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This is Jack
Anesthesia and neurotoxicity

GC Simpson

Moderator: C Nurse

UNIVERSITY OF
KWAZULU-NATAL

INYUVESI
YAKWAZULU-NATALI

School of Clinical Medicine
Discipline of Anaesthesiology and Critical Care

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This is Jack.

Introduction and preamble

I have a nephew. His name is Jack, and he is 2yrs old. He is very cute and very bright. As all nephews do, Jack has a mother and her name is Lauren.

Jack has a problem, he has an inguinal hernia that the surgeons have advised needs repair. Lauren is in her thirties and loves to Google. Unfortunately, when asked, Dr Google spits out the recent FDA warning for children undergoing anaesthesia.

It reads, “exposure to these medicine (anaesthetic agents) for lengthy periods of time or over multiple surgeries or procedures may negatively affect brain development in children younger than 3 years”.

Lauren freaks out. And it’s up to me to calm her down…

What would you tell her regarding safety of anaesthesia for her son?

Could you answer the following questions?

- Why are people concerned about anaesthetics and children?
- How did doctors find out about this problem?
- If anaesthetics cause problems in animals, won’t they cause similar problems in people?
- Does might my child need anaesthesia or sedation? Can my child have an operation without anaesthesia if anaesthesia is harmful to my child?
- What should I do if my child needs surgery or a procedure requiring anaesthesia or sedation?
- Should I consider putting off a needed procedure until my child is older?
- Is one anaesthetic or sedative better or worse than another?
- What can I do to lessen the harmful effects?
- Where can I learn more?

This FMM presentation aims to help all of us answer these questions by examining the current body of knowledge and recent publications of large scale multi-centre studies.

Preclinical data has definitively showed the neurotoxicity of many general anaesthesia agents, what remains unclear is the clinical effect and significance of these pre-clinical findings. There is an extensive body of knowledge starting in the late 1980's with animal studies, and then incremental advancement of study design. The basic sciences have established the neurobiochemical changes that anaesthetic agents can induce, and these changes have been confirmed by histopathological examination of multiple mammal and non-human primate brains. The modern studies aim to provide direction regarding the clinical and real-life impact of anaesthesia and neurodevelopment.

Why It Matters?

Investigations in animals reveal certain common anaesthetic and sedation drugs cause harm to the developing brain and can negatively affect behaviour, learning and memory.
Currently, major scientific and clinical knowledge gaps exist regarding the safe use of anaesthetics and sedatives in children. Recent observational studies suggest that there is a link between the development of learning disabilities with the use of multiple anaesthetics administered in infants and children prior to four years of age. Much more research is needed to definitively determine the risk. Multiple stakeholders are working on new research that will address these gaps in knowledge. Findings from these research studies will establish new practice guidelines and, as necessary, new age-appropriate anaesthetic practises and protocols, ultimately making anaesthesia and sedation safer for our children.

The Rodent Years: Where it all started

In the late 1990's investigators exposed laboratory mice to a variety of anaesthetic agents, including NMDA mediated anaesthetics and volatile agents/GABA acting anaesthetics agents. They then sacrificed these animals for science and dissected their brains. The investigators found evidence of neurotoxicity and neurodegenerative changes as well as increased apoptosis. These findings were confirmed during further experiments, and the damage continued to progress many hours after the exposure to anaesthetic agents. Neurotoxic changes were noted with both NMDA and GABBA acting agents.

The next set of studies looked at functional outcomes (learning and memory skills in rodents). These too were found to be impaired following exposure to anaesthetic agents. Anaesthetics may damage the brain during the synaptogenesis phase of neurodevelopment due to their properties as NMDA and GABA receptors. Neuron apoptosis is thought to be the primary

reason for the neurotoxicity. The mechanisms of anaesthesia-induced apoptosis have been studied and found that activation of proapoptotic proteins such as BAX and may lead to mitochondrial membrane breakage and activation of caspases, which execute cell apoptosis. On the other hand, generation of free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) leads to lipid peroxidation, which could cause brain damage. Such free radicals and ongoing damage may also elicit an inflammatory response, which further amplify the apoptotic process. By contrast, antioxidant enzymes such as superoxide dismutase (SOD), can scavenge excessive free radicals and alleviate their detrimental effect.

