Departmental statement regarding potential neurotoxicity of anaesthetic agents in children.

Over the last 15 years, paediatric anaesthetists have been considering the possible long-term effects of drugs currently used in paediatric anaesthesia. In particular, attention has focussed on the effect of anaesthesia drugs on later neurological outcomes. Concerns were initially raised by scientists who were exploring the effects of anaesthesia drugs on early brain development in animal models. In a range of animal species, exposure to anaesthesia drugs in early life resulted in immediate histological changes and behavioural changes in later life. This has prompted a search for corollary phenomenon in humans. In December of 2016, the FDA issued a drug safety announcement stating that repeated or lengthy use of general anaesthetic agents may affect the development of children's brains.

The animal experiments (rodent, murine, porcine, rabbit and non-human primates) have consistently shown histological changes (accelerated apoptosis) induced by exposure to a wide variety of common anaesthetic agents (including isoflurane, ketamine, nitrous oxide, benzodiazepines and propofol).
In many of the animal models, early (peri-natal) exposure has led to altered behavioural patterns (involving memory and learning) in later life. The effects are distinctly dependent on the age of exposure and this is thought to reflect a period of developmental vulnerability. The period coincides with rapid synaptogenesis during early brain development. It is clear that typical anaesthetic agents (GABAergic drugs and glutamate inhibitors) have long term effects on developing neurones in animals and that these result in behavioural changes in later life.

It is important to note that the animal studies were not prompted by a clinically recognised association between anaesthesia and neurocognitive deficits in humans. The relevance of these animal data to humans remains unclear. Direct extrapolation of the data to paediatric anaesthesia practice is not possible. Species differences, markedly different developmental time scales and the relatively prolonged duration of exposure (in animal experiments) make translation of the data difficult. Further complexity is added by differences in physiological monitoring and care during anaesthesia and hospitalisation, the effects of co-morbidities (indication for surgery) and surgically induced inflammation/pain.

Human corollaries to the animal data had not been suspected nor specifically reported in the clinical literature in the decades prior to the recent laboratory studies. A human correlate of the adverse behavioural outcomes in animals remains obscure. Despite this, efforts to explore the issue have proceeded and data from epidemiological, cohort and twin studies complement the one randomised trial available to date.

To date, several large epidemiological studies (datasets from registries or birth cohorts) have searched for associations between anaesthesia exposure in early life and adverse outcomes. Learning disabilities, academic achievement, intelligence quotients, rates of autism and individual neurobehavioural tests have been analysed in retrospective and a few prospective studies. The majority of these studies confirm that single brief anaesthesia exposure in infants does not lead to adverse outcomes in current educational and developmental measures. However, repeated anaesthesia (two or more exposures) is associated with an increased risk of learning disabilities and/or developmental and behavioural disorders. Importantly, none of these studies can separate the effect of anaesthesia per se from the effect of surgery, hospitalisation, underlying illness and co-morbidities. Each of these represent significant confounding factors that make interpretation of these studies difficult. Of particular

Locked Bag 4001
Westmead NSW 2145
Sydney Australia

Tel 61 2 9845 0000
Fax 61 2 9845 3489
www.schn.health.nsw.gov.au

ABN 53 188 579 090

DX 8213 Parramatta

note, a large proportion of children studied underwent ENT surgery whose indications (e.g. glue ear, OSA) have large confounding effects. It remains plausible that children with an indication for surgery have an associated vulnerability to poorer cognitive outcomes. Further, very significant confounding factors in large epidemiological studies of cognitive outcomes are male sex (a majority of infants who require surgery are male), maternal educational level, family socio-economic status, prematurity and month of birth. Study refinements such as 'case matching' and statistical adjustments attempt to adjust for these factors. Overall, the reported relative risk ratios for adverse outcomes following repeated (≥2) anaesthesia exposure is in the order of 2-4.

Several recent large database studies (from Taiwan, Sweden and Canada) each suggest that associations between anaesthesia and poor cognitive outcomes are modest. The risk to academic performance is likely to be an order of magnitude less than that posed by better recognised factors such as male sex and maternal education level. The measured risk, though statistically detectable- is small and must be balanced against the potential adverse effects of delaying surgery.

Twin and sibling-matched studies are powerful and strengthen the conclusions of the large published epidemiological studies. An important study of 71 monozygotic twin pairs who were discordant for anaesthesia exposure found no evidence that anaesthesia has an effect on learning related outcomes in children. Instead, the study suggested that childhood vulnerability to learning disability is likely correlated with the indication for surgery.

