Update in Paediatric Anaesthesia

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This update covers topics relevant to the episodic as well as the specialist paediatric anaesthetist.

An update on maintaining skills and competency, including courses and networks in New Zealand, will also be discussed on the day.

Neurotoxicity and Paediatric Anaesthesia

Background

Repetitive painful stimulation in neonatal animals is associated with cell death and adverse neurologic outcomes, changes in behavioural and cognitive function and chronic pain syndromes. Similarly, untreated painful stimulation in early life in humans is associated with diminished cognition and motor function in later life.

However, in the last two decades all routinely used sedatives and anaesthetics have been found to be neurotoxic in a wide variety of animal species, including nonhuman primates.

Animal Data

The neurotoxic effects observed in animals include apoptotic neuronal cell death, diminished neuronal density, decreased neurogenesis and gliogenesis, alterations in dendritic architecture, diminution of neurotrophic factors, mitochondrial degeneration, cytoskeletal destabilization, abnormal reentry into the cell cycle, as well as learning and memory impairment [1].

Extrapolation of this animal data to humans has some inherent difficulties.

Animal studies did not control for physiological variables like blood pressure, oxygenation, acidosis, hypoglycemia; factors that can induce apoptosis in these anaesthetized animals. Also drug doses and duration of exposure in animal studies cannot be transferred to humans. Apoptosis secondary to anaesthetic exposure is only seen at certain stages of brain development and is not uniform. It is not known how these vulnerable development stages (immature neurons) in animals correlate with development stages of human brain. Animal studies, also, do not include continuous stimulation of the central nervous system by surgical stress and pain [2].

Human Evidence

Several epidemiologic human studies have observed an association between (more than one) anesthesia exposure in patients younger than 3 to 4 years and subsequent learning disabilities and language abnormalities [3], whereas others have not found this link [4].

It remains unresolved whether anaesthetic exposure (type, duration) or other factors, such as the underlying medical condition, surgery, inflammatory response, pain, physiologic abnormalities during surgery, or other unknown factors, are causative for the observed association/abnormalities [2].

Current Status

It remains very unclear if the animal studies have any clinical relevance; or indeed how, or if, clinical practice needs to be altered. Answering these questions is of great importance given the huge numbers of young children exposed to general anaesthetics Additional animal and clinical research is urgently needed to identify the phenomenon's underlying mechanisms, to assess human applicability, and to devise mitigating strategies [5]

Take home messages

- no changes in anaesthetic clinical practice are recommended, anaesthesia and surgery is only undertaken when absolutely necessary in children (APAGBI consensus statement July 2015)
- surgical procedures performed under anesthesia be avoided in children under 3 years of age unless the situation is urgent or potentially harmful if not attended to
- (www .smarttots.org/resources/consensus .html) (6)
- parents and care providers should be made aware of the potential risks that anaesthetics pose to the developing brain (6)
- surgeons, anaesthesiologists, and parents should consider carefully how urgently surgery is needed, particularly in children under 3 years of age (6)
- No consensus statement from SPANZA

1   Jevtovic-Todorovic V, Hartman RE, Izumi Y, et al. Early exposure to common anaesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci 2003;23:876–82

2   Erica P. Lin, Sulpicio G. Soriano, Andreas W. Loepke. Anesthetic Neurotoxicity. Anesthesiology Clin 32 (2014) 133–155

3   Wilder RT, Flick RP, Sprung J, et al. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology 2009;110: 796–804

4   Sprung J, Flick RP, Wilder RT, et al. Anesthesia for cesarean delivery and learning disabilities in a population-based birth cohort. Anesthesiology 2009;111:302–10

5   Andrew J. Davidson, Karin Becke, Jurgen de Graaff, Gaia Giribaldi, et al. Anesthesia and the developing brain: a way forward for clinical research. Pediatric Anesthesia 25 (2015): 447–452

6   Bob A. Rappaport, Santhanam Suresh, Sharon Hertz, Alex S. Evers, Beverley A. Orser. Anesthetic Neurotoxicity — Clinical Implications of Animal Models. N Engl J Med 372;9: 796-797

Emergence Agitation

Background

Emergence delirium/agitation (ED/EA), discomfort, tantrums and pain are some of the early postoperative negative behaviour (e-PONB) observed after general anesthesia; more often in children (1).