Image A: Normal brain **Image B:** Isoflurane exposed brain, note apoptosis demonstrated by dark staining

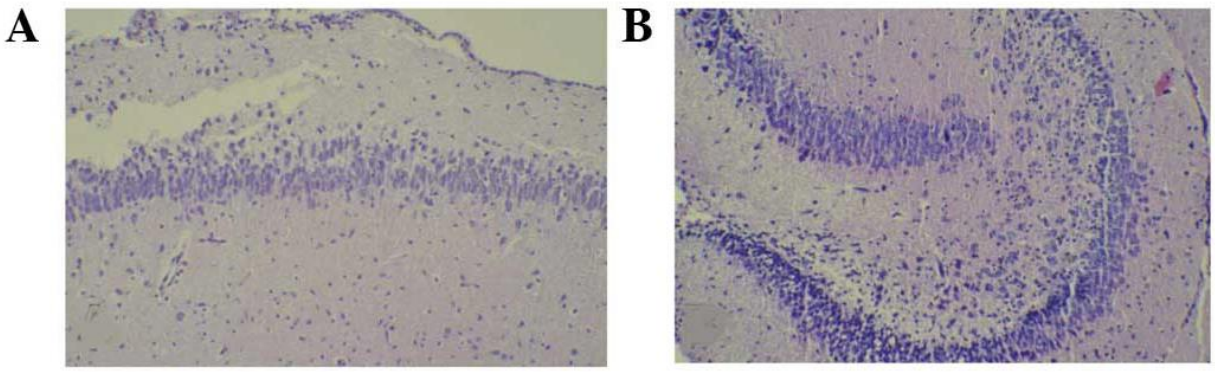

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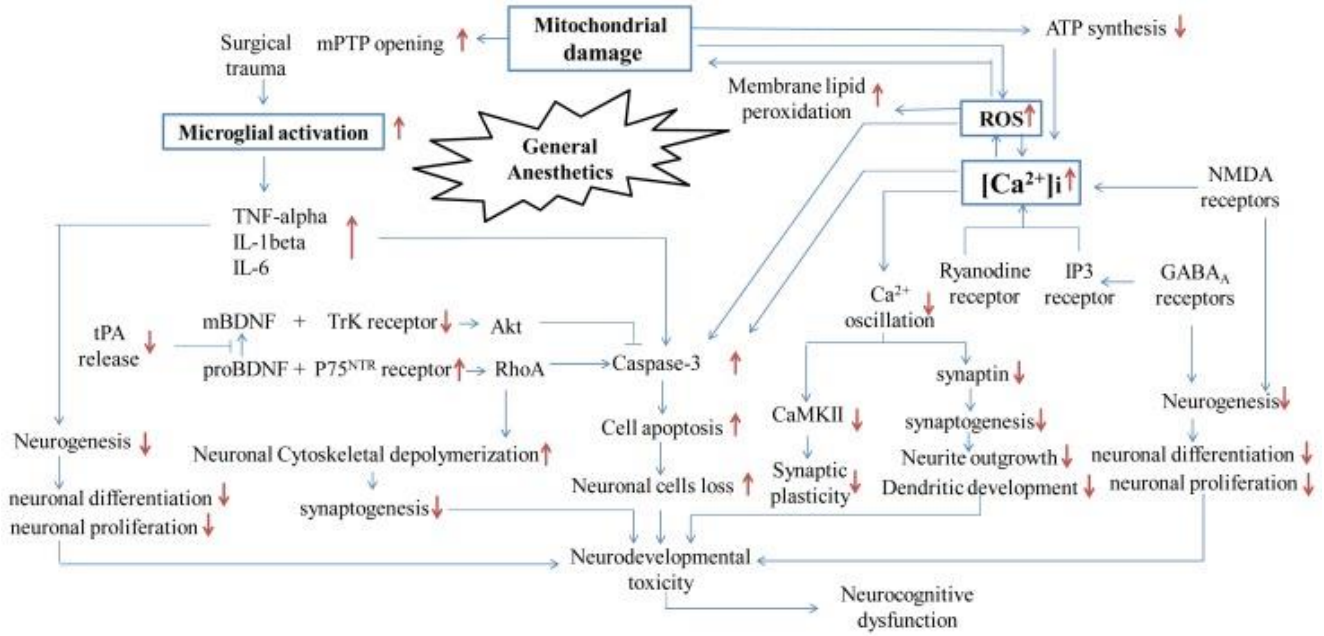
Image C: Illustrates a complex/multi pathway mechanism for proposed neurotoxicity.



