Published in final edited form as:
Curr Drug Targets. 2012 June ; 13(7): 944–951.

General anesthetics in pediatric anesthesia: Influences on the developing brain

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Keywords

neonate; anesthesia; neurotoxicity; neuroapoptosis; neurocognition

Introduction

Millions of newborn and infants receive anesthetic, sedative and analgesic drugs for surgery and painful procedures on a daily basis. Immature neonatal organ systems (cardiovascular, central nervous and respiratory) are highly sensitive to the depressant effects of anesthetic drugs, which translates to more than a 10-fold increase in perioperative morbidity and mortality in neonates when compared with other pediatric age groups [1]. However, recent laboratory reports clearly demonstrate that anesthetic and sedative drugs induced both neuroapoptosis and neurocognitive deficits in laboratory models. This issue is of paramount interest to pediatric anesthesiologists and intensivists because it questions the safety of anesthetics used for fetal and neonatal anesthesia [2, 3]. In an attempt to summarize the rapidly expanding literature on anesthetic-induced developmental neurotoxicity (AIDN), this review will examine published reports on the characterization, mechanisms, alleviation and clinical significance of this laboratory-based phenomenon.

Laboratory Findings

The developing central nervous system is exquisitely sensitive its internal milieu. Normal brain development involves neurogenesis and synaptogenesis and immature neurons that do not make synaptic connections are considered redundant and are physiologically pruned by apoptosis or programmed cell death. Since neuroapoptosis a normal part of the sequence of neuronal development, it is not surprising that the all animals studied thus far have demonstrated a critical time of vulnerability to the effects of anesthesia. In general, the time of maximal injury to cells seems to occur during the period of rapid synaptogenesis or when the brain is growing most rapidly [4]. This time frame varies from species to species with

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rats demonstrating vulnerability from postnatal day 1 through postnatal day 14 with a peak at postnatal day 7 in rats [5]. Non-physiologic exposure to various drugs and stressors (painful stimuli, maternal deprivation, hypoglycemia, hypoxia and ischemia) during this critical window, can also lead to neurodegeneration. The time frame of neurodevelopment varies among mammalian species and correlates loosely with the period of rapid brain growth which in turn correlates with the life span of the organism [6]. Previous reports have clearly demonstrated that anticonvulsant drugs and ethanol accelerate this normal “pruning” or apoptotic process[7, 8]. Profound disruption of this process by these neurotoxins can lead to CNS developmental abnormalities and even fetal death in humans [2]. These findings have been equated to the recent reports of AIDN mediated by N-methyl-D-aspartate (NMDA) antagonists and g-aminobutyric acid (GABA) agonist drugs in laboratory animals and raised questions about the long-term safety of general anesthetics given to human infants.

Characterization

Fetal and neonatal exposure to *N*-methyl-D-aspartate (NMDA) antagonists and γ-aminobutyric acid (GABA) agonist drugs leads to accelerated neurodegeneration. Since the immature brain undergoes some degree of neurodegeneration by apoptotic processes as part of normal development and the initial response from the scientific community was that anesthetic and anticonvulsant drugs and ethanol accelerate this normal “pruning” or apoptotic process. However, this notion was dismissed by a report that demonstrated both decrements histological parameters and behavioral and locomotor performance, in mature rodents that were exposed to these drugs during infancy [9, 10]. Nonhuman primates are most vulnerable from post conception day 122 through postnatal day 5 with no cell death demonstrated by postnatal day 35 [11]. Ketamine- and propofol- treated primary neuronal cell cultures exhibited blunted dendritic growth and arborization[12, 13]. Isoflurane also reduced dendritic spines in neonatal mice [14]. Several studies have shown that there are anesthetic induced effects occurring in juvenile animals beyond the period of synaptogenesis and may broaden the window of potential deleterious effects for humans beyond the period of peak brain growth that ends about age three[15, 16]. Although neuronal cell death and changes in dendritic arborization did not occur in juvenile rodents exposed to both injectable and inhaled anesthetics, these drugs increased dendritic spine density [17–19]. It is unknown whether these changes are permanent or what they portend. There is also evidence of decreased neurogenesis occurring after the period of peak synaptogenesis. Neuronal precursor cells derived from neonatal, not aged, rats have a reduced capacity to proliferate in the presence of isoflurane [16]. Taken together, these findings demonstrate age-specific effects of anesthetic exposure have the potential to regulate synaptic modeling and plasticity.

