

## Pure-AMC

### Optimal postoperative pain management: redefining the role for opioids

Hollmann, Markus W.; Rathmell, James P.; Lirk, Philipp

*Published in:*  
Lancet

*DOI:*  
[10.1016/S0140-6736\(19\)30854-2](https://doi.org/10.1016/S0140-6736(19)30854-2)

Published: 01/01/2019

*Citation for pulished version (APA):*

Hollmann, M. W., Rathmell, J. P., & Lirk, P. (2019). Optimal postoperative pain management: redefining the role for opioids. *Lancet*, 393(10180), 1483-1485. [https://doi.org/10.1016/S0140-6736\(19\)30854-2](https://doi.org/10.1016/S0140-6736(19)30854-2)

#### General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

#### Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

linked, population-level databases, is required. The investigators acknowledge these limitations in their report.

The results of this study, in conjunction with results of studies of pregnancy interval after early loss and with findings of studies using new approaches to study interval after a livebirth, suggest that interpregnancy interval might be less important than previously assumed, at least for women in high-income regions. Rather than adhering to hard and fast rules, clinical recommendations should consider a woman's current health status, her current age in conjunction with her desires regarding child spacing and ultimate family size, and particularly following a loss, her emotional readiness to become pregnant again.

#### Mark A Klebanoff

Center for Perinatal Research, The Research Institute at Nationwide Children's Hospital, Columbus, OH 43215, USA; and Departments of Pediatrics and Obstetrics and Gynecology, College of Medicine, and Division of Epidemiology, College of Public Health, The Ohio State University, Columbus, OH, USA  
mark.klebanoff@nationwidechildrens.org

I have prepared a grant application to the US National Institutes of Health, currently pending, to study the association of interpregnancy interval with pregnancy outcome. I declare no other competing interests.

- 1 Conde-Agudelo A, Rosas-Bermudez A, Kafury-Goeta AC. Birth spacing and risk of adverse perinatal outcomes: a meta-analysis. *JAMA* 2006; **295**: 1809–23.
- 2 Hughes E. Infant mortality—results of a field study in Gary, Ind. [print/digital]: based on births in one year [1916]. Washington, DC: Government Printing Office, 1923.
- 3 Ball SJ, Pereira G, Jacoby P, de Klerk N, Stanley FJ. Re-evaluation of link between interpregnancy interval and adverse birth outcomes: retrospective cohort study matching two intervals per mother. *BMJ* 2014; **349**: g4333.
- 4 Class QA, Rickert ME, Oberg AS, et al. Within-family analysis of interpregnancy interval and adverse birth outcomes. *Obstet Gynecol* 2017; **130**: 1304–11.
- 5 Hanley GE, Hutcheon JA, Kinniburgh B, Lee L. Interpregnancy interval and adverse pregnancy outcomes: an analysis of successive pregnancies. *Obstet Gynecol* 2017; **129**: 408–15.
- 6 Shachar BZ, Mayo JA, Lyell DJ, et al. Interpregnancy interval after live birth or pregnancy termination and estimated risk of preterm birth: a retrospective cohort study. *BJOG* 2016; **123**: 2009–17.
- 7 Kangatharan C, Labram S, Bhattacharya S. Interpregnancy interval following miscarriage and adverse pregnancy outcomes: systematic review and meta-analysis. *Hum Reprod Update* 2017; **23**: 221–31.
- 8 WHO. Report of a WHO technical consultation on birth spacing: Geneva, Switzerland 13–15 June 2005. Geneva: World Health Organization, 2007. <http://apps.who.int/iris/handle/10665/69855> (accessed Jan 8, 2019).
- 9 Regan AK, Gissler M, Magnus MC, et al. Association between interpregnancy interval and adverse birth outcomes in women with a previous stillbirth: an international cohort study. *Lancet* 2019; published online Feb 28. [http://dx.doi.org/10.1016/S0140-6736\(18\)32266-9](http://dx.doi.org/10.1016/S0140-6736(18)32266-9).
- 10 Hernan MA, Taubman SL. Does obesity shorten life? The importance of well-defined interventions to answer causal questions. *Int J Obes (Lond)* 2008; **32** (suppl 3): S8–14.