The caveat for these studies is that these animals were exposure to large cumulative doses (long duration and high concentration). When considering the life span of a lab rodent and the dose given, it would be like being under anaesthesia for many days! These animals were exposed to anaesthetic agents during the peak neurogenesis period of brain development and this cannot be readily extrapolated to human children and human brain development.

Another caveat for these studies is that physiological variables were not controlled as we do when administrating anaesthesia to humans. Low blood pressure, low oxygenation, minimal organ support could all be the reason behind the neurotoxicity noted. The first rodent studies failed to maintain normal physiology and these animals were unmonitored and allowed to become hypoxic and hypotensive. However, work sponsored by SmartTOTS has replicated some of these studies and maintained appropriate physiology and still have demonstrated the same neurotoxic results.

These experiments did raise some red flags about the potential neurotoxicity and its impact on our children's brains.

Naturally, as we are not rodents, non-human primates were the next step in evaluating the effects of anaesthetic agents. In the 2000's Isoflurane anaesthesia was maintained for 5 hours and found the rate of apoptosis was 13 times above the control group. Interestingly different brain regions showed different patterns of neurodegeneration. These studies seemed to confirm the previous finding made in rodent studies.

{Do we have to provide anaesthesia? For a period well before my time, there was a school of thought that neonates and premature babies did not feel pain. And in many instance analgesia and anaesthesia were not provided to these children. This has been debunked and we conclusively know pain experiences in neonate period have profound immediate and long-term sequelae. This subgroup of vulnerable children (premature and neonates requiring surgery will not be discussed as these children have far too many confounders to study) will always have poor neurocognitive outcomes but for another set of reasons not only the anaesthesia exposure.}

The real question we need answered is, “Will my child be negatively affected by receiving an anaesthetic?”. This is an awful research question, its too vague and lacks any definitions. What is negatively affected? When will this negative effect be shown, now or when my child goes to school?
The ethics involved in exposing humans to a potentially harmful agent is clear, you can’t do it. And ethics will certainly curtail any repeat of the studies performed on rodents and non-human primates., especially regarding brain dissections.

You need time and numbers to show a significant result and a means to eliminate any confounding effects of surgery, hospital stay and numerous other factors, all of which are pragmatically difficult to factor into the design of a large RCT.

Defining a negative effect has also been difficult to standardise across studies, is school performance, IQ, or ADHD traits a better indicator of neurotoxicity? (Brain biopsies are obviously not an option in human studies.)

Instead population, cohort and sibling/twin studies have been designed to try answer our questions.

A population-based study allows large numbers of patients records to be analysed but may lack the specific data required to answer questions as it would be a retrospective analysis. Sibling studies aim to remove the influence of family demographics in a child’s development, however not all children are treated equally. Do you and your siblings have the same level of intelligence in the same areas? Just because one sibling excels in school doesn’t mean the others will. These are just a few of the difficulties in designing studies to answer these important questions.

Table 1: Illustrates vast amount of research dedicated to neurotoxicity.					
INCREASED RISK			**NO INCREASED RISK**		
Study	**Year**	**Number of participants**	**Study**	**Year**	**Number of participants**
Wilder	2009	5357	Wider	2008	
Sprung	2012		Hansen	2011	
DiMaggio	2009		Bartels	2009	
DiMaggio	2011		Guerra	2011	
Andropoulous			Ing	2014	254
Ing	2011		Davidson	2016	532
Guerra	2013		Sun	2016	205
Backeljauw	2015	106	O'Leary	2016	28366
DeHeer	2016	3441	Graham	2016	18056
Mask			Stratman	2014	56
			Kemay	2016	115
			Glatz	2017	33514
Review articles and many others…			Review articles and many others…		

Outcome Studies

Most of the studies have found some relationship between anaesthetic exposure and worse school outcomes, rates of ADHD, memory, and learning. However, that rates reported by different studies varies considerably. They do however agree that its cumulative exposure that increases risk of neurotoxicity, but paradoxically seem to indicate exposure after 2yrs may have more effect on school performance than before 2years of age. (Generating a new set of questions as to why this may be.)

The ADHD association is also made by Sprung et al. they found that when exposed to general anaesthesia before the age of 2 there a was association with a higher rate of ADHD. The kids having general anaesthesia were also more likely to be male, have lower birth weight, lower gestational ages, and more comorbidities, that is, have all the risk factors for ADHD.

