Pediatric Anesthesia

EDITORIAL

Use of anesthetics in young children Consensus statement of the European Society of Anaesthesiology (ESA), the European Society for Paediatric Anaesthesiology (ESPA), the European Association of Cardiothoracic Anaesthesiology (EACTA), and the European Safe Tots Anaesthesia Research Initiative (EuroSTAR)

Background

Experimental studies have shown that general anesthetics may cause a variety of morphological changes in developing immature brain of laboratory animals (1). Additionally, there is some evidence that longterm and prolonged exposure may be worse than short-term exposure in some animal species (2,3). However, the relevance of these findings in human beings is currently unknown (4,5) and studies have shown controversial results (6-8). While a number of investigations in humans have demonstrated an association between surgical and anesthetic exposure and negative neurodevelopmental outcome (9-11), several others have been unable to find such an association or only in a minor subset of exposed children with or without extensive individual neurocognitive testing (12-18). It remains, therefore, very difficult to identify whether any negative neurodevelopmental effects are due to anesthetic drugs, the conduct of anesthesia, surgical trauma or the underlying clinical conditions(s) (3-19).

Importantly, however, two prospective human studies, with the most robust designs, indicate that short-term single exposure of 60 minutes or less to surgery and anesthesia is not associated with measurable long-term neurodevelopmental problems (12,16).

FDA statement

On December 14, 2016, the Food and Drug Administration (FDA) issued a warning statement for the USA regarding the use of anesthesia or sedation in young children (and pregnant women) (20). This statement highlights potential risk of anesthetic procedures that last longer than 3 h or multiple procedures required in children less than 3 years of age. The evidence to support such warning is currently insufficient and incomplete. Therefore, this FDA warning is not shared by the European Societies listed below.

The ESA/ESPA/EACTA/EuroSTAR Consensus Statement

No child or pregnant woman should ever undergo any medical procedure that is not necessary. Similarly, young children (and pregnant women) should not undergo surgery and general anesthesia for trivial reasons. However, delaying or avoiding surgery may result in a significant and real risk of a variety of adverse outcomes. If an invasive procedure is necessary adequate anesthesia/analgesia are mandatory. Indeed, there is good evidence that inadequate anesthesia and analgesia may result in significant and serious complications (21,22). There is currently no evidence to support the suggestion that a change from established techniques for prolonged or repeated procedures would have any impact on long-term outcomes including neurocognition and development in young children.

Furthermore, the implied 'safe' cut-off points of age 3 years or duration of procedure of 3 h quoted in the FDA warning statement are not currently supported by evidence derived from human studies.

Given, the uncertainty in this domain, it is reasonable to discuss all aspects of perioperative safety with patients, parents, and families. However, discussion of hypothetical risks based primarily on animal research not confirmed in human studies may create anxiety.

Established safe anesthetic techniques delivered by trained and experienced staff in a pediatric environment supported by the necessary clinical organization are essential factors for the delivery of safe anesthesia and sedation in children (23).

Conclusion

There is currently no compelling evidence to change anesthetic practice but anesthesiologists should provide ing a necessary s on the potenocedures. The The study received no external funding.

Conflicts of interest

The authors report no conflict of interest.

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adequate information on the risks of avoiding a necessary intervention/anesthesia procedure as well as on the potential risks associated with anesthetic procedures. The European Societies listed above participate in international collaborations and support the principles of safe conduct of anesthesia in children and pregnant women. Information for parents and information for anesthetists will be updated as and when new issues arise.