The period of vulnerability to AIDN for humans is unknown and the subject of much debate among neuroscientists. The period of maximal brain growth in humans occurs in the last trimester of gestation through age 3 years and many in the field believe this time period to be the period of vulnerability [4]. However, efforts to determine the point of maximum susceptibility for humans have also been addressed using neuroinformatics, an analysis that combines neuroscience, evolutionary science, statistical modeling and computer science and this analysis reveals that the maximal point of vulnerability for humans may be at 17–20

weeks postconception or in the end of the midtrimester of gestation[20, 21]. The infomatic models are bolstered by epidemiologic work examining the most ethanol-sensitive times for the human conceptus using data from seasonal alcohol consumption and determining lag times. This data suggest that the human fetus is most sensitive to Fetal Alcohol Syndrome during the 18^{th} to 20^{th} week postconception [22]. Ethanol has both NMDA antagonist and GABA agonist properties which make it an extremely potent neurotoxin to juvenile animals and Fetal Alcohol Syndrome may be one of the human manifestations of toxic neuroapoptosis [8]. So although the period of maximal vulnerability has been determined for several mammalian species, there are still great uncertainties about this period in humans.

NMDA receptor antagonists

Ketamine—Ketamine-induced neuroapoptosis has been extensively investigated in mice, rats and rhesus monkeys with the maximal effect occurring during the period of peak synaptogenesis. Postnatal day 7 (P7) rat pups that are given doses of 20–25 mg/kg every 90 minutes for at least 7 doses show evidence of neurotoxicity while rats given the same doses for 4 or less times did not [5, 23, 24]. However, single doses of ketamine of greater than 10 mg/kg neuroapoptosis and impaired learning ability in P7 mice when they are tested as adults [25, 26]. This contrasting finding reflects the interspecies variability that prevails in these comparative studies [27]. Rhesus monkeys also developed increased neurodegeneration when exposed to ketamine on their last trimester and day 5 of life for a 24-hour period, but not on day 35 of life [11]. The dose of ketamine utilized in these investigations is roughly 10 times the amount needed to sedate humans and resulted in almost 10 times the therapeutic levels of ketamine in humans[11]. AIDN only occurred in the prolonged exposure group. This 24 hour exposure to ketamine resulted in decrements in aspects of learning, motivation, color discrimination, and short-term memory [28]. These findings confirmed that ketamine-induced neurotoxicity is both dose and duration dependent. Ketamine induced neurodegeneration is amplified when the ketamine is combined with a GABAnergic agonist agent such as thiopental or propofol in mice. Mice given a single dose of ketamine 25 mg/kg subcutaneously on day 10 did not demonstrate any neurodegeneration but when the ketamine was combined with either thiopental 5 mg/kg or propofol 10 mg/kg there was increased neurodegeneration and impaired learning in adult mice [10]. Anesthetic drugs have intrinsic neuroprotective effects. Anand and colleagues examined the effect of low (sedative) dose ketamine on P-7 rat pups subjected to repetitive inflammatory pain which accentuates neuronal excitation and cell death in developmentally regulated cortical and subcortical areas. Subanesthetic doses of ketamine attenuated cell death and provided some degree of neuroprotection [29].

Nitrous Oxide—Exposure to 6 hours of nitrous oxide has been shown to induce increased capsase-3 expression in the infant mouse but not in the infant rat[9, 30]. It has also been found to significantly increase the degree of neuroapoptosis in neonatal rat pups and neonatal mouse hippocampal cultures exposed to isoflurane[31]. A salutary effect of nitrous oxide is that it may decrease the necrotic cell death found in juvenile animals exposed to hypoxic-ischemic injury [32].

GABAnergic Agonists

Commonly used sedative and anesthetic drugs are primarily GABA agonist and mediate AIDN. Benzodiazepines, barbiturates, ethanol, propofol and volatile anesthetics have all been implicated in causing accelerated neuroapoptosis. In general, apoptosis caused by GABAnergic agents occurs in different locations of the brain than the apoptosis from NMDA antagonistic agents. GABA is an inhibitory agent in mature animals but in immature animals it is an excitotoxic agent that may be a potential mechanism of toxicity of GABAnergic agonists [33].

