

Neurotoxic Treatments in the Newborn Period

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ABSTRACT

The neurotoxic substances might cause damage to neuronal tissue by altering the normal activity of the nervous system which could eventually disrupt or even kill the neurons. Fetal and neonatal life is very sensitive period because of the active brain development that could be easily affected by endogenous or exogenous factors. Many pregnant women and newborn infants receive some treatments because of their clinical conditions which may impair or disrupt the developing brain of the newborn. Therefore, clinicians should be aware of potential adverse effects of the certain medications which may cause permanent long term sequela.

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Key words: Brain; Drugs; Glutamate; N-methyl-D-aspartate receptors; Fetus; Newborn infant; Neurotoxicity; Neurodevelopment

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REVIEW

Neurotoxicity is defined as the alteration of the normal nervous system activity in an unfavorable manner by endogenous or exogenous substances. Examples of such endogenous molecules include glutamate, bilirubin, nitric oxide, histamine, while alcohol or carbon monoxide represents exogenous insults. Such alterations in the neurons are sometimes not limited to functions, but also involve the anatomy, i.e. the cell structure, of the neurons. The term “neuronopathy” refers to the death (necrosis or apoptosis) of the neuronal cell, and a dead neuron cannot be replaced by new neurons. Types of neurotoxicity other than neuronopathy include axonopathy, myelinopathy, or blockade of the neurotransmission. The duration and intensity of exposure to neurotoxic insult has a significant role on the outcome of the toxic effect. Most of the neurotoxins act by impairing the voltage-dependent ion channels (sodium, potassium, and calcium channels)^[1,2].

During the quick brain development phase in newborns, susceptibility of the immature brain to the noxious effects of neurotoxic agents is more marked due to the presence of significant synaptogenic activity. Experimental studies in animals have shown that general anesthetic agents may be potentially toxic for the developing brain. Exposure to anesthetic agents may cause neurodegeneration through induction of apoptosis and impaired neurogenesis at a critical stage of neurodevelopment, potentially leading to a significant impact on the neurocognitive functions in later life^[3-7]. Therefore, neurotoxicity should be considered as a significant potential drug-related side effect in susceptible populations, such as premature infants and pregnant women.

Despite their role in neuronal tissue physiology and synaptic plasticity, N-methyl-D-aspartate (NMDA)-type glutamate receptors, under certain circumstances, may be associated with acute or chronic neurotoxic effects (Figure 1)^[8]. In a multitude of neuropathological conditions, NMDA receptors are the foremost mediators of neuronal

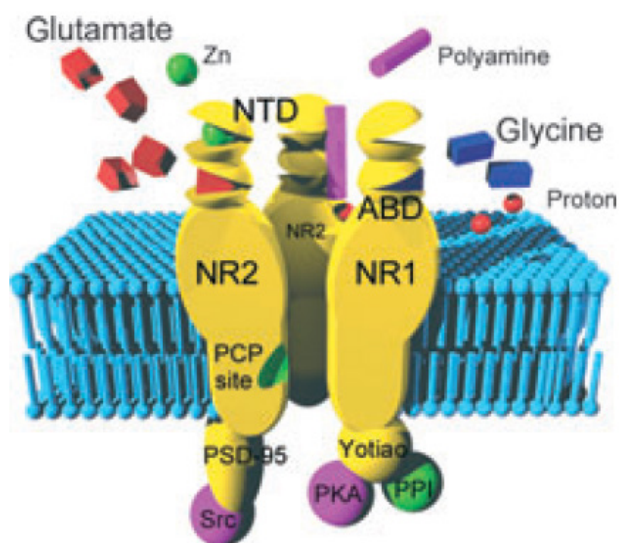


Figure 1 Scheme of the N-methyl-D-aspartate (NMDA) receptor (Mion G, Villeveille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). *CNS Neurosci Ther* 2013; 19: 370-380). Zn: Zinc ion, NTD: N-terminal domain, NR1 and NR2 subunits: Subunits of the NMDA receptor that form a receptor channel selective for the cations, ABD: Agonist-binding domain, PCP: N-1-phenyl-cyclohexylpiperidine, PSD protein: Postsynaptic density protein, Yotiao protein: A-kinase anchoring protein, Src family kinase: A family of non-receptor tyrosine kinases, PKA: cAMP-dependent protein kinase, PPI: Protein phosphatase type I.

cell death. Investigational data suggest that in addition to NMDA receptor antagonists, agents with a stimulatory effect on gamma-aminobutyric acid signal transduction may also exert potentially neurotoxic effects on the developing brain. Animal studies have established the role of NMDA receptors in the neurotoxic effects of general anesthetic agents commonly utilized in the clinical practice^[3,9-11].

