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Infantile postoperative encefalopathy and the perioperative risk factors: a systematic review of the literature

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Abstract: A systematic review of the literature was performed to describe the perioperative risk factors for developing postoperative encefalopathy in infants and how to avoid them. Intra-operative complications are more common in neonates than in the adult population, and perioperative complications in pediatric patients have an increased mortality risk. Several studies have demonstrated an association between general anesthesia in infancy and an increased risk of poor neurobehavioral outcome. The reasons for this association are still unclear. We performed an extensive literature search to describe the problem of postoperative encephalopathy and to determine the factors that contribute to infantile post-operative encefalopathy and how to avoid or treat them. Maintaining adequate cerebral perfusion is very important, as the brain is the most vulnerable organ. All factors leading to a decreased supply of oxygen to the brain should be eliminated.
Anesthesiologists could play a major role in preventing brain injury by providing safe anesthesia. This means maintaining normal homeostasis and avoiding hypotension, hypocarbia, hyponatremia, hypoglycemia and hyperglycemia, hypo-and hyperoxemia.

Keywords: infantile postoperative encephalopathy.

Introduction

Infants undergoing surgical procedures in the first few months of life are at higher risk of death and subsequent neurodevelopmental abnormalities (1). The perioperative period in newborns and infants carries the risk of cerebral perfusion disturbances due to potential hemodynamic or metabolic derangements as a consequence of patient, surgery and anesthesia related factors. For neonates and smaller children, the organ immaturity and smaller cardiorespiratory reserves are a major factor for the increased risk. However, inexperience of care providers also contributes to a higher perioperative morbidity and mortality. Anesthetists have a limited ability to monitor the most vulnerable organ, the brain, during general anesthesia. Several studies have demonstrated an association between general anesthesia in infancy and an increased risk of poor neurobehavioral outcome. The reasons for this association are still unclear (2-5). There is concern for potential neurologic injury during anesthesia because of possible neurotoxicity of anesthetic drug and because of cerebral hypoxia-ischemia due to hypotension and hypoxia during surgery. Possible neurotoxicity of anesthetic drugs will not be discussed in this review. The main focus in this article are other risk factors and how to avoid them.

Methods

This article was written based on an extensive literature search in which we refer to human studies as well as animal studies. In this article we try to find which factors contribute to infantile postoperative encefalopathy and how to avoid or treat them. A literature search, using databases Medline and Pubmed was performed on April 2th 2021, using following search strings: "postoperative infantile encephalopathy", "anesthesia brain injury infant", "anesthesia neurologic injury infant", "intraoperative hypotension neonates", "intraoperative hypotension infants", "hypotension cerebral oxygenation infants", "intraoperative hypocapnia infants", "intraoperative hypocapnia neonates", "hypocapnia brain injury infants", "cerebral oxygenation hypocapnia infant", "cerebral oxygenation anesthesia infants", "hyponatremic encephalopathy infant",

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"intraoperative hypoglycemia infant", and "hypoglycemic encephalopathy infants" and "hyperoxia and brain injury infants". Articles about anesthetic neurotoxicity and articles about neurologic injury after cardiac or brain surgery were excluded.

Results

Hypotension/ hypertension

Hypotension during general anesthesia in infants is considered a risk factor for poor neurological outcome. Cerebral perfusion pressure depends on mean arterial pressure and intracranial pressure. During general anesthesia measuring non-invasive blood pressure (BP) is done as a standard of care. But non-invasive blood pressure monitoring can be inaccurate and there is no consensus on the lower limits for neonates and infants undergoing general anesthesia. Oscillometer BPmeasurements should be obtained by placing an appropriate size cuff around the infant's right bicep. The cuff bladder width should be approximately 40% of the arm circumference at a point midway between the olecranon and acromion (6-7). In a retrospective study, comparing non-invasive blood pressure measurements with intra-arterial measurements in term neonates under general anesthesia, investigators found a reasonable agreement for mean blood pressure. When there was hypotension or hypertension, there was a larger discrepancy between both methods (8). Hypotension in pediatric patients was defined as a systolic blood pressure (SBP) below 60mmHg or a drop of 20% below the baseline blood pressure. However, blood pressure is rarely measured before induction in infants, and so there often is no reference blood pressure (9). The PALS guidelines and the British Working Group on Perinatology recommend using gestational age in weeks as the lower limit of mean blood pressure (10). This guideline is still used as a general rule in neonatal intensive care units. It corresponds to the tenth percentile of normative values for the first 48-72 hours of life. Using gestational age in weeks as the lower limit for mean arterial pressure (MAP) works for neonates but this rule can't be applied for older infants. Another possibility would be to use the definition of shock defined by the Pediatric Advanced Life Support and American College of Critical Care Medicine. In this consensus, septic shock is defined as a systolic blood pressure (SBP) below 60 mmHg for neonates and below (2x age) + 70 mmHg for children older than one year (11). General anesthetics always cause

