

Title:

Are Opioids Pediatric Anesthesiologists' Sword of Damocles? With great power comes great responsibility and risk.

Running head: Perioperative opioid guidance

Article Category: Editorial

Authors:

George Chalkiadis,^{1,2} Susan Goobie,^{3,4} Suellen M. Walker.^{5,6}

Affiliations:

¹Department of Paediatric Anaesthesia and Pain Management, Royal Children's Hospital, Melbourne, Australia

²Murdoch Children's Research Institute, Melbourne, Australia

³Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Boston, USA

⁴Harvard Medical School, Boston, USA

⁵Clinical Neurosciences (Pain Research), UCL GOS Institute of Child Health, London, UK

⁶Department of Anaesthesia and Pain Medicine, Great Ormond St Hospital NHS Foundation Trust, London, UK

Corresponding Author:

George Chalkiadis,

Department of Paediatric Anaesthesia and Pain Management,

50 Flemington Rd, Parkville, Victoria 3052, Australia.

Telephone: +61393455233, Fax: +61393456003

Email: george.chalkiadis@rch.org.au

MESH Keywords:

analgesia; analgesics, opioid; pain; pain, postoperative; child; infant, newborn

Should paediatric anaesthesiologists change their practice regarding opioid use in children perioperatively? Societal concerns regarding the “opioid epidemic” have led some anesthesiologists to advocate for opioid-free anesthesia; this is not the solution to that problem.

There are numerous factors that underpin the safe and effective use of opioids for perioperative pain in children including the availability of different opioid preparations, protocols for titration and delivery systems such as patient-controlled analgesia, improved knowledge about the developmental pharmacodynamic and pharmacokinetic profiles of opioids, and increasing evidence related to the relative benefit and harm in different patient populations and clinical settings. The latter are well summarised in the Society for Pediatric Anesthesia (SPA) evidence-based recommendations for perioperative use of opioids in children¹ in this issue of *Pediatric Anesthesia*.

It is an undisputed fact that adequate perioperative analgesia is essential to minimise acute stress responses and physiological instability, and facilitate mobilisation and recovery. There is increasing awareness of potential long-term effects of pain and tissue injury on developing pain pathways, and the risk of persistent post-surgical pain following major surgery in later childhood.² The benefits of multimodal analgesia techniques to improve analgesia and/or minimise opioid requirements and dose-related side-effects are well-established and outlined in the SPA document¹ and in previous international evidence-based guidelines.^{3,4} However, there is a need to distinguish between ‘opioid-sparing’ and ‘opioid-free’ anesthesia. Avoiding opioids at the cost of uncontrolled pain is unacceptable. Alternative analgesia modalities may not be adequate or feasible for all patients, and the use of opioids remains an essential part of pain management regimens for many children.⁵

Increased numbers of opioid-related deaths in recent years have prompted some to coin the terms “opioid crisis” and “opioid epidemic”, with significant political and media attention focussing on the potential for misuse or diversion of prescription analgesics. Increases in opioid-related deaths have been reported in children of all ages, particularly related to heroin and illicit synthetic opioids in 15-19 year olds,⁶ but the limitations of data indicating an ‘epidemic’ have been recently summarised.⁷ This is not to underplay the public health issues related to opioid misuse, the potential impact on care and well-being of children and/or families with substance abuse disorders,⁸ or the lack of childproof packaging and risk of accidental overdose with access to drugs prescribed for adults in the household.⁶ However, health care professionals or families should not fear appropriate medical use of opioids. The evidence that use of intraoperative opioids causes, or is even associated with long-term abuse in

adults is scant and, to our knowledge, completely lacking in children. It is certainly inappropriate to propose a change of intra-operative anesthesia practice without such evidence. We could also find no evidence that judicious and responsible prescribing of opioids for children in the acute postoperative period when acetaminophen and NSAIDs provide insufficient analgesia, leads to substance use disorder.

There is no doubt that opioids can be associated with significant and potentially life-threatening adverse effects. Regular assessment with titration of analgesia against individual response is an essential component of ongoing perioperative care, particularly in those at increased risk of respiratory depression (e.g., preterm-born neonates, obstructive sleep apnoea, co-morbidities, and potential sedative adjunct interactions).^{9,10} The dose and duration of each drug modality should be matched to the type, time-course and severity of pain. Reports of respiratory depression following use of oral morphine for a relatively brief procedure in neonates,¹¹ and worse neurodevelopmental outcome following infusion of morphine contributing to hypotension in ventilated neonate¹² highlight the need for judicious use and monitoring when opioids are used in high-risk populations. They should not be misinterpreted as a lack of safety or efficacy of opioids for perioperative pain.