## Optimal postoperative pain management: redefining the role for opioids



Fear of pain is deeply rooted among patients who are about to have surgery.<sup>1</sup> Satisfactory perioperative pain management is crucial to assuring a good patient experience, optimising postoperative outcomes, and enhancing functional recovery after surgery.<sup>2</sup> Despite decades of research showing the benefits of various new analgesic strategies, many patients endure severe postoperative pain,<sup>3</sup> and this holds true across all age groups and continents, even after surgery widely considered to be minor.<sup>4</sup> A 2016 study from the USA, which enrolled 799 449 patients, showed that reliance on opioid analgesics as the mainstay for perioperative pain management is still widespread.<sup>5</sup> This situation is worrying because several countries, most prominently the USA, Canada, and Australia, are struggling with an opioid crisis of unprecedented proportions.<sup>6</sup> There are an estimated 2 million patients in the USA who have an opioid use disorder,<sup>7</sup> with approximately

90 deaths occurring every day in the USA from an opioid overdose.<sup>8</sup> For many of these individuals, opioid dependency started with a prescription after minor trauma or surgery, highlighting the pivotal role of the health-care system in this epidemic.

In *The Lancet*, a new Series on postoperative pain management and opioids<sup>3,6,9</sup> details the current state of perioperative pain management with a strong focus on opioids, their role as analgesics, and the problems that accompany their widespread use. Paul Glare and colleagues<sup>3</sup> revisit the rationale for the use of opioids and other analgesics: to alleviate acute postsurgical pain and disrupt the transition from acute to chronic postsurgical pain. As the authors explain, it is now firmly established that poorly controlled acute pain after surgery is among the strongest predictors for the development of chronic postsurgical pain, but simply using escalating doses of opioids might only

See [Series](#) pages 1537, 1547, and 1558

worsen the problem. Mark Neuman and colleagues<sup>6</sup> recount how opioid overprescribing after surgery emerged and delineate prescribing, hospital, and public policy interventions to standardise and decrease the dispensing of opioids after surgery. Both groups of authors<sup>3,6</sup> advocate for an approach that includes transitional pain clinics for patients at high risk for prolonged opioid use after surgery as a model for the future.<sup>10</sup> Lesley Colvin and colleagues<sup>9</sup> review the basic mechanisms that underlie the adverse effects of opioid use, including opioid-induced hyperalgesia and tolerance. As our understanding of the limitations of opioid use has grown, multimodal analgesic regimens are increasingly used, helpful in decreasing opioid dose<sup>11</sup> and could be the key to avoiding long-term dependence.<sup>10</sup> By combining non-opioid analgesics with targeted regional anaesthetic techniques, multimodal analgesic regimens target multiple sites along the nociceptive pathway with the net effect of limiting opioid dose, improving analgesia, and enhancing safety.<sup>11</sup> Better understanding of the basic mechanisms underlying opioid-induced hyperalgesia and tolerance, including the role of the  $\beta$ -arrestin pathway, has led to the development of biased agonists that could provide similar analgesic effects to opioids with fewer side-effects in the future.<sup>9</sup>

Currently, the best approach is multimodal analgesia. The first component of an effective multimodal analgesic regimen should be one or two simple non-opioid analgesics: in the absence of contraindications, acetaminophen, a non-steroidal anti-inflammatory

drug, or a cyclo-oxygenase-2 inhibitor. An adjuvant analgesic, such as an antiepileptic,  $\alpha$ 2 agonist, or ketamine, is often added, on the basis of the procedure and patient's risk profile. Advanced techniques such as neuraxial (spinal and epidural) anaesthesia and analgesia, nerve blocks, and wound infiltration should be integrated into the multimodal analgesic regimen whenever feasible. Wound infiltration with local anaesthetic and regional analgesia can provide excellent dynamic pain relief, but care must be taken to align the duration of these advanced analgesic methods with the anticipated time course of pain, and the techniques must be meaningfully integrated into the overall plan of care.<sup>12</sup> Opioids should be used as rescue medication, intravenously for as short a time as possible, and orally as soon as feasible. The perioperative initiation of extended-release transdermal or fast-onset transmucosal opioids to treat acute pain should be avoided.