Detailed neuropsychological testing of cohorts is required to detect subtle impacts of surgery and anaesthesia exposure. Three well designed prospective studies that include such testing are nearing completion. The PANDA study- a matched sibling study that utilised a battery of neuropsychological tests, has found that single exposure to anaesthesia (up-to 4 hours) in children before 3 years of age has no detectable effect in later childhood. The anaesthesia community is awaiting the results of two further important prospective studies that will help clarify the issue. The GAS study – a randomised controlled study comparing infants exposed to either general anaesthesia or spinal anaesthesia for hernia repair- reported no difference in Bayley developmental scores at age 2 years. Further comparisons at age 5 years are expected soon. The MASK study is due to be reported soon. It is possible that current researchers have not yet identified the most relevant outcome measure. Further refinements in neuropsychological testing are awaited.

At this point in time (2017), the available evidence and balance of probabilities allows the following conclusions:

1. Single brief (<3hrs) exposure to anaesthesia drugs before age 3yrs does not lead to reduced scores in currently available developmental measures.

2. Having multiple procedures requiring anaesthesia before age 3yrs is associated with a measurable reduction in later cognitive outcomes but this reduction is modest and likely to be related to the 'indication for surgery' rather than drug exposure per se.

3. There are no data to inform us of the risk of anaesthesia drug exposure in infants who may be specifically vulnerable e.g. premature neonates, infants with pre-existing neurological disease and infants with congenital heart disease. There are no data to inform us of the risk of prolonged drug exposure.

This document has been prepared by a working group of CHW anaesthetists, surgeons and neonatologists (Convenor: Dr J de Lima). It has been endorsed by the surgeons and anaesthetists of the SCH and JHH and the Australian and New Zealand Association of Paediatric Surgeons (ANZAPS).
All efforts to ensure the accuracy of the information have been made. The document will be up-dated as more information becomes available.

The Sydney children's Hospitals Network
care, advocacy, research, education

Advice when obtaining consent for general anaesthesia and sedation

Surgical expertise, pre-and postoperative care and pain management in neonates and infants have all improved greatly in recent years. With this, the risk of anaesthesia for neonates and infants has reduced, allowing earlier surgical intervention for many paediatric conditions. The peri-operative risks of cardio-respiratory compromise, anaphylaxis, renal and liver damage are now proactively managed or mitigated.
In the last 15 years, the possibility that anaesthesia and sedative drugs may represent a previously unrecognised risk to neurobehavioral development has been raised. In December of 2016, the FDA issued a drug safety announcement warning that repeated or lengthy use of general anaesthetic agents may affect the development of children's brains. Carers and parents are increasingly aware of the debate and are likely to ask for further information.

This information can be provided at the time of obtaining consent with the acknowledgement that:

- At CHW, surgery is only carried out when necessary i.e. all surgery is done for defined clinical reasons. The benefit to the child (physical and/or psychological) of the intervention can be demonstrated and is a community expectation.
- Anaesthetic care is primarily focussed on safety and minimising the well-recognised complications (hypotension, hypoxia, hypothermia, hypoglycaemia) of drug induced unconsciousness.
- Our understanding of the neurotoxic potential of anaesthesia drugs is growing and recommendations will be regularly reviewed.

At CHW, the department of anaesthesia has reviewed the literature (up to 2017) regarding anaesthesia related neurotoxicity and suggests the following approach when proceduralists obtain consent to schedule infants for anaesthesia and surgery.

1. Anaesthesia and surgery for children (<3yrs) undergoing ***brief*** (<3hrs) ***single*** procedures can proceed without any change to current practice. (A discussion of potential neurotoxicity is ***not*** mandatory*).
2. Anaesthesia and surgery for children (<3yrs) who are likely to require ***repeated*** or ***prolonged*** (>3hrs) general anaesthesia for procedures that ***cannot*** be postponed can include a pre-operative discussion about potential neurotoxicity¥. The relevant points being:
    a. Current evidence confirms an association (not causality) between receiving multiple anaesthetics and reduced neurocognitive outcomes. The child's underlying indication for repeated surgery may be a more important risk factor than anaesthesia drug exposure per se.
    b. There are no known alternatives to current general anaesthetic drugs. No identified anaesthesia drugs or techniques have been proven to be safer than current standards and practice.
3. Anaesthesia and surgery for children (<3yrs) who are likely to require ***repeated*** or ***prolonged*** (>3hrs) general anaesthesia for procedures that ***can*** be postponed[€] should include a discussion about potential neurotoxicity and the timing of surgical intervention[£]. A demonstrated benefit of earlier (before 3yrs of age) intervention should be balanced against the potential risk of small reductions in later cognitive function.