An important potential source of prescription opioids is discharge medication. Local governance and education systems need to ensure that: discharge prescriptions are written by medical staff with adequate training and knowledge that should include psychosocial risk assessment; an appropriate formulation, dose, and limited number of doses are dispensed;³ and parents have instructions for the safe storage of opioids and safe disposal of unused medication. This is an opportunity for pediatric anesthesiologists to continue to lead in ensuring responsible prescribing and dispensing of all analgesics both within the hospital and upon discharge. Improved knowledge of expected pain trajectories after commonly performed surgeries helps guide how much, what type, and for how long analgesia will be necessary. It is desirable to provide regular follow-up of post-surgical patients, in particular those undergoing surgeries where postoperative pain is expected to last several weeks and where adequate analgesia may facilitate rehabilitation and functional restoration. In line with this, secure electronic and real-time prescribing (for example: www2.health.vic.gov.au/public-health/drugs-and-poisons/safescript/about-safescript; accessed April 24) may help identify aberrant pain outcomes and inappropriate analgesic use or prescription to facilitate earlier intervention.

The SPA guidelines for the perioperative use of opioids support the appropriate and responsible use of opioids by pediatric anaesthesiologists for pediatric surgical patients. The opioid *sword of Damocles*

places great power in the hands of the pediatric anesthesiologist; it can be appropriately drawn with noble purpose and without undue fear provided the potential risks are recognized, respected and managed responsibly.

ETHICS: Not applicable

FUNDING: No study was performed and author time was funded by departmental resources

DISCLOSURES: The authors report no financial conflict of interest. George Chalkiadis is an Associate Editor of Pediatric Anesthesia. Susan Goobie and Suellen Walker are Section Editors of Pediatric Anesthesia.

ACKNOWLEDGEMENTS: The signatories listed below have read and commented on the content of this editorial and have agreed to endorse its content.

Mark Alcock
Department of Anaesthesia and Pain Management
Queensland Children's Hospital
Brisbane, Australia

Brian J Anderson
Department of Anaesthesiology
University of Auckland
Auckland, New Zealand

Karin Becke
Department of Anesthesiology and Critical Care Medicine
Cnopf Children's Hospital/Hospital Hallerwiese
Nuernberg, Germany

Charles Berde
Department of Anesthesiology, Critical Care and Pain Medicine
Boston Children's Hospital
Boston, USA

Patrick K. Birmingham MD
Department of Anesthesiology
Ann & Robert H. Lurie Children's Hospital of Chicago
Northwestern University Feinberg School of Medicine
Chicago, USA

Adrian Bosenberg
Department of Anesthesiology and Pain Management
Seattle Children's Hospital
Seattle, USA

Fiona Campbell
Department of Anesthesia and Pain Medicine
The Hospital for Sick Children

University of Toronto
Toronto, Canada

Joseph P. Cravero
Department of Anesthesiology, Critical Care, and Pain Medicine
Boston Children's Hospital
Harvard Medical School
Boston, USA

Andrew Davidson
Department of Paediatric Anaesthesia and Pain Management
Royal Children's Hospital
Murdoch Children's Research Institute
University of Melbourne

Jurgen C. de Graaff
Department of Anesthesiology
ErasmusMC - Sophia Children's Hospital
University Medical Center Rotterdam
Rotterdam, Netherlands

Thomas Engelhardt
Department of Anaesthesia
Royal Children's Hospital Aberdeen and School of Medicine
University of Aberdeen
Aberdeen, UK

Kenneth R. Goldschneider
Professor, Clinical Pediatrics and Anesthesia
Director, Pain Management Center
Cincinnati Children's Hospital Medical Center
Cincinnati, USA

Elliot J. Krane
Department of Anesthesiology, Perioperative and Pain Medicine
Department of Pediatrics
Stanford University School of Medicine
Stanford Children's Health System
Palo Alto, USA

Stefan Lundeberg PhD
Pediatric Pain Treatment Service
Astrid Lindgren Children's Hospital
Karolinska University Hospital
Stockholm, Sweden