Research that extends well beyond the immediate postoperative period is needed. Brandal and colleagues<sup>13</sup> summarised the experiences of one institution in implementing opioid-sparing anaesthesia as part of an enhanced recovery plan in the operating room. Intraoperative opioid use was reduced, but the quantities of opioid medication given at the time of hospital discharge remained unchanged. Changing the analgesic plan in the operating room alone without adopting a comprehensive strategy that extends through recovery from surgery will decrease the effect of opioid-sparing strategies. Clarke and colleagues<sup>14</sup> describe their experience with a transitional pain service consisting of a multidisciplinary team of pain physicians, specialised nurses, and pain psychologists. A cohort of 250 Canadian patients (ranging from 19–81 years; 44.4% female), who had surgery and were at high risk of poor compliance with use of opioid analgesics after surgery, showed a marked reduction in opioid consumption and 26% of long-term opioid users were weaned of the drugs completely, without any negative effect on pain or physical function. Additionally, they saw a reduction in the length of hospital stay with an improvement in quality of life in those managed by the transitional pain service.

Education will need to include patients, hospitals, health-care systems, and the graduate schools where health-care providers are trained. By educating patients



about the risks and alternatives to opioids, health-care providers can help empower patients (and themselves) to request alternatives and demand closer attention if they are struggling after surgery. Opioid-free anaesthesia has been put forward as a panacea for the opioid problem, but there is no evidence that opioid-free anaesthesia is superior to multimodal analgesia.<sup>15</sup> For now, opioids remain an essential and reliable tool for treating moderate to severe pain.

Can we reduce or eliminate the transition from acute to chronic pain? Based on systematic reviews, there is preliminary evidence that regional anaesthesia can be protective against chronic postsurgical pain after thoracotomy and mastectomy,<sup>16</sup> and ketamine can decrease the risk of chronic postsurgical pain.<sup>17</sup> A wide range of demographic, genetic, clinical, perioperative, psychosocial, and psychophysical risk factors suggest that there might be no one single intervention that can protect all patients.<sup>3</sup> In the future, we believe standardised preoperative patient stratification will guide clinicians in designing an optimal and individualised analgesic plan.<sup>18</sup> That treatment plan should start preoperatively, integrate with the care provided in the operating room and during the course of hospitalisation, and be continued after hospital discharge until pain has subsided, in transitional pain clinics when necessary.<sup>9</sup>

The current debate around opioids calls for education and moderation. The authors of the new *Lancet* Series on postoperative pain management and opioids<sup>3,6,9</sup> are to be commended for their comprehensive account of opioids and their current use and misuse in perioperative pain management, for detailing strategies to reduce inappropriate prescribing, and for improving our understanding of the adverse effects and dangers of opioids. Each Series paper has pointed a way forward, and laid out how constructive change can be implemented on many levels from drug discovery to direct communication with patients, all the way to legislative action.

\*Markus W Hollmann, James P Rathmell, Philipp Lirk  
Department of Anaesthesiology, University Medical Center Amsterdam, Amsterdam 1105AZ, Netherlands (MWH); and Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA (JPR, PL)

m.w.hollmann@amc.uva.nl

MWH declares consulting fees from Eurocept BV, a speaker's fee from CSL Behring, and travel expenses reimbursement for work on the editorial board of *Anesthesia and Analgesia*. JPR is a member of the American Board of Anesthesiology and an Executive Editor for *Anesthesiology*. PL is Associate Editor for the *European Journal of Anaesthesiology*.