Locked Bag 4001
Westmead NSW 2145
Sydney Australia

Tel 61 2 9845 0000
Fax 61 2 9845 3489
www.schn.health.nsw.gov.au

ABN 53 188 579 090

DX 8213 Parramatta

Notes

**Neurotoxicity should be discussed if raised by parents. Consent is still valid even if neurotoxicity is not specifically addressed. See: Anaesthesia departmental web page for further reading and parent information sheet. Anaesthesia and risk in infants*

¥Where the risks of delaying surgery are evident and demonstrable, consent is still valid even if neurotoxicity is not specifically addressed.

£Occasionally, the primary indication for surgery may be a psycho-social benefit (e.g. facial appearance and related school bullying). In this setting, parents should be provided with adequate support as they balance the perceived benefit with the potential risk of repeated or prolonged anaesthesia.

€This refers to interventions that can be delayed until the child is older than 3 years of age without adding any material (physical or psychological) risk.

Reference list for departmental discussion 2017

Jevtovic-Todorovic V, Hartman R, Izumi Y et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. The Journal of Neuroscience 2003: 23 (3);876-882

Brambink A, Evers A, Avidan M et al. Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. Anesthesiology 2010; 112 (4): 834-841

Zhou L, Wang Z, Zhou H et al. Neonatal exposure to sevoflurane may not cause learning and memory deficits and behavioural abnormality in the childhood of Cynomolgus monkeys. Nature Scientific Reports. 2015 doi:10.1038/srep11145

Wilder R, Flick R, Sprung J et al. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology 2009;110 (4): 796-804

DiMaggio C, Sun L, Kakavouli A, Byrne M, Li G. A retrospective cohort study of the association of anesthesia and hernia repair surgery with behavioural and developmental disorders in young children. J Neurosurg Anesthesiology 2009; 21 (4):286-291

Bartels M, Althoff R, Boomsma D. Anesthesia and cognitive performance in children: no evidence for a causal relationship. Twin Res Hum Genet. 2009;12(3):246-253

DiMaggio C, Sun L, Li G. Early childhood exposure to anesthesia and risk of developmental and behavioural disorders in a sibling birth cohort. Anesth Analg 2011 ;113 (5):1143-1151

Flick R, Katusic S, Colligan R et al. Cognitive and behavioural outcomes after early exposure to anesthesia and surgery. Pediatrics 2011; 128 (5): e1053-e1061

Hansen T, Pedersen J, Henneberg S et al. Academic performance in adolescence after inguinal hernia repair in infancy: a nationwide cohort study. Anesthesiology 2011;114(5):1076-85.

Ing C, DiMaggio C, Whitehouse A et al. Long term differences in language and cognitive function after childhood exposure to anesthesia. Pedictraics 2012;130(3):e476-85

Sprung J, Flick R, Katusic S. Attention deficit disorder after early exposure to procedures requiring general anesthesia. Mayo Clinic proc. 2012;87 (2) 120-129.

Davidson A, Disma N, de Graff J et al. GAS consortium. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre randomised controlled trial. Lancet 2016;387(10015):239-250

Sun L, Li G, Miler T et al. Association between a single general anesthesia exposure before age 36 months and neurocognitive outcomes in later childhood. JAMA 2016;315 (21):2312-2320

O'Leary J, Janus M, Duku E et al. A population-based study evaluating the association between surgery in early life and child development at primary school entry.

Ko W, Huang J, Chiang Y et al. Risk of autistic disorder after exposure to general anaesthesia and surgery a nationwide retrospective matched cohort study. Eur J Anaesthesiology 2015;32:303-301

Glatz P, Sandin R, Pedersen N et al. Association of anesthesia and surgery during childhood with long long-term academic performance. JAMA Peds 2017;171 (1):

Hu D, Flick RP, Zaccariello MJ, Colligan RC et al. Association between exposure of young children to procedures requiring anesthesia and learning and behavioural outcomes in a population-based birth cohort. Anesthesiology, 2017 doi;10.1097/ALN.0000000000001735

Ing C, Sun M, Olfson M, DiMaggio CJ, Sun LS, Wall MM and Li G. Age at exposure to surgery and anesthesia in children and association with mental disorder diagnosis. Anesthesia & Analgesia 2017; 125 (6) 1988-9