ED is a very common occurrence in children; the reported incidence being as high as 70% after sevoflurane or desflurane anaesthesia (1). Children of pre-school age are most commonly affected. It is self-limiting but may cause distress to patients, parents and staff, and may result in physical harm to the child, particularly at the site of surgery, dressings and intravenous cannulae (2).

More than 10 points on the Pediatric Anesthesia Emergence Delirium (PAED) scale (3), that incorporates cognitive and agitation assessment, has been found to be the a valid and reliable method of diagnosing ED and is used in most studies studying ED in children.

Update

Paediatric Anesthesia Behaviour (PAB) score has been used to predict occurrence of postoperative ED in children (4).

Pathophysiology

At the termination of sevoflurane anaesthesia the electroencephalogram (EEG) in children with ED shows, coinciding with arousal with delirious behaviour, a variety of EEG patterns occuring during the

indeterminate state before the appearance of normal wake or sleep patterns. In children without ED, the indeterminate state transits to classifiable sleep or drowsy states, before peaceful awakening (5)

Diagnosis

It is difficult to differentiate pain at wakeup from ED in children. Somaini et al showed that even though it is difficult to differentiate between ED and pain using FLACC and PAED scores, 'No eye contact', 'No purposeful action', and 'No awareness of surroundings' criteria (PAED Score) significantly correlated with ED whereas 'Inconsolability' and 'Restlessness' are not reliable enough to identify pain or ED in the first 15 min after awakening (6)

Etiology

Sevoflurane, Isoflurane or Desflurane anaesthesia all have similar incidence of ED in children whereas Halothane and propofol TIVA or propofol for maintenance with sevoflurane anaesthesia have lower incidence of ED (7)

Adjuncts

Compared with no adjunct, effective adjuncts for reducing the risk of EA during sevoflurane anaesthesia include dexmedetomidine (7,8,9), clonidine (7,8,9) and opioids, particularly fentanyl (7,9). Even though these interventions were associated with delay in discharge from PACU, there was no delay in discharge from the hospital (7,8,10).

Evidence for a bolus of propofol, ketamine or midazolam at the end of anaesthesia for decreasing the incidence of ED was of only moderate strength in the Cochrane review by Costi et al (7). In the same review parental presence at wake up and midazolam oral premedication did not decrease the incidence of ED. Similarly, depth of anaesthesia, rapid awakening and type of surgery have not been shown to influence the incidence of ED (10). Melatonin premedication has not shown to decrease the incidence of ED post sevoflurane anaesthesia when compared to midazolam premedication (11)

In a recently published RCT, Costi et al showed that a short transition to propofol 3 mg/kg over 3 min at the end of sevoflurane anesthesia is a simple and effective means of reducing EA in children undergoing MRI scans, without any adverse effects except slight delay in discharge form PACU (12).

Treatment

If treatment of ED becomes necessary, a single bolus of propofol (0.5–1.0 mg/kg IV), fentanyl (1–2.5 mg/kg IV), or dexmedetomidine (0.5 mg/kg IV) (8) has been successful in decreasing the severity and duration of the episode (9)

Consequences

The odds ratio of having new-onset postoperative maladaptive behaviour is 1.43 for children with marked ED, as compared with children with no symptoms of ED (13)

Take Home message

ED is common in 2-5year olds, especially after inhalational anaesthesia with ether class of inhalational agents.

Propofol anaesthesia has a low incidence of ED but does not completely prevent it.

There is strong evidence for adjuncts like propofol (3mg/kg over 3 minutes), clonidine, dexmedetomidine or fentanyl (1mcg/kg), given at the end of the case, for decreasing incidence of ED. Evidence is not as strong for smaller bolus of propofol, midazolam or ketamine.

Speed of wakeup, parental presence, melatonin or midazolam pre-med and type of surgery has no

correlation/effect on the incidence of ED.

Control of pain is paramount even though ED is a distinct physiological entity compared to post-operative behaviour disturbance secondary to pain.

Occurrence of ED may have persistent postoperative maladaptive behaviour and should be managed actively, despite its self-limiting nature and parents should be informed of the same.