Glatz et al from Sweden examined a cohort of all children born between January 1973 and December 1993, 2,174,083 children of whom 33514 had anaesthesia before the age of 4. They found some difference in mean school grades at 16 years old and IQ test scores. But multiple exposures didn't increase the magnitude of difference, and importantly the overall difference was much less than differences related to sex, maternal educational level, or even month of birth. Is it clinically meaningful to have some such a small difference?

The MASK study showed learning disability following multiple exposures but no increased risk of learning disabilities following single exposure to anaesthetic agents.

Our current body of knowledge concludes that a single exposure in healthy children did not increase risk of neurotoxicity, however further research focusing on vulnerable sub-groups (e.g. premature infants), children with multiple exposures and cumulative increased doses of anaesthetic agents.

Regional and Neuraxial techniques

A prospective randomised trial published in 2017 by Lee et al showed caudal blocks with a high volume of local anaesthetic can cause a greater increase in ICP than caudal block with a low volume of local anaesthetic. However, caudal block with 1.0 ml kg of local anaesthetic can also result in a significant increase in ICP. This group gave 80 patients caudal blocks of high (1.5mls/kg) or low (1ml/kg) and then measured the optic nerve diameter with ultrasound to assess intracranial pressures. They found significant changes in ICP measurements. The clinical significance of the raised ICP is not known but does add more mud to the water. If our previous studies are comparing GA to regional, maybe they both are bad for the developing brain?

In 2015 Anaesthesia and Analgesia published a review of over 18000 caudal blocks to elicit the rate of harm they may cause. They looked for complications that included block failure, vascular puncture, intravascular test dose, dural puncture, seizure, cardiac arrest, sacral pain, or neurologic symptoms. They found less than 2% of patients had experienced a complication and no patients had permanent sequalae following those complications. They concluded safety concerns should not be a barrier to the use of caudal blocks in children assuming an appropriate selection of local anaesthetic dosage is made. This large review however did not investigate neurodevelopment delays or impact of caudal blocks.

Latest Information: GAS, PANDA, and others
(published 2016 onwards)

In 2016 Anesthesiology published a retrospective matched cohort study by Graham et. al. of 18056 children that found evidence to refute the assumptions that early exposure to GA increased the likely hood of long term neuro-cognitive problems. It paradoxically showed single exposure to GA in children older than 2years old was associated with neurocognitive deficits, not exposure when younger than 2years old. They also concluded multiple GA exposure at the age of 2 to 4 years did not confer greater risk than a single exposure. These findings seem to

go against the assumed pathophysiological basis of neurotoxicity and previously held assumptions.

And later in 2016 Anaesthesiology also published a population-based study by O'Leary out of Canada. This study examined records from 188557 children, it matched 28366 children who were exposed to GA to 55910 children who were not exposed. Their conclusions were that children who undergo surgery (note they say surgery, not anaesthesia or which type) before primary school age are at increased risk of early development vulnerability, but, the magnitude of the difference between exposed and unexposed children is small. Essentially, they say there probably is a difference, but is it significant?

The General anaesthesia and awake-regional anaesthesia in infancy study or GAS, only reported on its secondary outcome at 2yrs, and needs to wait until participants are 5yrs old before being able to write about its primary outcome for which it was powered. The investigators of the GAS trial reported in Anesthesiology in January 2016. Their conclusion for the secondary outcome (NB not adequately powered) was they found no evidence that less than one hour of sevoflurane anaesthesia in infancy increases the risk of adverse neurodevelopment outcomes at two years of age compared with awake-regional anaesthesia.

A few points to remember when reading the GAS trial are:

- A caudal, ilioinguinal-iliohypogastric or field block with a maximum dose of 2.5mg/kg of bupivacaine was allowed in BOTH groups, this study only shows the difference between sevoflurane exposure.
- The primary outcome required 598 participants to be adequately powered, but only 532 participants enrolled.
- They note, strong evidence for equivalence between awake and general anaesthesia. Not that either is safe or doesn't influence neurodevelopment.
- The findings of equivalence after short exposure (Average length of anaesthesia exposure was 54min) doesn't rule out the possibility that longer exposure to anaesthetics might influence neurodevelopment.
- Although not definitive, this data from GAS probably represents the strongest clinical evidence that short single exposures to sevoflurane in infancy does result in substantial harm or neurotoxicity.