Benzodiazepines—Preclinical data on benzodiazepine administration appears to be species specific with neonatal mice being more susceptible to the effects of benzodiazepines than neonatal rats. Young mice given a single dose of diazepam 5 mg/kg developed increased neurodegeneration although these mice later did not develop neurocognitive behavioral deficits [34]. No effects on neonatal rats were found until the diazepam dose was increased to 10 mg/kg [7]. Similar findings were demonstrated with midazolam with mice being susceptible to a dose of 9 mg/kg but rats were not [9, 26]. Single doses of clonazepam, and diazepam are associated with increased neurotoxicity when given to neonatal rats intraperitoneally or subcutaneously [7, 34]. So single dose toxicity to a variety of benzodiazepines has been seen in both rats and mice.

Barbiturates: There is evidence in neonatal rats that both pentobarbital 5–10 mg/kg and phenobarbital 40–100 mg/kg leads to increase apoptosis [7, 35]. However, thiopental given to neonatal mice in a dose of 5–25 mg/kg did not lead to neuroapoptosis [10]. The toxicity from pentobarbital and phenobarbital was ameliorated by the simultaneous administration of estradiol. Estradiol is believed to increase intracellular concentration of extracellular signal regulated kinase (ERK) and protein kinase B thereby shifting the balance within the cell towards survival[7, 35].

Propofol—Exposure of 50–60 mg/kg intraperitoneally will lead to increases neuroapoptosis in neonatal rats and mice even though this is a subanesthetic dose for these animals [36]. In addition, animals exposed to the above dose also demonstrate functional impairments when they are mature.

Volatile agents—Volatile anesthetics are primarily GABA agonists with some NMDAPrenatal exposure to either halothane or enflurane for only one half hour prenatally was associated with learning deficits in mice. Rats demonstrated the same findings when they were exposed to halothane prenatally for 2 hours [37]. In addition, prolonged exposure to subclinical doses of halothane is associated with decrease dendritic numbers and synaptic density in rats[38, 39].

Postnatal exposure to isoflurane exposure in young rats and mice has been found to lead to increased apoptosis in a dose and duration dependent manner. The time of exposure in mice is at least 4 hours of 0.75% before there is evidence of neurotoxicity as demonstrated by increased capsase 3 and 9 activation[9, 16, 31]. The toxic effects of isoflurane are potentiated by the concomitant exposure to midazolam and nitrous oxide. The combination

of isoflurane, midazolam and nitrous oxide has also been shown to increase neuroapoptosis in guinea pigs[40].

Even a subclinical 2 hour exposure to sevoflurane will increase neuroapoptosis in neonatal mice as measured by increased caspase 3 activation. A six hour exposure to sevoflurane in neonatal mice is associated with increase neuro-apoptosis and abnormal social and learning behaviors [41].

Mechanisms

Several possible mechanisms of anesthetic neurotoxicity in the developing mammalian brain have been determined using *in vitro* and *in vivo* studies. Therefore, an examination of the mechanisms involved in AIDN is paramount in the development of strategies of ameliorating these problems and determining if it is clinically relevant. Anesthesia removes the input and suppresses normal neural traffic. Lack of physiologic activation of neuronal populations by anesthetic drugs decreases synaptogenesis and cell-to-cell interaction. Several potential mechanisms have been proposed that result in activation of apoptotic signally pathways.

Apoptosis differs from necrotic cell death in that it is non inflammatory in nature and generally involves single scattered cells rather than groups of cells. Morphologically, apoptosis differs from other types of cell necrosis in that the outer cell membrane remains intact and does not “leak out” cellular contents therefore limiting the amount of inflammatory response by the organism. The signals to create synapses and form normal neuronal circuitry are influenced by external cues and alterations in the extracellular environment such as medications can amplify these normal neurodegenerative processes. Most of the common general anesthetics, sedatives and some anticonvulsants have been implicated as neurotoxins when given to immature non-human mammals. These agents are believed to alter synaptic transmissions involving the GABA or NMDA receptors and lead to an increase in the level of apoptosis causing an abnormal loss of neurons. The final common pathway is mediated by the caspase enzyme system in the cytosol [30]. The two main pathways to apoptosis involve the extrinsic pathway-which is a death receptor mediated pathway and the intrinsic which is mitochondrial dependent pathway [42].

