# Neonatal neurotoxicity: fact or fiction

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Until recently it was believed that anaesthetic agents caused no longer-term consequences for the brain, and if anything were neuroprotective. However, a growing body of evidence suggests that anaesthetic agents may indeed have harmful consequences, particularly in the very young and very old.[1]

In 1981 Chalon published evidence of impaired learning in mice exposed to halothane and enflurane while still in utero.[2] This evidence went largely unnoticed however, and so the topic of possible harmful effects of anaesthetics received little attention for another two decades. In 1999 Ikonomidou demonstrated that the NMDA antagonist MK801 caused neuronal apoptotic degeneration in rat pups (7 day old rats), and soon after that alcohol was caused neurotoxicity by a similar mechanism.[3,4] However, it was only after publication of the work of Jevtovic-Todorovic, showing that commonly used anaesthetic agents cause widespread neuronal degeneration accompanied by learning deficits,[5] that the topic really caught the attention of the anaesthetic community and eventually of the public. Since then numerous studies have confirmed that a wide range of sedative and anaesthetic agents (including benzodiazepines, $N_2O$, ketamine, propofol and volatile anaesthetic agents) tested in a wide range of animal species (up to non-human primates [6]) are neurotoxic following exposure to the immature brain.[7-9] Notable exceptions so far include dexmedetomidine and xenon. An interesting facet of the susceptibility of neonatal animals to the neurotoxic effects is that the period of susceptibility is very short-lived (in the case of rat pups it is a matter of a few days), and appears to coincide with the peak period of synaptogenesis, a process by which new connections are formed between active neurons, and during which neurons are genetically programmed to enter a programmed cell death (or apoptosis) process if they are inactive. Soon after this phase neurons are genetically programmed to stay alive and to only enter an apoptotic phase in specific, harmful circumstances.

Despite concerns about the methodology used in some of the animal studies,[10] attention has naturally turned to the issue of whether anaesthetics are harmful to human neonates. Attempting to answer this question is complex, particularly with regard to ethical issues – it is not ethical to administer an unnecessary anaesthetic to a baby! Initial efforts centered mostly on epidemiological studies of long-term cognitive function after early exposure to anaesthetic agents, often using clever strategies, such as studies of twins. [11] These studies produced conflicting results, and failed to provide a clear answer to the question. The interpretation of the epidemiological findings was confounded by differences in methodology, doubts about causality – children needing surgery during the early months of life may be a group that would show poor cognitive performance later on, whether or not exposed to anaesthesia.

Although there is some uncertainty about when the peak of synaptogenesis occurs in humans, it is now generally agreed that the human period of susceptibility extends from some time during the third trimester of pregnancy, until about 6 months after birth. Many of the epidemiological studies included children first exposed to anaesthetics well after 6 months, leading to significant doubts about their validity.

In the past few years, two groups have performed meta-analyses of the available epidemiological evidence, using overlapping datasets but some differences in statistical methodology.[8,12] In short, both found only weak evidence of an association between early exposure to anaesthesia and impaired cognitive performance. Both concluded that the evidence was not strong enough to support any change in practice, and that avoiding or delaying surgery may in some cases be more harmful than the possible dangers of anaesthesia.

Given the weaknesses of epidemiological approaches, two groups have performed prospective randomized controlled trials. The GAS study was a randomized controlled trial of children younger than 6 months requiring inguinal hernia repair.[1] A total of 720 children were included, and randomized to receive either general anaesthesia with sevoflurane, or spinal anaesthesia. Inclusion was completed in January 2013. The children have been followed up to determine cognitive and intellectual performance at 2 and 5 years. The 2 year outcome results showed no differences in cognitive outcome.[13] The 5 year results should be published soon.

The other trial was the PANDA trial (Pediatric Anesthesia and NeuroDevelopment) which included 500 children requiring hernia surgery before the age of 3 years. In this observational cohort study, each child (and a matched sibling as control) underwent neuropsychological assessment between 8 and 15 years after exposure. As in the GAS trial, no differences in cognitive outcomes were found between exposed and unexposed children.[14]

There is thus no evidence that brief exposure (< 1 hour) to anaesthesia at a young age is harmful. The question of course remains whether prolonged exposure, or multiple exposures is harmful, but that will be far more difficult to prove or disprove. Despite this all, the FDA has recently published an alert which has generated some discussion.[15]

**References:**

1