A group of paediatric anaesthesiologists from Boston reported that in preterm babies undergoing ligation of the patent ductus arteriosus, the major hormonal responses to surgery, as indicated by changes in plasma adrenaline, noradrenaline, glucagon, steroids, in the insulin/glucagon molar ratio, and in blood glucose, lactate and pyruvate concentration were significantly greater in the non-fentanyl than in the fentanyl group [4]. The same group stated a few years later that in neonates undergoing cardiac surgery, the physiological responses to stress were attenuated by deep anaesthesia and postoperative analgesia with high doses of opioids. Deep anaesthesia continued postoperatively reduced not only catecholamine demand, but also the vulnerability of these neonates to complications, and mortality [5].

The American Academy of Pediatrics, in a policy statement published in 1987, expressed the belief that the available local or systemic pharmacologic agents permitted relatively safe administration of anaesthesia or analgesia to neonates undergoing surgical procedures and that such administration was indicated, according to the usual guidelines [6].

PAIN IN A NEONATE

Nowadays, the need of providing adequate pain relief to neonates and infants is undisputable. The first nociceptors appear early during gestation, and by the 22nd week they are abundant throughout the fetus. The myelination of the pain pathways occurs by the 22nd week of gestation [7], and the fetus can process pain at the subcortical level even before cortical structures develop. There is a sufficient body of evidence that neonates, including those born preterm, demonstrate physiological responses to surgical procedures, similar to those demonstrated by adults [8], and neonatal cortical function is far greater than previously thought.

DRUGS USED FOR ANAESTHESIA

A variety of anaesthetic agents are now employed, usually in combination, to provide anaesthesia to a neonate: propofol, ketamine and (infrequently) tiopental to provide sleep; inhalational anaesthetics: sevoflurane, desflurane, isoflurane and (less frequently) nitrous oxide; opioids: fentanyl, sufentanil, remifentanyl (infrequently, off-label), and morphine for postoperative analgesia; muscle relaxants: atracurium, cis-atracurium, rocuronium, vecuronium, pancuronium (if the endotracheal tube is left in place for the postoperative period) and (less and less often) succinylcholine; and, finally, local anaesthetics: bupivacaine and ropivacaine.

NEUROTOXICITY OF ANAESTHETICS

Increasing evidence from animal studies suggests that both intravenous (propofol, ketamine, barbiturates and benzodiazepines), and inhalational anaesthetics may produce adverse neurobehavioral effects if used in infancy during the critical developmental period of the growth spurt of the brain. Some studies of infants and young children undergoing anaesthesia or sedation have shown long-term deficits in learning or behavior, while others have not. It would obviously be considered unethical to withhold sedation and anaesthesia, when necessary [9, 10, 11], but further studies, in non-human primates and in humans, were mandated.

The International Anaesthesia Research Society (IARS) and the Food and Drug Administration created a partnership called SmartTots (Strategies for Mitigating Anaesthesia-Related Neurotoxicity in Tots, [12]) to study the effects of commonly used anaesthetics on the developing brain, and establish practice guidelines. In December 2012, SmartTots, together with the American Academy of Pediatrics, Society for Pediatric Anesthesia, Society for Neuroscience, American Society of Anesthesiologists and European Society of Anaesthesiology published a consensus statement regarding anaesthesia safety in children [13], urging anaesthesiologists to:

„Discuss with parents and other caretakers the risks and benefits of procedures requiring anesthetics or sedatives, as well as the known health risks of not treating certain conditions

Stay informed of new developments in this area

Recognize that current anaesthetics and sedatives are necessary for infants and children who require surgery or other painful and stressful procedures”

Further studies performed in non-human primates confirmed the results of the earlier studies in rodents [14, 15]. Commonly used anaesthetics and sedatives, such as propofol, etomidate, midazolam and inhalational anaesthetics, acting at the GABA receptors in the brain, as well as ketamine, acting at the NMDA receptors, were found to be neurotoxic in non-human primates. Exposure of fetal or neonatal monkeys to propofol anaesthesia for 5 hours caused a significant increase in the apoptosis of neurons, as well as oligodendroglia, at a stage when oligodendrocytes were just beginning to myelinate axons. As a result, a long-term attention and memory deficit was observed [16].