The extrinsic pathway involves the activation of Fas, a cell membrane protein receptor which activates the procaspase 8 and initiates the caspase cascade. Tumor necrosing factor or TNF is another known death receptor protein which can form a ligand known as the TNF related apoptosis inducing ligand or TRAIL. Trail can also activate the caspase cascade by associating with Fas.

The intrinsic pathway involves anesthetic drugs or other toxins, which cause an increase in the mitochondrial membrane permeability that leads to a release of cytochrome C into the cytosol and activation of the caspase-signaling pathway. It is believed that anesthetic drugs cause the increase in mitochondrial permeability by the involvement of the Bcl-2 proteins, in particular, the Bax proteins. This system is activated relatively quickly (within 2 hours of exposure to anesthetic drugs). Melatonin has been found to decrease the release of cytochrome c to the cytosol and therefore decrease the degree of apoptosis [30, 43].

Prolonged antagonism of the NMDA receptor by ketamine results in upregulation of the NR1 subunit and accelerated neurodegeneration of the NMDA receptor in rodent and monkey primary neuronal cell cultures. Upregulation of the NMDA receptor by prolonged exposure to ketamine potentially leads to increase Ca^{2+} influx into the neuron. This leads to oxidative cell death by activation of both apoptotic and necrotic cell death pathways [44]. Experimental models of neurodegeneration have also implicated cell cycle–related proteins and cell cycle reentry as a potential mechanism for apoptotic cell death of the primary neurons. Ketamine has been shown to activate aberrant cell cycle reentry death pathway [45]. Prolonged exposure to isoflurane and nitrous oxide modulates brain derived neurotrophic factor (BDNF) and AKT signaling and activates both the intrinsic and extrinsic apoptotic cell death pathways [30, 46]. Isoflurane activates the $p75^{NTR}$ receptor, reduces dendritic filopodial spines and induces neuronal apoptosis. Blockade of this pathway attenuated AIDN *in vitro* [14] It is important to realize that anesthetic neuroapoptosis has also been shown to effect the spinal cord as well as the brain. Isoflurane, nitrous oxide, ketamine but not morphine have caused apoptosis in the dorsal horn of the spinal column [47–50].

Specific drugs have intrinsic neuroprotective effects and provide insight into to developing strategies to protect the developing brain from the potentially damaging effects of anesthetic drugs. The objective is to alter the balance of pro and anti-apoptotic factors within the cell and thereby ameliorate the effects of general anesthesia by tipping the balance in favor of the anti-apoptotic (prosurvival) factors such as the Bcl proteins [42].

Estradiol

17 beta estradiol but not 17 alpha estradiol ameliorates neuro-apoptosis in infant rats. This compound does not alter GABA or NMDA currents in hippocampal neuronal cultures, indicating that direct modulation of neurotransmitter receptor/channel properties by this compound cannot explain neuroprotective effect. It does increase the intracellular levels of phosphorylated extracellular signal-regulated kinase 1/2 and AKT, suggesting that activation of these prosurvival proteins may represent one mechanism for its neuroprotective action [7, 35, 51].

Melatonin

Both the intrinsic and extrinsic pathways of apoptosis can activate the mitochondria to release cytochrome c to potentiate the caspase enzymes leading to cell death. Methods of stabilizing mitochondrial membranes in theory should lead to less apoptosis. It has been demonstrated that melatonin in 7 day old rats decreases apoptosis in both the cerebral cortex and anterior thalamus. It is believed that this neuroprotection was mediated at least in part by upregualtion of the anti-apoptotic protein bcl-X(L) which leads to a reduction in cytochrome C release [43].

Xenon

Xenon gas which is a N-methyl D apartate antagonist like nitrous oxide may decrease the neuro-apoptosis induced by isoflurane in both rat and mice pups[52]. While nitrous oxide

potentiates the neuro-apoptosis seen in rat pups anesthetized with isoflurane, xenon when administered with isoflurane reduces the degree of apoptosis seen[31]. Although xenon did not induce apoptosis in rat pups when given as a solitary agent, it did induce apoptosis in mice pups[52]. The mechanism of the neuroprotective function of xenon in attenuating isoflurane-induced apoptosis is unknown at this time.

