Are anaesthetic agents neurotoxic for the developing brain?

Kirstin Engelhard
Professor, University Medical Center of Johannes Gutenberg University, Mainz, Germany

Animal Data

Various experimental studies in animals have shown that general anaesthetics are potentially toxic to the developing brain. By inducing apoptosis or interfering with neurogenesis anaesthetic exposure during a critical period of neuronal development can have significant impact on the neurocognitive functions later in life. In animal studies three main factors affect the toxicity of anaesthetics. The first is the timing of exposure, because the neurotoxicity of anaesthetics occur more often in the early stage of brain development. The second factor is the frequency and duration of anaesthetic exposure. Various in-vitro and in-vivo animal experiments have shown that frequent and long anaesthetic intervention are correlated with an increased neurotoxicity. Thirdly, numerous animal experiments reveal a clear dose-dependent element to toxicity. Increasing the dose of anaesthetics increases the number of apoptotic neurons, the degree of developmental impairment, cellular differentiation and synaptogenesis.

Retrospective Clinical Studies

Meanwhile it is well proven that anaesthetic agents do harm the developing brain of rodents and non-human primates. To answer the question whether these data can be transferred to paediatric patients many retrospective clinical studies have been performed. They investigate the interrelation between early exposure to anaesthesia during the first three to four years of life to learning and behaviour abnormalities in adulthood. Most of the studies have been performed in the USA, Australia, or Europe. The data for the studies were drawn from different birth cohorts or registries They explored e.g. the association between exposure to anaesthesia for inguinal hernia repair under the age of three and learning disabilities. Some of the studies from the USA and Australia detected a correlation between single or multiple exposure to anaesthesia and an increase in the incidence of learning disabilities. In contrast, several studies from Europe showed no such relationship. For instance, a Swedish study compared more than 33,000 children who were operated on within the first four years of their lives with those who have never been operated. The authors compared the academic performance in a standardised nationwide school test in the ninth grade in both groups, and were able to prove that gender or the maternal educational level influences the outcome ten times more than an operation. A twin research study is a possible method to exclude genetic difference. A retrospective analysis of the Dutch Twin Registry compared monozygotic twins of which one of the two children was exposed to general anaesthesia under the age of three years. They found no difference in the incidence of learning disabilities between the exposed and the unexposed twin. However, the incidence of learning disabilities was higher in pairs of twins in whom one underwent anaesthesia compared to the set of twins of where neither was exposed. The authors speculated that there might be a vulnerability about these twin pairs, rendering them more susceptible to conditions requiring anaesthesia such as diseases of the middle ear or herniotomy. Interpreting retrospective studies is generally difficult. One has to take into account that many of the data of the retrospective studies were generated in the late 1970´s and early 1980´s. At that time, the quality of paediatric anaesthesia was significantly

different from the present day. Commonly used anaesthetics such as halothane were much more cardiodepressant than modern agents, hypotonic infusion therapy often led to hyponatraemia, and the lack of warming technologies led to severe hypothermia. Furthermore, the identification of disturbances was difficult, because measuring and monitoring respiratory, haemodynamic and metabolic changes was challenging or even impossible as capnometry, pulse oximetry and non-invasive arterial pressure monitoring did not enter clinical practice to complement the clinical expertise of anaesthetists until the 1990's.

Prospective Clinical Data

During the last years the results of three major prospective randomized multicentre clinical studies, the PANDA, MASK and GAS studies, have been published.

1) The PANDA study (Pediatric Anesthesia and Neurodevelopment Assessment). This was a multicentre study which examined the long-term effects of anaesthesia on cognitive function in children exposed to anaesthesia for inguinal hernia repair up to the age of 36 months. The neurodevelopmental and cognitive functions were tested at the age of eight and 15 years and were compared with the results of non-anaesthetised siblings. The study revealed that there was no correlation between anaesthetic intervention and IQ score.