Ketamine, an NMDA receptor antagonist, is a widely used general anesthetic agent in procedures involving pediatric patients. However, significant concerns have been raised in terms of the safety of ketamine in pediatric anesthesia. Repeated doses of ketamine have resulted in permanent learning and memory disorders through the induction of neuroapoptosis and injury in the developing brain, mainly at the hippocampal area in animal studies. On the other hand, the exact mechanism of ketamine related neurotoxicity is not very well known. The major factor responsible for ketamine neurotoxicity is the reactive oxygen species-mediated neuronal apoptosis occurring via the mitochondrial pathways. Up-regulation of NMDA receptors lead to toxic levels of intracellular calcium accumulation, thus resulting in neurotoxicity. Although experimental work has suggested that certain antioxidant agents such as L-carnitine may partly alleviate this injury, novel strategies that may help prevent injury are warranted (Figures 2-4)^[12-15]. Otherwise, in a study conducted by Tariq *et al*^[16] it is demonstrated that chronic administration of the dexmedetomidine, a highly selective and specific alpha-2 adrenergic agonist with sedative, analgesic and sympathetic activities, significantly reduced the body weight and crown-rump length of pups, whereas a single acute dose did not affect these parameters.

Local anesthetics are used clinically for peripheral nerve blocks, epidural anesthesia, spinal anesthesia and pain management; large concentrations, continuous application and long exposure time can cause neurotoxicity. The mechanism of neurotoxicity caused by local

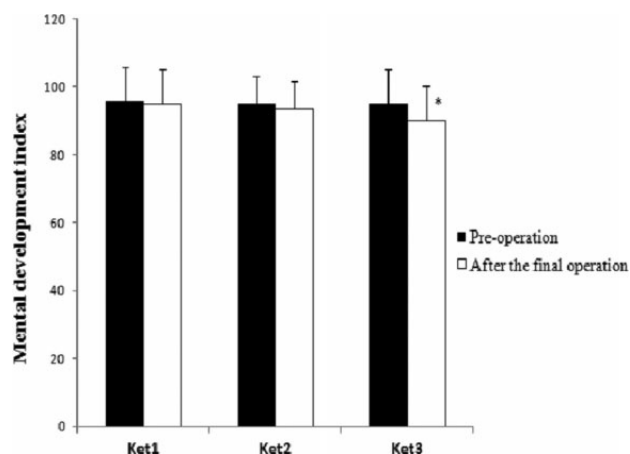


Figure 2 The mental development index scores from Bayley Scales of Infant Development-II evaluation of infants in the ketamine groups before the first procedure and after the final procedure (Yan J, Li YR, Zhang Y, Lu Y, Jiang H. Repeated exposure to anesthetic ketamine can negatively impact neurodevelopment in infants: a prospective preliminary clinical study. *J Child Neurol* 2014; 29: 1333-1338).

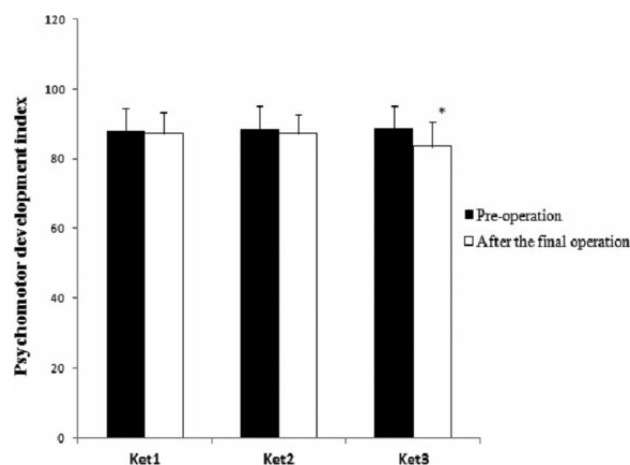


Figure 3 The psychomotor development index scores from Bayley Scales of Infant Development-II evaluation of infants in the ketamine groups before the first procedure and after the final procedure (Yan J, Li YR, Zhang Y, Lu Y, Jiang H. Repeated exposure to anesthetic ketamine can negatively impact neurodevelopment in infants: a prospective preliminary clinical study. *J Child Neurol* 2014; 29: 1333-1338).