Greta M Palmer
Department of Paediatric Anaesthesia and Pain Management
Royal Children's Hospital
Murdoch Children's Research Institute
University of Melbourne

Melbourne, Australia

David Polaner
Department of Anesthesiology and Pain Management
Seattle Children's Hospital
University of Washington School of Medicine
Seattle, USA

Chandra Ramamoorthy
Department of Anesthesiology, Perioperative and Pain Medicine
Packhard Children's Hospital at Stanford
Palo Alto, USA

Navil F Sethna
Department of Anesthesiology, Critical Care and Pain Medicine
Boston Children's Hospital
Harvard Medical School
Boston, USA

Mark Thomas
Department of Anaesthesia and Pain Medicine
Great Ormond St Hospital,
London, UK

Britta S von Ungern-Sternberg
Department of Anaesthesia and Pain Management
Perth Children's Hospital
University of Western Australia
Telethon Kid's Institute
Perth, Australia

Francis Veyckemans MD
Clinique d'Anesthésie Pédiatrique
Hôpital Jeanne de Flandre, CHRU de Lille,
Lille, France.

Laszlo Vutskits
Department of Pediatric Anesthesiology
University Hospitals of Geneva
Geneva, Switzerland

Gary A. Walco
Department of Anesthesiology and Pain Medicine
University of Washington School of Medicine
Seattle Children's Hospital
Seattle, USA

Steven J. Weisman,
Department of Anesthesiology and Department of Pediatrics
Children's Hospital of Wisconsin
Medical College of Wisconsin

Milwaukee, USA

Robert T. Wilder
Department of Anesthesiology and Perioperative Medicine
Mayo Clinic
Rochester, USA

References:

1. Cravero J, Agarwal R, Berde C, et al. The Society for Pediatric Anesthesiology recommendations for the use of opioids in children during the perioperative period. *Pediatric Anesthesia*. 2019;in press.
2. Rabbitts JA, Fisher E, Rosenbloom BN, Palermo TM. Prevalence and Predictors of Chronic Postsurgical Pain in Children: A Systematic Review and Meta-Analysis. *J Pain*. 2017;18(6):605-614.
3. Schug SA, Palmer GM, Scott DA, Halliwell R, Trinca J, Medicine. *Acute Pain Management: Scientific Evidence (4th Edition)*. Melbourne: ANZCA & FPM; 2015. http://fpm.anzca.edu.au/documents/apmse4_2015_final; accessed April 24th 2019
4. Association of Paediatric Anaesthetists of Great Britain and Ireland. Good practice in postoperative and procedural pain management, 2nd edition. *Paediatr Anaesth*. 2012;22 Suppl 1:1-79.
5. Veyckemans F. Opioid-free anaesthesia: Still a debate? *Eur J Anaesthesiol*. 2019;36(4):245-246.
6. Gaither JR, Shabanova V, Leventhal JM. US National Trends in Pediatric Deaths From Prescription and Illicit Opioids, 1999-2016. *JAMA Netw Open*. 2018;1(8):e186558.
7. Krane EJ, Weisman SJ, Walco GA. The National Opioid Epidemic and the Risk of Outpatient Opioids in Children. *Pediatrics*. 2018;142(2).
8. Feder KA, Letourneau EJ, Brook J. Children in the Opioid Epidemic: Addressing the Next Generation's Public Health Crisis. *Pediatrics*. 2019;143(1).
9. Howard RF, Lloyd-Thomas A, Thomas M, et al. Nurse-controlled analgesia (NCA) following major surgery in 10,000 patients in a children's hospital. *Paediatr Anaesth*. 2010;20(2):126-134.
10. Jay MA, Thomas BM, Nandi R, Howard RF. Higher risk of opioid-induced respiratory depression in children with neurodevelopmental disability: a retrospective cohort study of 12 904 patients. *Br J Anaesth*. 2017;118(2):239-246.
11. Hartley C, Moultrie F, Hoskin A, et al. Analgesic efficacy and safety of morphine in the Procedural Pain in Premature Infants (Poppi) study: randomised placebo-controlled trial. *Lancet*. 2018;392(10164):2595-2605.
12. Hall RW, Kronsberg SS, Barton BA, Kaiser JR, Anand KJ. Morphine, hypotension, and adverse outcomes among preterm neonates: who's to blame? Secondary results from the NEOPAIN trial. *Pediatrics*. 2005;115(5):1351-1359.