1   Stargatt R, Davidson AJ, Huang GH, et al. A cohort study of the incidence and risk factors for negative behavior changes in children after general anesthesia. Paediatr Anaesth 2006; 16: 846–59
2   Wong D D L, Bailey C R.Emergence delirium in children Anaesthesia 2015, 70, 375–392
3   Sikich N, Lerman J. Development and psychometric evaluation of the post anesthesia emergence delirium scale. Anesthesiology 2004; 100: 1138–45.
4   Beringer RM, Greenwood R, Kilpatrick N. Development and validation of the Pediatric Anesthesia Behavior score – an objective measure of behaviour during induction of anesthesia. Pediatric Anesthesia 2014; 24: 196–200.
5   Martin JC, Liley DT, Harvey AS, Kuhlmann L, Sleigh JW, Davidson AJ. Alterations in the functional connectivity of frontal lobe networks preceding delirium in children. Anesthesiology. 2014 Oct;121(4):740-52.
6   Marta Somaini, Emre Sahillioglu, Chiara Marzorati, Federica Lovisari, Thomas Engelhardt & Pablo M. Ingelmo Emergence delirium, pain or both? a challenge for clinicians Pediatric Anesthesia 25 (2015) 524–529

Fluids in Paediatric Anaesthesia

Background

For more than half a century, hypotonic fluids (sodium concentrations as low as 30 mmol/L) have been used for maintenance of hydration in children, mostly due to fear of hypernatremia with use of isotonic fluids (1).

Hypotonic fluids in children have since been shown to cause hyponatraemia; with some children having severe outcomes such as seizures, cerebral oedema, and death (2,3).

Current Status

Maintenance fluids in all hospitalised children -

Cochrane review of >1000 children (4) showed that isotonic fluids (in the first 24hrs of administration) were the best maintenance fluids for in-hospital children, isotonic fluids having substantially lower risk of hyponatraemia (17% versus 34%; RR 0.48; 95% CI 0.38 to 0.60, high quality evidence).

These findings were confirmed by the largest RCT (670 in-hospital children needing >6hrs of maintenance fluids, monitored for 72hrs with safety removal of children from study if with severe hyponatremia; using plasmalyte with 5%D as maintenance fluids) (5)

This trial confirmed that, in children who need maintenance fluid therapy, use of an isotonic fluid reduces the risk of hyponatraemia compared with use of a hypotonic fluid (0.45%NS with 5%D), with no increases in the risk of adverse outcomes.

It also showed a 7times (possible) increased risk of severe hyponatremia and seizures in the hypotonic fluid group **(5 children were removed due to safety concern with hyponatremia).**

The increased risk of hyponatremia with hypotonic fluids (compared to isotonic fluids) was seen in surgical (OR 0·32, 95% CI 0·12–0·82; p=0·02) and non-surgical patients (OR0·32,0·12 85;p=0·02) as well as patients in the intensive care unit (OR 0·15, 0·01–2·08; p=0·16).

Smaller studies from around the world (6,7) have shown similar results and confirmed the notion that isotonic maintenance fluid administration is safe in general pediatric patients and may result in fewer cases of hyponatremia.

Risk of Hypernatremia

No studies (RCTs or reviews) have shown hypernatremia with isotonic fluids (0.9%NS/RL/PL) for maintenance in the first 24 hrs of treatment (4,5, 6,7). There is no consensus on time for peak fall in sodium levels; varying from 6hrs (5) to 24hrs (4).
In one study (n=119, children with pneumonia)(7), in the isotonic group, there was significant increase in serum sodium between 24 and 48 hours (4.3, 95% CI: 0.1, 8.4 mEq/L; P=0.04). The authors recommended reduced volume isotonic fluids for maintenance after 24hrs with serum electrolyte measurements to guide treatment.

Maintenance fluids in critically ill children

Safety of isotonic fluids, as maintenance fluids, for children in intensive care unit has been proven by the results of the RCT by McNab et al (5)

Volume of intravenous fluid required for treatment will however vary according to disease states in critically ill children and will be directed by fluid status (hypervolemia, euvolemia, or hypovolemia), glucose and electrolyte levels (should be routinely monitored at regular intervals) in critically ill children (8).

Carcillo, in his review, recommended that both intravenous fluid composition and quantity of infusion should be adjusted accordingly on an evolving basis (8).

Questions

How much glucose and potassium, which isotonic fluid?

There is no conclusive evidence on addition of glucose and how much.