PANDA (JAMA June 2016) is a sibling matched cohort study conducted in the USA. They studied sibling pairs within 36months of age who are currently between 8 and 15years. They noted the exposed sibling was healthy at the time of surgery/anaesthesia. This study group looked at global cognitive function and behaviour. They studied 105 sibling pairs and concluded that among healthy children with single exposure to anaesthesia before 36months of age, when compared to healthy siblings with no exposure there was no statistically significant differences in IQ scores in later childhood. They do note that further studies of repeated exposure, prolonged exposure and vulnerable subgroups are needed.

The most recent summaries of available literature and pragmatic approach can be found in the SmartTOTS update published in Anesthesiology in April 2018. It reviews current understanding, recent study results and outlines future projects to provide these fundamental yet elusive answers.

Let's take a step back: What is damaging the brain?

Recent work presented at PACSA 2017 held in Durban, KZN, RSA, by a research group from Sweden showed although we quoted target MAP ranges we intended to defend in patients undergoing anaesthesia, we often never achieved them. Could hypotension simply be the cause of all these derangements? Similar finding regarding periods of hypotension during anaesthesia in adults seems to support this notion.

Table 2: FACTORS INFLUENCING CEREBRAL PERFUSION
Arterial Pressure (Age/Gestation specific MAP targets)
Metabolic picture and glucose control
PaO2
PaCO2
Temperature

Caudal blocks may induce hypoperfusion in the CNS by means of raising ICP when a volume is injected into the caudal space, could this contribute to poor neurocognitive outcomes after surgery?

The index pathology, the surgical stimulus, and the post anaesthetic period all pose distinct yet cumulative exposure to factors that may contribute to poor neurocognitive development and outcomes.

Time away from family structures, play groups, siblings, and home environment all predispose these children to slowed development for reasons other than the individual anaesthetic agents.
When is the brain most vulnerable to these neurotoxic effects? We're not sure, and it depends on which part of the brain is developing and when that part of the brain is developing. We are still learning about neurodevelopment and need more information before we can begin to understand how we may be affecting it by exposing it to anaesthesia. We also may not have the right tools to diagnose neurocognitive delay precisely or in a reproducible manner. (The Bayley3, IQ testing, Mac-Arthur Bates are but a few of the tools used to assess the outcomes, they tool all have their strengths and weaknesses and inherent problems)

"We all think of neuroplasticity as this is wondrous thing that allows kids brains to recover from insults. Well at least I did. This is true, sort of, really what we should realise is that neuroplasticity just means that neurons are susceptible to influence. The neurons are not able to choose what influences they fall under. They just respond. Influences can also be bad or lead to damaging changes. It seems that when your inhibitory pathways mature that period of susceptibility probably ends. The timing for when that happens is still being established. What's more is that neurons and groups of cells that look the same under the microscope turn up in different parts of the brain and in each part of the brain the timing of maturation, and hence the period of susceptibility to influences, is different."

Image D: Different parts of the brain affected differently and at different stages of development.