- 1 Shafer A, Fish MP, Gregg KM, Seavello J, Kosek P. Preoperative anxiety and fear: a comparison of assessments by patients and anesthesia and surgery residents. *Anesth Analg* 1996; **83**: 1285–91.
- 2 Joshi GP, Schug SA, Kehlet H. Procedure-specific pain management and outcome strategies. *Best Pract Res Clin Anaesthesiol* 2014; **28**: 191–201.
- 3 Glare P, Aubrey K, Myles PS. Transition from acute to chronic pain after surgery. *Lancet* 2019; **393**: 1537–46.
- 4 Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. *Anesthesiology* 2013; **118**: 934–44.
- 5 Ladha KS, Patorno E, Huybrechts KF, Liu J, Rathmell JP, Bateman BT. Variations in the use of perioperative multimodal analgesic therapy. *Anesthesiology* 2016; **124**: 837–45.
- 6 Neuman MD, Bateman BT, Wunsch H. Inappropriate opioid prescription after surgery. *Lancet* 2019; **393**: 1547–57.
- 7 Schuchat A, Houry D, Guy GP. New data on opioid use and prescribing in the United States. *JAMA* 2017; **318**: 425–26.
- 8 Bonnie RJ, Kesselheim AS, Clark DJ. Both urgency and balance needed in addressing opioid epidemic: a report from the National Academies of Sciences, Engineering, and Medicine. *JAMA* 2017; **318**: 423–24.
- 9 Colvin LA, Bull F, Hales TG. Perioperative opioid analgesia—when is enough too much? A review of opioid-induced tolerance and hyperalgesia. *Lancet* 2019; **393**: 1558–68.
- 10 Katz J, Weinrib A, Fashler SR, et al. The Toronto General Hospital Transitional Pain Service: development and implementation of a multidisciplinary program to prevent chronic postsurgical pain. *J Pain Res* 2015; **8**: 695–702.
- 11 Kumar K, Kirksey MA, Duong S, Wu CL. A review of opioid-sparing modalities in perioperative pain management: methods to decrease opioid use postoperatively. *Anesth Analg* 2017; **125**: 1749–60.
- 12 Abdallah FW, Halpern SH, Aoyama K, Brull R. Will the real benefits of single-shot interscalene block please stand up? A systematic review and meta-analysis. *Anesth Analg* 2015; **120**: 1114–29.
- 13 Brandal D, Keller MS, Lee C, et al. Impact of enhanced recovery after surgery and opioid-free anesthesia on opioid prescriptions at discharge from the hospital: a historical-prospective study. *Anesth Analg* 2017; **125**: 1784–92.
- 14 Clarke H, Azargive S, Montbriand J, et al. Opioid weaning and pain management in postsurgical patients at the Toronto General Hospital Transitional Pain Service. *Can J Pain* 2018; **2**: 236–47.
- 15 Lirk P, Rathmell JP. Opioid-free anaesthesia: con: it is too early to adopt opioid-free anaesthesia today. *Eur J Anaesthesiol* 2019; **36**: 250–54.
- 16 Levene JL, Weinstein EJ, Cohen MS, et al. Local anesthetics and regional anesthesia versus conventional analgesia for preventing persistent postoperative pain in adults and children: a Cochrane systematic review and meta-analysis update. *J Clin Anesth* 2019; **55**: 116–27.
- 17 Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I. Pharmacotherapy for the prevention of chronic pain after surgery in adults. *Cochrane Database Syst Rev* 2013; CD008307.
- 18 Schreiber KL, Martel MO, Shnol H, et al. Persistent pain in postmastectomy patients: comparison of psychophysical, medical, surgical, and psychosocial characteristics between patients with and without pain. *Pain* 2013; **154**: 660–68.