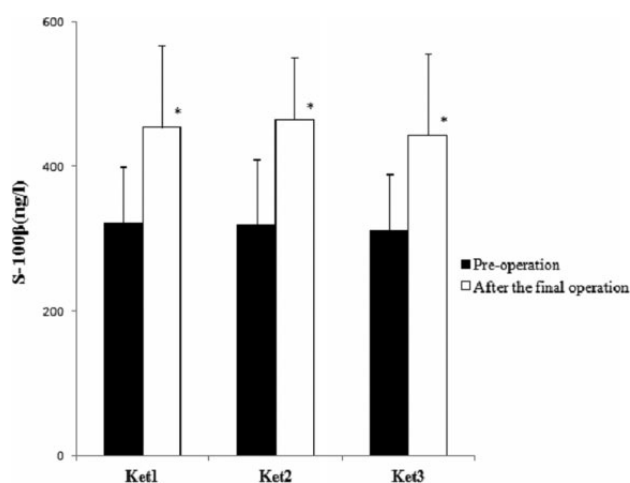


Figure 4 Mean plasma levels of the central nervous system injury biomarker S-100β of infants in the ketamine groups before the first procedure and after the final procedure (Yan J, Li YR, Zhang Y, Lu Y, Jiang H. Repeated exposure to anesthetic ketamine can negatively impact neurodevelopment in infants: a prospective preliminary clinical study. *J Child Neurol* 2014; 29: 1333-1338).

anesthetics is unclear. Neurite outgrowth and apoptosis can be used to evaluate neurotoxic effects. Many previous studies have been reported neurological injury caused by local anesthetics. Lidocaine, a local anesthetic, may also be used systemically for an antiarrhythmic effect in certain dysrhythmias and for an anticonvulsant effect in refractory convulsions. Its higher plasma concentrations may cause seizure activity (“proconvulsant” effect). In addition, neurotoxic effect of lidocaine in the newborn period has also been reported^[17,18]. In a study, local anesthetics had produced toxic effects by neurite inhibition at low concentrations and by apoptosis at high concentrations^[17].

Other agents with demonstrated neurotoxic effects include some sedatives and analgesic agents. For instance, chloral hydrate has been found to be associated with lower performance intelligence quotient (PIQ) and cumulative doses of benzodiazepines were associated with lower visual motor integration (VMI). Chloral hydrate is commonly used as a sedative and a hypnotic in pediatric medicine. It has the embryotoxic effects and an increase in the number of malformed offspring. Midazolam is known to increase the convulsion frequency in premature infants and in patients with a lower threshold for convulsions. Again, serious concerns have been expressed regarding the safety of phenobarbital, in terms of its potential role in the development of hyperactivity, behavioral problems, and even dementia. Phenobarbital exposure at the critical stages of brain development has adverse consequences with regard to the functions of the nervous system. Exposure to phenobarbital at earlier stages of life leads to neuronal apoptosis and impairs the physiological maturation of the neuronal synapses. Similarly, barbiturate exposure has been linked to the development of autism^[19-21].

In prenatal alcohol exposure, particularly in cases with fetal alcohol syndrome, psychosocial adaptation problems in later stages of life are more likely to be observed. Long-term use of psychostimulant agents, like morphine, lead to some pathological consequences including neurotoxicity and neuronal dysfunction, hepatotoxicity, kidney dysfunction by causing injury on biomolecules through oxidative stress and apoptosis. Amphetamine-like psychostimulant agents are commonly used for their potent stimulatory effects on the central nervous system, and have been associated with long-term neuro-toxicity as well as related behavioral problems^[22-24].

Intrauterine exposure to antidepressants is also associated with some short- or long-term risks. Antenatal exposure to selective serotonin re-uptake inhibitors (SSRI) may lead to serotonin toxicity and withdrawal symptoms in the short term, while latent functional behavioral disorders have been reported in the long term^[25,26]. For instance, in a study involving pediatric subjects, assessments based on The Bayley Scales of Infant and Toddler Development, Third Edition showed lower motor scores, mainly in fine motor skills of the participants^[27]. In addition, exposure to SSRI during the third trimester of the pregnancy was associated with a poorer motor development, lower APGAR score, a method to quickly evaluate the health of newborn infants after birth which summarized using words chosen to form a backronym (Appearance, Pulse, Grimace, Activity, Respiration), at 5 minutes, and shorter gestational age^[28]. Considering the important role of serotonin in central nervous system development, more studies are needed to assess the possible adverse effects on long-term neurodevelopment. Thus, SSRI's should only be used when the benefits clearly outweigh the risks during pregnancy and those children with a history of exposure to SSRI use during pregnancy should be closely monitored for potential adverse effects.