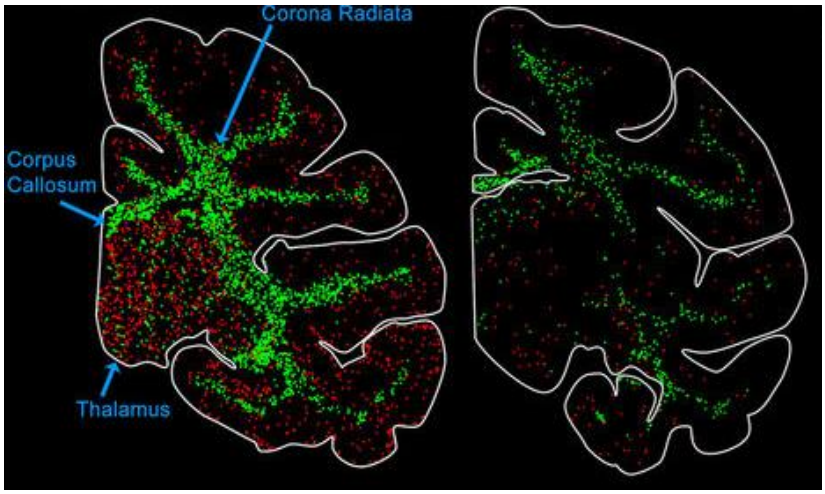
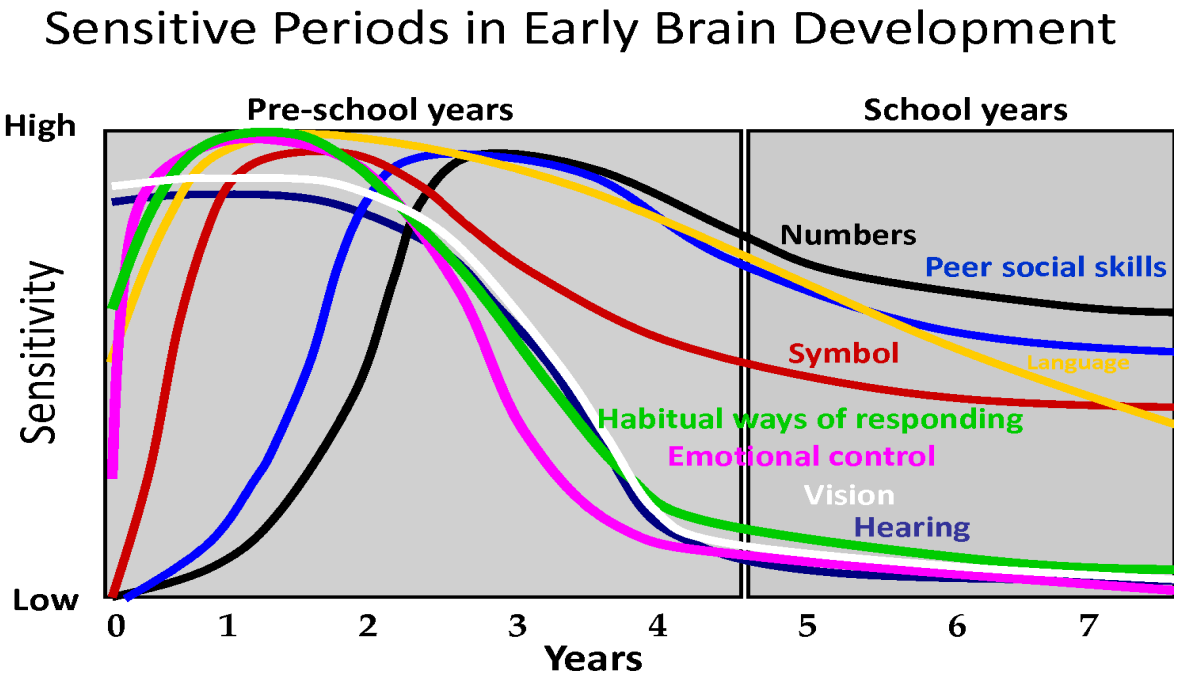
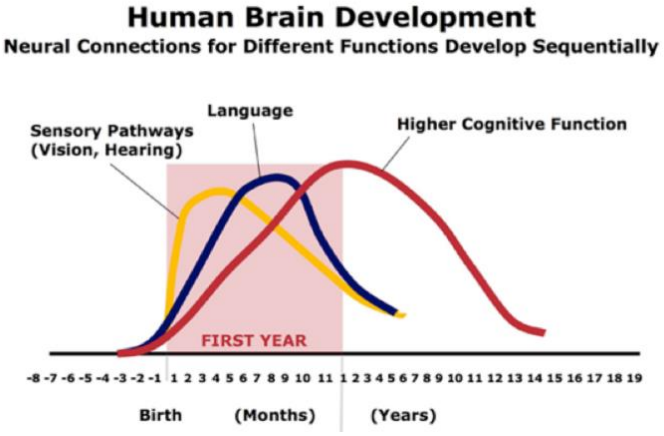


Image E: Different development at different stages of different areas of brain…



The implications of this are significant and complicated the issues exponentially. We need to know which parts of the brain are susceptible to our agents and at which specific times of neurocognitive development. For example, if there is an impact of our agents on development, then it might not be as simple as “kids are at risk under 2”. We might need to frame it as “a kid’s functioning in the area of speech development is at risk when we give an anaesthetic between these months, but spatial elements are not at risk at that age”.

Image F: Different development at different stages



Can we protect the brain?

Xenon and beyond…maybe.

Inflammation and ischaemia coupled with the stress response of surgery is blunted by anaesthesia and so does anaesthesia not infer protection against these harmful effects of surgery? Morbidity and abnormal neurodevelopment has been shown in non-human primates and other animal studies exposed to pain and stress that is not alleviated by analgesia and anaesthesia.