A growing body of data from animal studies suggest that under certain circumstances, such prolonged or multiple anaesthesia administering commonly used anaesthetic agents could adversely affect the neurologic, cognitive, and social development of neonates and infants [17]. Observational studies in children suggest that similar deficits may occur. Information concerning the ongoing clinical trials assessing the effects of anaesthetics on neurocognitive development can be found on the SmartTots webpage <http://www.smarttots.org>.

In order to limit the risk of anaesthesia, using opioids and muscle relaxants, or regional techniques, rather than high-concentration inhalational anaesthesia seems a reasonable choice. The time of the exposure to anaesthetics should be limited to the necessary minimum.

NEONATAL PHYSIOLOGY, AND THE CRITICAL EVENTS RELATED TO ANAESTHESIA

The majority of critical events are related to airway management and respiration [1]. Neonates and infants have high O_2 consumption (2-3 times higher than adults), and a higher closing volume (CV, the volume at which alveoli begin to close, producing a shunt; in neonates CV may be bigger than the functional residual capacity, FRC). If any problems with airway patency occur, oxygen saturation decreases rapidly. The pulmonary circulation of the newborn infant is extremely sensitive to low pO_2 . Hypoxaemia constricts pulmonary arteries, therefore pO_2 should be maintained above 50 mmHg, and pCO_2 – preferably <60 mm Hg.

The tidal volume (V_t /kg body weight) of the neonate is similar to that in adults (7 ml/kg), but, since oxygen consumption is significantly higher, minute ventilation must be higher too. This requires a high respiratory rate (30-50/min). The work of breathing is high. The diaphragm is the most important respiratory muscle, but the composition of muscle fibers is different than in adults: the neonatal diaphragm, as well as the intercostal muscles, have a lower proportion of fatigue-resistant (type I) muscle fibers. The ribs are compliant, and chest retractions indicating the increased work of breathing, and respiratory distress or failure, may occur. Respiratory failure may develop during anaesthesia, or in the postoperative period.

Because of the high minute volume (MV), and high MV:FRC ratio, inhalational induction of anaesthesia is rapid, which makes an anaesthetic overdose a potential risk, with possible circulatory and respiratory depression.

Newborn infants (both full-term and premature ones) up to 2-3 weeks of age show a biphasic response to hypoxaemia [18]. The initial response is an increase in ventilation, which is transient and followed by a sustained respiratory depression. Hyperpnoea does not occur in a cool environment, at least in preterm infants. Ventilation is resumed when oxygen is administered. This biphasic response to hypoxemia is attributed to the depression of the central nervous system (as opposed to the peripheral chemoreceptors). Biphasic response to hypoxaemia increases the risk of postoperative apnoea. Premature infants may show a biphasic response up to 25 days after birth.

The heart of the neonate has a reduced compliance, and the ability of increasing its contractility is limited to approx. 30% (300% in adults, [19]). Infants are dependent on the heart rate to maintain cardiac output, and bradycardia should be avoided. The most common cause of bradycardia is hypoxaemia.

The routine use of anticholinergic agents (atropine) became a matter of controversy [20]. Opponents claim that bradycardia during anaesthesia usually results either from hypoxaemia, or from the anaesthetic overdose, and anticholinergic agents are not suitable treatment. Proponents underline that the vagal response is more intense in infants and young children than in adults. Some drugs used for anaesthesia, i.e. propofol and remifentanyl, can provoke severe bradycardia. Atropine makes it possible to avoid critical situations. If bradycardia is already present, the onset of atropine is delayed, even after intravenous administration [21].