Fetal exposure of animals to antiepileptic drugs can produce cognitive and behavioral abnormalities, but cognitive effects of

fetal exposure of humans to antiepileptic drugs are uncertain. Accumulating evidence suggests an association between prenatal exposure to antiepileptic drugs and increased risk of both physical anomalies and neurodevelopmental impairment. Neurodevelopmental impairments are characterized by either a specific deficit or a constellation of deficits across cognitive, motor and social skills and can be transient or continuous into adulthood. Exposure to certain antiepileptic drugs during the early stages of life also constitutes the risk factor for neuropsychiatric abnormalities, as exemplified by studies that show that antenatal exposure to valproic acid was associated with lower IQ, which is sufficient to affect education and occupational outcomes in later life; and antenatal exposure to carbamazepine was associated with lower developmental quotient (DQ)^[29]. In a study, it is demonstrated that in utero exposure to valproate, as compared with other commonly used antiepileptic drugs, was associated with an increased risk of impaired cognitive function at 3 years of age^[30]. Therefore, it is of paramount importance that these potential risks are taken into account or minimized in these vulnerable populations.

Theophylline, a methylxanthine derivative commonly used during the newborn period for apnea of prematurity, may also induce apoptosis, and corticosteroids, particularly dexamethasone, are known to induce similar effects such as neurodevelopmental retardation and cerebral palsy in the long term. In an experimental study, theophylline was found to induce convulsive activity through free radicals (reactive oxygen species and reactive nitrogen species). In animals, aminophylline was shown to increase hippocampal neuronal cell injury^[31,32]. But there is conflicting data for caffeine; even it may have neuroprotective effects^[33]. Therefore, additional randomized trials are needed to determine possible long-term neurologic benefits of caffeine. Again, in animals, corticosteroids were associated with neurodevelopmental problems, with a particularly marked adverse effect on neuronal cell division and myelination in the first days of life, which are critical for brain development^[34-38]. However, in an experimental study, hydrocortisone has been demonstrated safer than dexamethasone in the immediate postnatal period in neonatal rats^[39].

Antibacterial agents may also be related to a variety of neurotoxic reactions, such as direct neurotoxicity (e.g. penicillin, cephalosporin, imipenem, colistin, metronidazole), cranial nerve toxicity (e.g. vancomycin, aminoglycosides) or neuromuscular blockade (e.g. clindamycin, aminoglycosides). For example, cefepime related non-convulsive status epilepticus have been reported in adults as well as clarithromycin associated neuropsychotic disorders, and convulsions in those with a low threshold for epileptic activity^[40-42].

Other known neurological side effects due to drugs administered to newborns include apnea and convulsions due to prostaglandin E1 infusion for duct-dependent congenital heart disease, dystonic reactions due to metoclopramide for gastroesophageal reflux disease, and elevated intracranial pressure due to high dose vitamin A^[43-45]. Vitamin A toxicity is a good model of vitamin neurotoxicity, because it shows the importance of the vitamin and vitamin-binding proteins ratio to causes vitamin toxicity and passes over to central nervous system barriers. Folic acid and thiamine cause seizures and excitation when administered in high dosage directly into the brain or cerebrospinal fluid of experimental animals but have rarely been reported to cause neurotoxicity in human. Ascorbic acid influences brain cell differentiation and 2-deoxyglucose accumulation by cultured glial cells after peripheral administration. Biotin also influences gene expression in animals and alters astrocyte glucose utilization^[46].

In conclusion, since the antenatal and neonatal periods are very

sensitive periods with rapid brain development occurring, the fetuses and newborn infants might exposure to potentially neurotoxic side effects of commonly used many drugs. Therefore, potential neurotoxic side effects of commonly used drugs in the both pregnant women and newborns, especially in preterm infants, should be taken into account; and therefore, before starting a treatment to these vulnerable populations, the necessity and benefit to harm ratio should be questioned.

CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

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