L-Carnitine

L-Carnitine also acts as a mitochondrial membrane stabilizer. It decreases the expression of the pro-apoptotic proteins from the Bax family and slightly increases the expression of the prosurvival family of Bcl-X (L). In 7 day old rat pups exposed to both isoflurane and nitrous oxide for 6 hours the co-administration of L-carnitine intraperitoneally effectively protected neurons from anesthetic induced damage[53].

Lithium

Both ethanol and anesthetic drugs cause neuro-apoptosis which is preceded by suppressed phosphorylation of extracellular signal-regulated protein kinase (ERK). This suppression is conteracted by lithium in 5 day old mice pups who were anesthetized with propofol, ketamine or a combination of the two. In addition, the neuro-apoptotic action of these anesthetic drugs was counteracted [54].

Dexmedetomidine

Because alpha2 adrenoreceptor signaling plays a trophic role during development and can be neuroprotective in some settings investigators have studied the effects of dexmedotomidine in ameliorating the neuronal damaging effects of isoflurane.

In both in vitro and in vivo experiments with 7 day old rat pups, dexmedotomidine has been shown to attenuate but not eliminate apoptotsis due to isoflurane[55, 56]. Isoflurane was shown to decrease the Bcl-2 and pERK protein expression which was reversed by dexmedetomidine treatment. And in functional experiments, isoflurane induced long-term memory impairment in 7 day old rat pups was prevented by the concomitant administration of dexmedetomidine, which also inhibited isoflurane-induced caspase-3 expression in organotypic hippocampal slice cultures in vitro.

Hypothermia

Rat pups exposed to moderate hypothermia (29 degrees Celsius) showed no neuroapoptotic response to isoflurane and ketamine compared with controls [57]. Of interest, the amount of neuroapoptosis seen was approximately half that of normothermic control pups suggesting that hypothermia also suppressed the rate of spontaneous neuroapoptosis. It is unknown whether suppressing the rate of normal developmental neuroapoptosis has adverse effects on rat pups.

Dexmedetomidine

Dexmedetomidine is an α-2 selective adrenergic agonist with sedative, anxiolytic and analgesic properties and is used as a general anesthetic adjunct and sedative. These receptors located primarily in the locus ceruleus which when activated cause sedation and anxiolysis, the spinal cord which when activated cause analgesia and the autonomic nerves which when activated cause hypotension. The primary action of the alpha 2 receptors of the heart are chronotropic causing bradycardia, and dexmetetomidine causes a dose dependent decrease in heart rate. Dexmedetomidine is FDA approved for adult use and there is a paucity of literature on its use in neonates and infants. It is not associated with neuro-apoptosis in murine studies and may attenuate the apoptosis seen with isoflurane [56]. However because in neonates the cerebral autoregulatory capacity is limited, and thus hypotension is not well tolerated, dexmedetomidine not be a great choice for general anesthesia. In addition, there are case reports of sustained severe hypertension in young children given glycopyrrolate to counteract bradycardia[58].

Narcotics

Opioids in general are considered less likely to cause neuroapoptosis than other sedatives and general anesthetics. However, experiments in adult rats made tolerant to morphine reveal that there is activation of the caspase enzyme system thus indicating apoptosis[59]. There is not much literature looking specifically at the apoptotic potential of opioids in the developing brain. There is a report of ketamine but not morphine being associated with neuro-apoptosis in the rat pup spinal cord[48, 49]. There are several reports of neuro-apoptosis in the developing brain of animals exposed to nociceptive stimuli, which was attenuated by ketamine leading researchers to believe that pain is a potent cause of neuro-apoptosis possibly mediated by the Il-1b family of inflammatory proteins[29, 60]. Narcotics given in anti-nociceptive doses have not been associated with neuro-apoptosis in the spinal cord of rat pups.