Even though the anaesthetic demand of neonates may be lower than of older (i.e. 6 m.o.) infants, an attempt to provide analgesia solely with inhalational anaesthetics may produce a significant drop of blood pressure. Adding nitrous oxide enhances analgesia without any further depression of the cardiovascular system, but it may contribute to neurotoxicity. Opioids are efficient as analgesics, and they usually have minimal influence on circulation. When using opioids in neonates, one must keep in mind their pharmacokinetics. Sufentanyl clearance in neonates is 3-fold lower than in infants [22]. The pharmacokinetics of fentanyl, as well as morphine, is similar, therefore the risk of postoperative apnea is real. Only remifentanyl, which is metabolized in plasma, must be administered in slightly higher doses in neonates than in older children, or in adults.

Neonates are more sensitive to all non-depolarizing muscle relaxants than older children [23]. Vecuronium, and to a lesser extent also rocuronium, behave more like long-acting drugs, and the risk of a residual neuromuscular block after surgery is higher [24]. Sugammadex (Bridion, MSD), the first selective relaxant binding agent for the reversal of the neuromuscular block produced by rocuronium, is registered for routine use in children older than 24 months, but not for neonates. The usual solution is using other muscle relaxants, i.e. atracurium

(or cis-atracurium), which have an organ-independent metabolism.

Regional anaesthesia, usually used as an adjunct to a light-plane general anaesthesia, offers several advantages. Lower doses of opioids are required, and the infants can be extubated sooner after surgery. The most often used regional block is caudal epidural. Ultrasonography, which enables real-time visualization of the tip of the needle in the epidural space, as well as the spread of the local anaesthetic, [25] makes this technique both easier, and safer. Spinal anaesthesia, which can be performed without prior general anaesthesia, is seldom performed [26], because of the short duration of the block.

TECHNICAL ISSUES

Operating suites are usually designed for adults, and not for neonates. The air flows through a high-efficiency particulate air filtration system (HEPA), usually by means of a vertical air-flow system, and rapidly cools down the exposed body of the baby. The laminar flow is used to reduce the risk of the surgical site infection.

In the preparatory phase, some procedures, like anaesthetic induction, intubation of the trachea, or arterial and venous line placement, can be performed in an open incubator equipped with a radiant warmer. Surgery itself can also be performed in the incubator, with a warming mattress placed under the infant, but this is uncomfortable both for the surgeon and for the anaesthesiologist, who has very limited access to the patient.

Using warming blankets with a forced-air warming system is very efficient, provided that the blanket is kept dry. A warming blanket operated by circulating warm water through a leak-proof pad is a good alternative.

Anaesthesia machines are built primarily for adult patients, and not for neonates or small infants, and ensuring appropriate ventilation may be difficult, even if pressure-controlled ventilation (PCV) is used. Factors contributing to a discrepancy between the set and delivered tidal volumes include a large compression volume in the circle system (breathing hoses) relative to the infant's lung volume, leaks around uncuffed endotracheal tubes, and mechanical difficulty of setting a small tidal volume using adult bellows. Through compliance and leak testing and compensation, the risk of the injury to the lungs is decreased, but the testing site (next to the endotracheal tube versus the gas module of the anaesthesia machine) is of paramount importance [26].

Capnometry (on-line carbon dioxide monitoring in the expired air) is less accurate in neonates than in older children. The results seem better if a main-stream, rather than side-stream type capnometer is applied. Borrowing transcutaneous CO₂ monitoring system from the NICU seems to be another option.

An anaesthesiologist providing anaesthesia to a neonate faces multiple physiological, pathological and equipment problems, which may be difficult to manage in a community hospital, so it would be reasonable to refer neonates requiring surgery to well-equipped centers. A systematic review performed by Gonzalez et al. [20] seems

to support this thesis. In Australia, where neonates are transferred to the nearest community hospitals rather than to specialized centres, the perioperative mortality rate is closer to the numbers observed in developing, rather than developed, countries.

With the philosophy that "the smaller they are, the harder it is to provide anaesthetic", neonatal perioperative groups, whose members include representatives from neonatology, surgery, anaesthesiology and nursing are created to improve neonatal perioperative care. Admitting that neonatal anaesthesia is challenging may be the first step to improve the quality of anaesthesia for this demanding group of our patients.

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