Acknowledgment

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References

- Jevtovic-Todorovic V, Hartman RE, Izumi Y, et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J Neurosci* 2003; 23: 876-882.
- 2 Vutskits L, Xie Z. Lasting impact of general anaesthesia on the brain: mechanisms and relevance. *Nat Rev Neurosci* 2016; **18**: 705-717.
- 3 Zou X, Patterson TA, Divine RL, et al. Prolonged exposure to ketamine increases neurodegeneration in the developing monkey brain. Int J Dev Neurosci 2009; 27: 727-731.4.
- 4 Todd MM. Anesthetic neurotoxicity: the collision between laboratory neuroscience and clinical medicine. *Anesthesiology* 2004; 101: 227-230.
- 5 Andropoulos DB, Greene MF. Anesthesia and the developing brains - Implications of the FDA warning. *N Engl J Med* 2017; **376**: 905-907.
- 6 Hansen TG. Anesthesia-related neurotoxicity and the developing animal brain is not a significant problem in children. *Pediatr Anesth* 2015; 25: 65-72.
- 7 Rappaport BA, Suresh S, Hertz S, Evers AS, Orser BA. Anesthetic neurotoxicity-clinical implications of animal models. *N Engl J Med* 2015; **372**: 796-797.
- 8 Psaty BM, Platt R, Altman RB. Neurotoxicity of generic anesthesia agents in infants and children: an orphan research question in search of a sponsor. JAMA 2015; 313: 1515-1516.

- 9 Ing C, DiMaggio C, Whitehouse A, et al. Long-term differences in language and cognitive function after childhood exposure to anesthesia. *Pediatrics* 2012; 130: e476-e485.
- 10 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.
- 11 Ing CH, DiMaggio CJ, Malacova E, et al. Comparative analysis of outcome measures used in examining neurodevelopmental effects of early childhood anesthesia exposure. *Anesthesiology* 2014; **120**: 1319-3214.
- 12 Sun LS, Li G, Miller TL, et al. Association between a single general anesthesia exposure before age 36 months and neurocognitive outcomes in later childhood. *JAMA* 2016; **315**: 2312-2320.
- 13 Hansen TG, Pedersen JK, Henneberg SW, et al. Academic performance in adolescence after inguinal hernia repair in infancy: a nation-wide cohort study. *Anesthesiology* 2011; **114**: 1076-1085.
- 14 Hansen TG, Pedersen JK, Henneberg SW, Morton NS, Christensen K. Educational outcome in adolescence following pyloric stenosis repair before 3 months of age: a nation-wide cohort study. *Pediatr Anesth* 2013; 23: 883-890.
- 15 Glatz P, Sandin RH, Pedersen NL, Bonamy AK, Eriksson LI, Granath F. Academic performance after anesthesia and surgery during childhood - a large scale nation-wide study. *JAMA Pediatr* 2017; **171**: e163470.

- 16 Davidson AJ, Disma N, de Graaff JC, et al. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awakeregional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. *Lancet* 2016; **387**: 239-250.
- 17 O'Leary JD, 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. *Anesthesiology* 2016; **125**: 272-279.
- 18 Graham MR, Brownell M, Chateau DG, Dragan RD, Burchill C, Fransoo RR. Neurodevelopmental assessment in kindergarten in children exposed to general anesthesia before the age of 4 years. A retrospective study. *Anesthesiology* 2016; **125**: 667-677.
- 19 Weiss M, Hansen TG, Engelhardt T. Ensuring safe anaesthesia for neonates, infants and young children: what really matters. *Arch Dis Child* 2016; **101**: 650-652.
- 20 FDA Drug Safety Communication. www.fda.gov/Drugs/DrugSafety/ucm532356. htm. Accessed April 21, 2017.
- 21 Anand KJS, Hickey PR. Halothane-morphine compared with high dose sufentanil for anesthesia and postop analgesia in neonatal cardiac surgery. N Engl J Med 1992; 326: 1-9.
- 22 Anand KJS. Revisiting a dilemma: repetitive pain vs. opioid exposure? *Acta Paediatr* 2016; **105**: 736-737.
- 23 Weiss M, Vutskits L, Hansen TG, Engelhardt T. Safe anesthesia for every tot - the SAFETOTS initiative. *Curr Opin Anaesthe*siol 2015; 28: 302-376.