We also have a few promising agents that offer protective effects above that of merely preventing harmful effects of stress and surgery. Dexmedetomidine was shown to reduce neuro-apoptosis in rats exposed to Isoflurane. Melatonin has also showed a reduction in neuro-apoptosis when administered with other neurotoxic agents.

Xenon adds another layer of confusion to the picture, whilst also acting on NMDA receptors, it doesn't have the same negative effect as other drugs and has been shown to reduce neuro-apoptosis when used in combination with other volatiles. Why do two agents that act on the same receptors have apparently opposing effects?

Sun et al reported that IV Astragaloside protects new born rats from anaesthesia-induced apoptosis. Their study published in 2016 does raise some interesting avenues for further pharmacological developments. Astragaloside is a saponin purified from a traditional Chinese herbal medicine component Astragalus membraneaceus. It has exhibited antioxidant activity and anti-apoptosis function in various types of cells. These anti-oxidants and anti-apoptosis features seem to mitigate damage caused by isoflurane.

We can also highlight the issue to families and social support structures. Integrating a "catch up" programme for children and their families before and after the surgical procedures, planning and scheduling procedures so they do not interfere with regular home life (day case surgery, procedures during school holidays to minimise missed teaching time, "hospital school' and outreach teachers)

SmartTots @ https://smarttots.org/

SmartTots is a collaboration between the IARS, the FDA and other organisations who are working to make anaesthesia safer for infants and children. Their mission is to coordinate and fund research with the goal of ensuring safe surgery for millions of children who undergo anaesthesia. Theses organisations work together and try to leverage their collective resources to address this important issue.

SmartTOTS funds paediatric anaesthesia research with the goal of making surgery safer for children. Guided by top experts in multiple fields (anaesthesiology, paediatrics, neuroscience, and epidemiology) they facilitate and support studies of existing anaesthetic drugs and their effects on childhood development. Anaesthetic and sedative types, dosages and number of exposures are studied to determine if anaesthetics pose hazards to children. Findings from our research will allow for the safest anaesthetic regimes and potentially foster the development of new anaesthetic drugs.

So now what?
More confusion, can we really re-assure our parents?

Pragmatism needs to be applied, and many of these elements are already corner stones of paediatric anaesthetic practise. Emergency surgery must go ahead. Not providing analgesia is absolutely debunked, we must provide anaesthesia for these children. So, when we do we must consider what we do and be mindful of possible implications of our practise.

- Exercise balance – as opioids seem to be neurodevelopmentally neutral, higher dose opioids seem to be a starting point however they also come with their own set of issues. Avoid ketamine and high dose of prolonged volatile agents. (IV induction, quickly changing to lowest dose possible, supplementing with other agents and nitrous oxide to reduce MAC and regional techniques/LA)
- Be efficient –reduce exposure time. (A two-hour CVC placement may not be what's best for the child)
- Regional options – this might be another way to balance or exposure the child to less anaesthetic agent. (NB be aware of neuraxial techniques, peripheral blocks and local infiltration may be better)
- Defend physiology aggressively, improve monitoring and response to changes in physiological parameters.

- Dexmeditomidine, Xenon and Melatonin…
- “Catch up” support for family and children in the pre- and post-surgical time.

Smarttots.com is an interactive website that has specific pages for parents and clinicians and provides tailored information to each group of interested stake-holders.

The data we have seems to support our current thinking that, a single, as brief as is required anaesthetic, in which we optimise all physiological parameters infers no further harm to other wise well children. Vulnerable subgroups (septic, premature, congenital abnormalities), repeated exposures and prolonged exposures are likely to pose more risk, but we are unable to quantify it. If the child needs surgery, the child needs a ‘good’ anaesthetic. We need to be able to offer this family a ‘good’ anaesthetic.

Some practical answers to parents’ questions
Trust me, I’m a doctor isn’t good enough!

- What are the concerns about anaesthetics and children?
- How did doctors become aware of the problem?
- If anaesthetics cause problems in animals, will they cause similar problems in people?
- Why might my child need anaesthesia or sedation? Can my child have an operation without anaesthesia if anaesthesia is harmful to my child?
- What should I do if my child needs surgery or a procedure requiring anaesthesia or sedation?
- Should I consider putting off a needed procedure until my child is older?
- Is one anaesthetic or sedative better or worse than another?
- What can I do to lessen the harmful effects?
- Where can I learn more?

(PACSA position statement, full statement available on sasaweb.com)

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