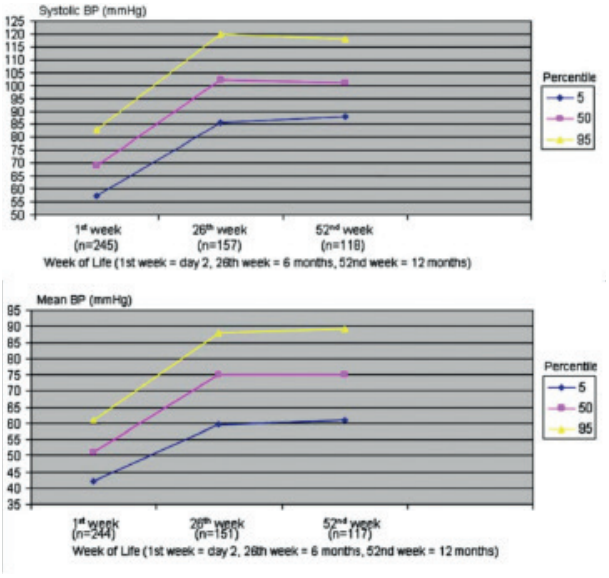

Fig. 1 & 2. — Blood pressure in the first year of life in healthy infants born at term (12).

some degree of hypotension but are thought to decrease cerebral metabolic rate and therefore also decrease oxygen demand. For infants this may not be the case. Anesthetic agents are GABA receptor agonists, which are inhibitory in the adult brain but in the developing brain may be excitatory. The switch from excitatory effect to inhibitory effect is complete around 1 year of age (12).

In a case series described by McCann et al. there were 6 infants who developed postoperative encephalopathy. In these 6 cases intraoperative mean blood pressures were lower than the gestational age but not lower than the lower limits for systolic blood pressure suggested by the Association of Paediatric Anaesthetists for infants undergoing general anesthesia. A survey of members of the SPA (Society for Pediatric Anesthesia) and the Association of Pediatric Anaesthetists of Great Britain and Ireland identified an SBP threshold value for neonates as 45.5 ± 8.5 mm Hg and 49.6 ± 8.4 mm Hg, respectively. This value is 20% to 25% below the definition of hypotension used in the PALS for awake neonates and represents a 40% to 46% drop in expected normative SBP for awake healthy neonates aged >1 week and awake preterm infants that are aged >70 days. In this case series most infants were born preterm and some had neurological problems preoperative but all 6 patients were considered neurologically stable before anesthesia (10).

In another case report Lopez et al. describe a case of postoperative neonatal encephalopathy with seizures occurring, in a term newborn, despite normal intraoperative blood pressure. There were no

episodes of hypoxemia, hypocapnia, hypoglycemia or hypotension (14).

Hypotension is very common during general anesthesia in infants and neonates but only a small number of them develop neurological problems postoperative. In a retrospective analysis Weber et al. analyzed the data of 1091 cases of infants under the age of 1 year that underwent general anesthesia. They defined hypotension as a MAP less than 35 mmHg for patients less than 6 months and a MAP less than 43 mmHg for patients older than 6 months. They found a high incidence of hypotension postinduction and during surgery especially in neonates. In the group of patients less than 1 month old the incidence was 25.5% (15).

Definition of hypotension in this study was based on the results of Rhondali et al. They studied the effects of sevoflurane anesthesia on MAP and regional cerebral blood oxygenation (rSO2) in infants under 2 years of age. Based on their results, they recommended to keep MAP above 33mmHg for infants less than 6 months old and above 43 mmHg for infants more than 6 months old (16).

A recent multicenter prospective observational study was set up to try and identify thresholds for intervention during general anesthesia in infants up to 60 weeks postmenstrual age. In 35.3% of the cases a critical intraoperative event was reported. Most of these critical events were cardiovascular problems (60%). The most important issue was intraoperative hypotension (50%). Physicians intervened when SBP was below 46.2 mm Hg or if MAP was below 32.7 mmHg (17).