Local Anesthetics

Local anesthetics are associated with both early apoptotic neuronal cell death and late necrotic cell death in a dose dependent manner. A study of rat neuron cells derived from the dorsal ganglion of P7 rat pups revealed that the earliest manifestations of lidocaine neurotoxicity were complete loss of mitochondrial membrane potential, followed by release of cytochrome c into the cytosol at a concentration and caspase activation. Another experiment found that many local anesthetics investigated were neurotoxic at concentrations observed intrathecally after spinal anesthesia in humans [61]. The *in vitro* toxicity of the local anesthetics correlated with their octanol/buffer partition coefficient and thus from a study examining a cell line derived from human neuroblastoma cells their relative clinical potency with the following order of apoptotic potency from high to low toxicity (tetracaine > bupivacaine > prilocaine = mepivacaine = ropivacaine > lidocaine > procaine = articaine) [62]. The neuroapoptotic potential of either ketamine or bupivacaine administered intrathecally to P7 rat pups revealed apoptosis in the ketamine but not the bupivacaine-exposed rats.[48, 50]

Human Data

There are several difficulties in extrapolating the results from rat and small mammal studies to the human population. In many of the animal studies, there has been a high mortality of the rat or mice pups while under anesthesia-a finding, fortunately, not found with human anesthetics. The reasons for this are clear; it is simply impossible to monitor the health of these tiny neonatal animals as well as even the most premature human infants. Several studies have tried to address this confounder with measuring serum glucoses and venous gases perioperatively (need reference). In addition, there is no certainty about when the time of potential vulnerability in humans would occur.

There are other formidable hurdles to adequately studying the issue of anesthetic toxicity in human infants. In general, the need for surgery or radiologic imaging studies in human infants is associated with underlying pathology so prospective cohort studies or retrospective epidemiologic studies can be confounded by this underlying pathology. In addition, the traumatic effects of surgery such as perioperative fasting, transport, hypothermia, hemodynamic instability, and stress response secondary to surgical stimulus may independently affect neurologic outcomes. The magnitude of these effects of these confounders on eventual neurocognitive outcomes may mask any subtle deleterious effects that general anesthesia may cause in humans.

Prenatal Human Exposure to General Anesthesia

In a study of 159 Japanese full-term infants, those that were exposed to nitrous oxide during the last stages of delivery had statistically significant increase in neurologic sequelae at postnatal day 5 compared with infants that were not exposed to anesthesia [63]. These sequelae included weaker habituation to sound, stronger muscular tension, fewer smiles and resistance to cuddling.

An epidemiologic study based on a birth cohort from Olmstead County in Minnesota found that children exposed to general anesthesia for caesarean section deliveries are not more likely to develop learning disabilities than those born of vaginal deliveries[64]. However, the risk of learning disabilities was lowest in the group of children who were born by caesarean section whose mothers received regional anesthesia. One of the limitations of this study is that it involved two different modes of delivery. A separate study, using this same data base found that there was no impact of neuroaxial labor analgesia on the incidence of childhood learning disabilities [65].

Neonatal and Young Childhood Human Exposure to General Anesthesia

There are many studies which report an association between surgery at a young age and poor neurodevelopmental outcome but in most of these studies the primary exposure examined has been surgery not general anesthesia. In the Victorian Infant Collaborative Study Group, it was found in a case control study of infants born less than 27 weeks post conception that those infants that had PDA ligation, inguinal hernia repair, GI surgery, neurosurgery and tracheotomy was an increased incidence of cerebral palsy, blindness, deafness and WPPI<3 SD below the mean [66]. Another study involving almost 4000 extremely low birth weight

infants found that there was a higher incidence of CP and lower Bayley Scales of Infant Development 2 scores in patients who had been treated surgically for Necrotizing Enterocolitis (NEC) compared to those treated with treated with peritoneal drainage [67]. This finding was corroborated in five other smaller studies[68–72]. However it was found that in infants with isolated tracheo-esophageal fistula repaired at birth when tested in late childhood did not have statistically different IQ measurements compared with the general population [73, 74]. One difference between this study and the NEC studies is that the postconceptual age of the TEF patients was greater. Multiple outcome studies in children who have had cardiac surgeries as neonates have demonstrated increased incidence of cerebral palsy, lower IQs, speech and language impairment and motor dysfunction [75–83]. A prospective randomized trial comparing surgery for transposition of the great vessels followed 155 patients and did neurologic assessments at age 1, 2.5, 4 and 8 years of age found that the although the mean scores for most outcomes were within normal limits, the neurodevelopmental status of the cohort as a whole was below expectation including academic achievement, fine motor function, visual spatial skills, working memory, hypothesis generating and testing, sustained attention and higher-order language skills [75–77].