2) The GAS study (General Anesthesia and Spinal): This study compared the effects of anaesthesia on neurodevelopmental outcome and apnoea in infants undergoing inguinal hernia repair up to the age of six months. They were randomly assigned to receive either general or spinal anaesthesia. The children then underwent developmental testing at the age of two years and neurodevelopmental and intelligence testing at the age of five. The authors concluded that slightly less than 1 h of general anaesthesia in early infancy does not alter neurodevelopmental outcome at age 5 years compared with awake-regional anaesthesia in a predominantly male study population.

3) The MASK study (Mayo Safety in Kids): This was a collaborative cohort study involving researchers from the Mayo Clinic and National Center for Toxicological Research in the USA. Children in Rochester, Minnesota, who received one or more anaesthetics before the age of three years were compared to with children no anaesthetic exposure. They use an extensive battery of neurocognitive tests, including the 'operant test battery', which is already evaluated in children and non-human primates. These authors also found that anesthesia exposure before age three years was not associated with deficits in the primary outcome of general intelligence.

In conclusion, after 20 years of concern and controversy it seems to be proven that anaesthetic agents do not harm the developing brain. The animal studies were alarming, but the human evidence overwhelmingly suggests that any effect of well-conducted paediatric anesthesia is insignificant or non-existent. Nevertheless, there are still many editorials, commentaries, and opinions stating that more studies are needed to characterise the potential mechanisms of anaesthetic neurotoxicity, develop alternatives to the current anaesthetic agents or even avoid any operation in children younger than four years. This is aggravated by the warning of the American Food and Drug Administration and the Australian Therapeutic Goods Administration that the use of anaesthetic agents in children younger than three years or in pregnant women may affect the development of children's brain.

At the same time the undue focus on the safety of anaesthetic drugs detracts the attention from other factors which possibly have a much higher impact on the outcome in paediatric anaesthesia. It is well known that the cardiovascular, central nervous and respiratory systems of the premature or newborn baby are extremely sensitive and vulnerable to haemodynamic and metabolic changes and derangements. We still do not

even know which target values for blood pressure, blood glucose, oxygen or carbon dioxide partial pressure can be considered safe for anaesthetised children in this age group. Therefore, it might be rather the unexperienced anaesthetist than the anaesthetic agent who is a threat to developing brain. To investigate these potentially harmful factors during paediatric anaesthesia in large clinical trials (APRICOT and NECTARINE studies) a group of leading paediatric anaesthetists have formed the “Safe Anaesthesia for Every Tot” (SafeTots) initiative.

Practical advice to clinicians

There is no data to support the omission of anaesthesia or analgesia in newborn babies, infants or small children. As known from infants who received a circumcision without anaesthesia and analgesia, the pain and stress reaction induced by the surgery reduces the pain threshold in these children for several months. Animal studies revealed that painful stimuli in the absence of anaesthesia enhance pain perception, behaviour and learning disabilities and brain damage.

In practice, therefore, adequate anaesthesia and/or sufficient pain therapy during an indicated surgical procedure or painful examination are essential. In addition, transient or profound disturbance of physiologic parameters like hypotension, hypocapnia, hypoglycaemia or hypothermia, should be avoided as these changes might also affect neurodevelopment. To reduce the amount of anaesthetic agent required, a balanced anaesthetic technique including intraoperative multimodal pain therapy with local/regional anaesthetics, non-opioid analgesics and opioids is recommended.

In addition, anaesthetists, paediatricians and paediatric surgeons should define clear indications for surgical or non-surgical procedures under anaesthesia in the first years of life if postponement is inadvisable e.g. orchidopexy because of a non-descended testicle. Further, several surgical interventions with multiple anaesthetics can be avoided if there is the possibility of performing more than one surgical procedure during the same anaesthetic.

Parents are usually well informed because of the rapid availability of information via the internet. The main problem with this source of information is the lack of reliability and validity. There should be an empathic and objective discussion with the parents to make sure they are properly informed, and two key points should be communicated:

· Anaesthesia is not an end in itself. It is necessary and indispensable for the indicated operation. To omit adequate sedation and/ or analgesia has damaging effects for the child.

· There are barely any indications that a competent and clinically well-performed anaesthesia with modern, short-acting anaesthetics has negative consequences such as cognitive developmental problems or learning disabilities.