In a prospective randomized controlled trial McCann et al. found that infants undergoing general anesthesia had a higher incidence of hypotension and intervention for it than infants who received regional anesthesia. In this study 722 infants undergoing inguinal herniorrhaphy were randomized to the general anesthesia (GA) or the regional anesthesia (RA) group. Although there was a higher incidence of hypotension in the GA group there was no neurocognitive difference in follow up after 2 years between both groups. The importance and consequence of transient perioperative hypotension in neonates and infants seems to be unknown (3, 18).

Lack of good definition of what hypotension in neonates and infants is and what would be the lower limits make it difficult. Maybe a more physiological approach is needed. In this approach the main focus is the brain as the most vulnerable organ. The most useful physiological definition of hypotension is the MAP at which cerebral autoregulation is lost. Cerebral blood pressure autoregulation maintains relatively constant cerebral blood flow (CBF) across changes in systemic blood pressure. When perfusion pressure is on the autoregulatory plateau, cerebral vessels dilate with decreasing blood pressure and constrict with increasing blood pressure. When blood pressure decreases further under the limit of autoregulation, there is no vasodilatory reserve anymore and CBF will decrease. At this point ischemic injury can occur. When blood pressure exceeds the upper limit of the autoregulatory curve, the vessels cannot constrict any further and hyperemic brain injury is possible (19). In preterm infants the autoregulatory plateau is very narrow. In older infants the constriction and dilatation of vessels keeps cerebral blood flow constant over a wider range of blood pressures. So preterm infants are definitely more at risk for developing neurological injury (6, 20).

In a prospective observational study Michelet et al. determined when a decrease in cerebral blood oxygen saturation of more than 20% occurred. They concluded, based on their results, that a fall in systolic blood pressure of more than 20% and a decrease of more than 15% of mean arterial blood pressure should be avoided (9).

In an observational prospective study Razlevice et al. included 43 infants. They found that a 20% decrease in cerebral oxygenation occurred in 8 patients. They observed lower NIRS values when MAP was 30 mmHg or less (21).

Olbrecht et al. included 453 infants under the age of 6 months undergoing general anesthesia for more than 30 minutes in an observational, multicenter study. Cerebral oxygenation was measured with near infrared spectroscopy. Cerebral desaturation events were defined as mild (11-20% below baseline), moderate (21-30% below baseline) or severe (more than 30% below baseline). They found that mild and moderate events occurred frequently while severe desaturation was rare. In their study low arterial pressure was very common and not well associated with low cerebral oxygenation (22). In an animal study piglets undergoing general anesthesia with sevoflurane were randomly divided in four groups: a control group, a hypotensive group, a group with hypocapnia and a combined group (hypotension and hypocapnia). The main finding was that the combination of hypotension and hypocapnia led to alteration of cerebral perfusion with signs of neuronal dysfunction and early neuronal ischemia (23).

So, anesthetists should avoid blood pressures dropping too low. But what is too low? We should