Most of the studies done in these infants were case control or cohort studies rather than randomized control trials. Thus, there were many possible confounding variables that may have impacted on the neurologic outcome measures. The degree of presurgical morbidity may be one of the reasons that some infants had surgery for PDA and necrotizing enterocolitis rather than medical therapy. In children undergoing inguinal herniorrhaphies, a possible confounder might be a complicated respiratory neonatal course which has been linked to both a higher incidence of inguinal hernias and to poorer neurologic outcomes [84]. Also the effects of surgery in these studies cannot be separated from the effects of general anesthesia. Neonates often during transport to the operating rooms and during surgical procedures receive increased inspired oxygen which can be another source of neurotoxicity [85]. In the elderly, the inflammatory response activated by the trauma of surgery can accelerate neurodegenerative disease [86, 87]. It is unknown if the surgical inflammatory response leads to long-term neurologic development issues in children.

Recently there has been interest in epidemiologic studies designed to determine whether general anesthesia is associated with learning disabilities. In a large retrospective cohort study of 5357 children, 593 patients were identified as having one or more general anesthetics before age four [88]. This study found that there were significantly more reading, written language and math learning disabilities in children who had been exposed to 2 or more general anesthetics but no increase in disabilities in those children who had been exposed to a single anesthetic. The risk of learning disabilities also increased with the cumulative duration of the general anesthesia. In another epidemiologic study, a birth cohort of 5000 patients was identified from the New York State Medicaid billing codes [89]. Of this group, 383 patients underwent inguinal herniorraphy at a young age. After controlling for gender and low birth weight, the authors found nearly a two-fold increase in developmental and behavioral issues. A pilot study to test the feasibility of using a validated child behavior checklist in 314 children who had urologic surgery, it was determined that there was more disturbed neurobehavioral development in children who underwent surgery

prior to 24 months compared with those who underwent surgery after 24 months of age although the differences between the 2 groups were not statistically significant [90]. These studies are provocative but the data does not reveal whether anesthesia itself may contribute to developmental issues or whether the need for anesthesia is a marker for other unidentified factors that contribute to these.

Several retrospective reports have positively linked exposure to general anesthesia. A recent abstract presented at the FDA IARS Safekids symposium in 2010 found that children ages 7–17 who had undergone inguinal hernia repair, pyloromyotomy or circumcision as infants had double the incidence of scoring below the 5th percentile in the Iowa Test of Basic Skills (Personal communication Thomas 2010). Another epidemiologic study from the New York State Medicaid Data set examined the developmental behavioral outcomes of 304 children with no risk factors for neurodevelopmental difficulties exposed to anesthesia before age 3 and compared them with a cohort of 10,450 siblings and found a 60% greater incidence of developmental or behavioral problem in children exposed to general anesthesia [91].

In contrast to these findings, at least two other large studies have shown no association between receipt of general anesthesia and academic performance. A very large epidemiologic study comparing the academic performance of 2689 children who had undergone inguinal herniorrhaphy in infancy to a randomly selected, age matched control 5% population derived from the Danish Civil Registration System from 1986–1990 found that after adjusting for known confounders, there was no statistically significant difference between exposure and control groups [92]. A similar finding was reported in a Mayo cohort study, which found no increase in learning disabilities in children exposed to a single anesthetic[88]. Bartels et al from the Netherlands also found no difference in the educational achievements of1143 identical twins who were discordant in their exposure to general anesthesia [93].

Conclusion

In light of the reports detailing the anesthetic-induced neurodegeneration and learning deficits, should anesthetic, analgesic and sedative drug be withheld, again, from neonates undergoing surgery and painful procedures? Certainly, no parent or anesthesiologist/ intensivist would allow neonates or pregnant mothers to be exposed to a neurotoxin. Furthermore, methodological issues make the interpretation of results in rats questionable in the setting of the administration of anesthetic drugs to humans.40 The mechanism of anesthetic action has not been fully interrogated and most likely affects several signaling pathways.41 Therefore, uncovering the toxic effect of anesthetics on the developing CNS will involve a multitude of factors as well. Since a clinical manifestation or phenotype of anesthetic-induced neurodegeneration has not been identified, clinicians should continue administering but anesthetics during surgery and painful procedures in pediatric patients. However, the irrefutable findings in the neuroscience literature should prompt clinicians to be more aware of this issue and develop clinical studies to interrogate the potential long-term neurological sequelae of anesthetics.

Acknowledgments

This work was supported by the CHMC Anesthesia Foundation

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