There is risk of hypoglycemia in critically ill children and in prolonged starvation postop with secondary starvation ketosis (8). All large studies in the last 5 years have used isotonic fluids with 5% glucose (5,6,7) or not studied hypoglycemia as primary outcome (4). However, perioperative administration of 5% glucose for prevention of hypoglycemia may result in stress- induced hyperglycemia. Postoperative hyperglycemia was observed in 94% of children receiving 5% glucose and in 37% of group with 3.33% glucose in 0.3%NaCl intraoperatively (9).

Fluid therapy with a Na^+-content close to the physiologic range with addition of 1.0-2.5% instead of 5.0% glucose has been advised (10). There are, however, no studies with fluids containing this concentration of glucose.

Similar lack of evidence exists with respect to potassium and risk of hypokalemia. In the RCT by McNab et al about 1/3 of the isotonic group had potassium added to the solution. Need for adding potassium to solutions on the wards raises substantial safety concern because of the risk of inadvertent drug error (5,10).

Different isotonic fluids might have different risk profiles due to differences in sodium load, the risk of drug and blood product incompatibilities due to added magnesium/potassium/bicarbonate/acetate, or higher chloride concentration leading to hyperchloremic acidosis.

Availability of commercial preparations and cost may be other limiting factors.

Take home message

Isotonic salt solutions with glucose, although more expensive, should be used for volume resuscitation, maintenance and perioperatively.

There is no role of hypotonic solutions in children needing maintenance fluids for more than 6 hours.

Intravenous fluid in children is therapy like other drugs and should be prescribed and altered regularly vis-à-vis volume and composition of fluid used.

Finally, there is a need for new balanced fluids with glucose to be developed for paediatrics and to be tested in well-designed trials

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2. Halberthal M, Halperin ML, Bohn D. Acute hyponatraemia in children admitted to hospital: retrospective analysis of factors contributing to its development and resolution. *BMJ* 2001; 322: 780–82.
3. Hughes PD, McNicol D, Mutton PM, Flynn GJ, Tuck R, Yorke P. Postoperative hyponatraemic encephalopathy: water intoxication. Intravenous fluids for seriously ill children: time to reconsider. *Lancet* 2003; 362: 1320–23.
4. McNab S, Ware RS, Neville KA, Choong K, Coulthard MG, Duke T, Davidson A, Dorofaeff T. Isotonic versus hypotonic solutions for maintenance intravenous fluid administration in children. Cochrane Database Syst Rev. 2014 Dec 18;12:CD009457. doi:10.1002/14651858

Dexmedetomidine, the new wonder drug in paediatric anaesthesia?

Dexmedetomidine has been attributed to have sedative, anxiolytic, sympatholytic, and analgesic properties. It has been used for sedation during regional anesthesia, for radiology cases, for sedation in the intensive care unit and for premedication as well as for decreasing the incidence of emergence delirium and shivering in postanesthesia care units (1,2). Its alpha-2 selectivity, limited renal elimination, and relatively short half-life are desirable properties for paediatric anaesthesia. It has a buccal bioavailability of 82%.

Increasing doses of dexmedetomidine (1–3 mcg/kg) in children with no obstructive sleep apnea (OSA) is not associated with decrease in airway reflexes and does not appear to be associated with clinical signs of airway obstruction. The effect on airway of children with OSA is however not clear.

Based on animal studies, dexmedetomidine might be a useful adjunct to an opioid-based technique than current volatile anaesthetic techniques in neonates to decrease possible neurotoxic effects of anaesthetics on the developmental brain (3). However the dose and combinations need to be studied in more detail before it becomes standard practice.

Bradycardia, hypotension, cardiac conduction delay, and evoked potential changes all require greater scrutiny in the pediatric population and particularly with respect to different age groups (4). Similarly, systemic absorption and supra-spinal effects of dexmedetomidine in prolongation of effect of regional blocks needs to be explored further.

1. Costi D, Cyna AM, Ahmed S, Stephens K, Strickland P, Ellwood J, Larsson JN, Chooi C, Burgoyne LL, Middleton P. Effects of sevoflurane versus other general anaesthesia on emergence agitation in children. Cochrane Database Syst Rev. 2014 Sep 12;9:CD007084. doi: 10.1002/14651858.CD007084.pub2
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