Table 1

Summary of studies regarding hypotension in infants and neonates

Study	Type	Study group	Results
Rhondali et al. 2014 (16)	Observational prospective study	- 195 children < 2 years, ASA I & II, abdominal and orthopedic surgery, effects of sevoflurane anesthesia on MAP and cerebral blood oxygen saturation	- MAP should not be bellow 33mmHg for infants < 6 months and not bellow 43mmHg for infants > 6 months
Michelet et al. 2015 (9)	Observational prospective study	- 60 infants, less than 3 months of age reductions in intraoperative systolic blood pressure (SBP) and mean blood pressure (MBP) associated with decreases in cerebral blood oxygen saturation of >20%	- A decrease of SBP of >20% or a decrease of MBP of >15% predicted a probability of cerebral desaturation of < 10% (cerebral desaturation was defined as a reduction of 20% compared to baseline)
Razlevice et al. 2016 (21)	Observational prospective study	43 infants, < 3 months of age Cerebral oxygenation monitoring with near infrared spectroscopy	- 20% drop from baseline in 18.6% - NIRS values were lower, when MAP was 30 mmHg or less
Ringer et al. 2016 (23)	Blinded randomized study	28 piglets 4-6 weeks of age undergoing sevoflurane anesthesia randomized in four groups: control, hypotension (MAP< 30mmHg), hypocapnia, hypotension + hypocapnia baseline MRI was taken, control MRI after 120min of treatment	- Hypotension + hypocapnia group: alteration of cerebral perfusion with signs of neuronal dysfunction and early neuronal ischemia - Hypotension or hypocapnia group: absence of detectable cerebral perfusion alterations but metabolic disturbances
McCann et al. 2017 (15)	Prospective randomized control trial	722 infants (less than 60 weeks post-menstrual age) undergoing herniorrhaphy randomized in regional anesthesia group and a general anesthesia group	- More hypotensive events in GA group - No difference in neurodevelopmental outcome at two years of age between GA and RA
Olbrecht et al. 2018 (22)	Multicenter observational study	453 infants, < 6 months of age, undergoing general anesthesia > 30 minutes measured regional cerebral oxygenation using NIRS mild desaturation (11-20% below baseline), moderate (21-30% below baseline) or severe (more than 30% below baseline)	- Mild and moderate cerebral desaturation occurred frequent - Low MAP not well associated with cerebral desaturation
Disma et al. 2021 (NECTARINE study) (17)	Prospective multicenter observational study	5609 infants up to 60 weeks postmenstrual age undergoing general anesthesia Identifying tresholds for medical intervention	- 35.3% critical incidents - 60% of incidents cardiovascular mainly hypotension (50%) - Intervention tresholds 46.2 mmHg for SBP and 32.7 mmHg for MAP

avoid a decrease of SBP of more than 20% or a decrease of MBP of more than 15%. In general, we don't measure blood pressure until after induction so it would be difficult to have a baseline to compare to. In a case series of 6 infants developing postoperative encephalopathy, mean arterial blood pressures were below 35 mmHg (10).

Hypocapnia

Hypocapnia is a common event that has been reported to be present in 69% of neonates during general anesthesia. Hypocapnia causes cerebral vasoconstriction and decreased cerebral blood flow. When cerebral blood flow decrease is greater than the reduction in cerebral blood volume, cerebral ischemia can occur (24). Hypocapnia increases cerebral oxygen demand and increases neuronal excitability, seizure activity and anaerobic metabolism. Furthermore, hypocapnia decreases partial pressure of arterial oxygen and decreased release of oxygen from hemoglobin. Pediatric critical care specialists are defining hypocapnia as mild (EtCO2 30-35 mmHg), moderate (EtCO2 25-30mmHg) and severe (EtCO2 < 25 mmHg). Data from neonates clearly suggest that severe hypocapnia after hyperventilation, high-frequency ventilation, and extracorporeal membrane oxygenation is associated with severe adverse neurological outcomes (25, 26). Pappas et al. used data from the National Institute of Child Health and Human Development Neonatal Research Network randomized, controlled trial of whole-body hypothermia for neonatal hypoxic-ischemic encephalopathy for a secondary observational study. They reported an association between hypocarbia in neonates with hypoxic-ischemic encephalopathy (HIE) and poor neurologic outcome at 18-22 months of age. Even mild hypocapnia was associated with adverse outcome. It is unclear whether hypocapnia

was a marker or a risk factor for poor outcome in this study (27). In a retrospective cohort study Lopez et al. found that in asphyxiated newborns treated with hypothermia, hypocapnia seemed to be causing more severe brain injury. Intubated newborns developed more severe hypocapnia. Newborns needing to be intubated were probably already sicker. However, after adjusting for baseline characteristics, in this study hypocapnia was still independently associated with an increased risk of brain injury (28). An animal study of Ringer et al. showed reduced invasively measured cerebral blood flow and brain tissue oxygenation and an increase in blood lactate during moderate and severe hypocapnia. While there were no changes in regional oxygen saturation measured with near infrared spectroscopy. Literature suggests maintaining EtCO2 between 35-45 mmHg because there is evidence of adverse outcome even in the presence of only mild hypocapnia (10, 26, 27). Some studies showed poor correlation between end tidal CO2 and arterial CO2 even in the absence of pulmonary disease (26, 29).

Study	Type	Study Group	Results
Pappas et al. 2011 (27)	Secondary Observational study	Used data from the National Institute of Child Health and Human Development Neonatal Research Network randomized, controlled trial of whole-body hypothermia for neonatal hypoxic-ischemic encephalopathy 204 encephalopathic infants, 36 weeks gestational age or older Relationship between PCO2 and outcome (18-22 months of age)	- Hypocapnia in the first hours after birth in neonates with hypoxic- ischemic encephalopathy was associated with adverse outcome (disability, death)
Lopez et al. 2019 (28)	Retrospective cohort study	198 asphyxiated newborns, treated with hypo-thermia between 2008-2014	- Group of intubated newborns had more hypocapnia - 95% of intubated newborns developed brain injury, 43% of non-intubated newborns - Newborns developing brain injury had lower PCO2
Ringer et al. 2019 (24)	Randomized control study	30 piglets randomly divided in 3 groups: moderate hypocapnia, severe hypocapnia and combined (moderate hypocapnia + hypotension) Cerebral oxygenation measured invasively and non-invasively with NIRS	- Hypocapnia was associated with a decrease in tissue oxygenation measured invasively with no changes in NIRS values

Hyponatremia

Hyponatremia is the most commonly observed electrolyte disturbance in children. The specific infant physiology, the secretion of antidiuretic hormone in the postoperative period and the administration of hypotonic fluids can cause hyponatremia. The majority of hyponatremia in hospitalized children is iatrogenic and due to the administration of hypotonic fluids and elevated arginine vasopressin levels. The most serious complication of hyponatremia is hyponatremic encephalopathy. In hyponatremic encephalopathy, hypoosmolality results in cerebral edema. This cerebral edema will cause an elevated intracranial pressure and can evoke brain ischemia. Infants and children have a higher risk of developing hyponatremic encephalopathy because they have a relatively larger brain to intracranial volume ratio compared to adults (30).

Ellouze et al. report a case of postoperative hyponatremic encephalopathy in a 10-month-old child. The probable causes in this case report were indeed the administration of hypotonic fluids and a postoperative period characterized by an increased secretion of antidiuretic hormone (31).

So use of hypotonic fluids, including Ringer's Lactate (Na < 130 mEq/L), should definitely be avoided in the peri- and postoperative period. The use of hypotonic fluids should be restricted to patients with hypernatremia (> 145 mEq/L) or patients with ongoing urinary or extrarenal free-water losses (30).

Hypoglycemia

Normoglycemia is essential for energy supply to the brain. So, maintaining normoglycemia is an important goal during anesthesia for neonates and infants.

In neonatal encephalopathy hypoxic-ischemia is the main focus for investigation but other metabolic derangement can also be the cause

Study	Type	Study Group	Results
Tam et al. 2012 (33)	Prospective cohort study	94 term neonates born between 1994-2010, at risk for encephalopathy Hypoglycemia defined as serum blood glucose of less than 46 mg/dL	- Adverse motor and cognitive outcomes at 12 months of age - Hypoglycemia associated with increased corticospinal tract injury
Mc Kinlay et al. 2015 (35)	Prospective cohort study	404 infants, with a gestational age of 35 weeks or more Treated to maintain serum blood glucose of at least 47 mg/dL	- No adverse neurological outcome at 2 years of age
Qiao et al. 2019 (34)	Prospective cohort study	157 infants born to diabetic mothers, low blood glucose within 30 minutes after birth 144 infants in control group Hypoglycemia defined as 2.6 mmol/ L (47 mg/ dL)	- Long and repeated hypoglycemia was associated with increased risk of poor adaptability

of neurologic injury. A large multicenter retrospective cohort study demonstrated a 3.9% incidence of perioperative hypoglycemia (32). In a prospective cohort study, term neonates at risk for encephalopathy, hypoglycemia was associated with additional risks in the setting of neonatal encephalopathy with increased corticospinal tract injury and adverse motor and cognitive outcomes at 12 months of age (33). Qiao et al. concluded that long and repeated neonatal hypoglycemia affected neurodevelopment and was associated with a higher risk for poor adaptability (34). In a large prospective cohort study 528 neonates, at risk for hypoglycemia, were treated to maintain a blood glucose concentration no lower than 47 mg/dL.

After 2 years neurocognitive function was assessed. This study concluded that 47 mg/dL was a safe threshold for treatment as there was no association between neonatal hypoglycemia and neurological impairment (35). Avoiding long fasting intervals is important for young children. Children are more sensitive to fasting than adults due to smaller stores of glycogen in liver and muscles. The younger the child, the faster hypoglycemia and ketogenesis will develop (36, 37).

Hypoxia/Hyperoxia

Hypoxia must be avoided at all times but we also must avoid hyperoxia as it generates oxygen free radicals (38, 39).

An excess of oxygen causes the formation of reactive oxygen intermediates that cause DNA damage. Several clinical and experimental observations have shown that hyperoxia can be a trigger of brain injury especially in preterm neonates who have reduced antioxidant defense systems compared to term neonates (39, 40). The optimal target for oxygen saturation would be 90-94% in preterm infants. The risk for serious oxygen toxicity from high oxygen saturation is less in term infants. Higher levels of oxygen saturation can be tolerated in the term infants (40-42). In a retrospective cohort study of Klinger et al. outcomes of 218 infants with post-asphyxia hypoxic ischemic encephalopathy were studied. In this study an associating was made between severe hyperoxemia (PaO2 >200mmHg) and adverse outcome. With the worst outcome when associated with severe hypocapnia (PaCO2< 20mmHg) (43).

Discussion

Infants undergoing general anesthesia early in life seem to be developing more neurodevelopmental abnormalities. Although, the reasons for this association remain unclear, there are several modifiable risk factors for neurological injury. Maintaining adequate cerebral perfusion is a key factor. Hypotension and hypocarbia can lead to decreased cerebral perfusion. Safe lower limits for blood pressure are still up for debate. Studies proved that a decrease in SBP of more than 20% and a decrease of MBP of 15% from baseline lead to a decrease in rSO2 of more than 20% (9, 19-21). The significance of short hypotensive periods is still unclear. Blood pressure is rarely measured before induction of anesthesia, so comparing to baseline values would be difficult. We would rather recommend, using lowest mean arterial pressures during anesthesia. Lowest tolerable mean arterial blood pressure would be 30-35 mm Hg for neonates and for infants 40-50mm Hg (44).

NIRS is used for high-risk procedures or infants and neonates at risk for developing neurologic injury. So far there is not sufficient evidence for routine use of NIRS during general anesthesia. NIRS only provides information about a small part of the

brain so local ischemia will be missed Hypotension can cause cerebral hypoperfusion and should be treated by fluid bolus and vasoactive medication after exclusion of other causes. Hypovolemia is a common cause of hypotension during surgery and can be corrected with fluid boluses. Overcorrection should be avoided because the neonatal heart has a limited ability to react to an increase in preload.

Hypocapnia causes cerebral vasoconstriction and therefore also can cause decreased cerebral perfusion. A prospective, randomized control trial showed that even mild hypocapnia (ETCO2 30-35mmHg) in infants with neonatal encephalopathy led to poor outcome. It would be wise to maintain EtCO2 within normal range (35-45mmHg) and definitely avoid severe hypocapnia (24-26).

A pitfall could be that EtCO2 isn't always well correlated with arterial CO2 even in the absence of severe lung disease. In high-risk patients (very premature infants, infants with severe lung disease) arterial gas measurements of CO2 should be performed (1).

Metabolic disturbances can also cause cerebral injury. In case of hypoglycemia and hypoxia metabolic demand is not fulfilled. Maintaining normoglycemia is important. Hypoglycemia can also be caused by very long fasting times. For preoperative fasting the 6-4-2 rule should be followed. This means 6 hours for solids, 4 hours for breastfeeding and 2 hours for clear fluids. In studies there was no difference in gastric content 4 or 6 hours after a light meal. For clear liquids there was no increase in pulmonary aspiration if they were given less than 2 hours preoperative (37, 44). Hyponatremia leads to cerebral edema and this will also cause neurologic injury.

Hypotonic fluids have to be avoided in the peri-and postoperative period (30).

Cerebral injury can also occur because of the production of neurotoxic mediators from hypoxia, ischemia and reperfusion as well as from free radicals caused by hyperoxia. Especially in preterm infants maintaining an SpO2 of 90-94 seemed to be safe without increasing the risk of injury. In term infants' higher levels of SpO2 are safe (38-43).

Conclusion

In conclusion we can say that infants and especially neonates undergoing general anesthesia might have an increased risk for developing neurological injury. So careful perioperative monitoring of vital signs and cerebral perfusion should be mandatory in this population. The etiology and timing of brain injury remains unclear and further investigation and long-term follow up studies will be necessary. Although there are many nonmodifiable risk factors, like the infant or neonate underlying condition, anesthesiologists could play a major role in preventing injury by providing safe anesthesia. This means maintaining normal homeostasis and avoiding hypotension, hypocarbia, hyponatremia, hypoglycemia and hyperglycemia, hypo-and hyperoxemia.

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