

- 4 Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. *Anesthesiology* 2008; **109**: 723–40
- 5 Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. *Anesth Analg* 2011; **112**: 1392–402
- 6 Michard F. The burden of high-risk surgery and the potential benefit of goal-directed strategies. *Crit Care* 2011; **15**: 447
- 7 de Waal EEC, Wappler F, Buhre WF. Cardiac output monitoring. *Curr Opin Anaesthesiol* 2009; **22**: 71–7
- 8 Schober P, Loer SA, Schwarte LA. Perioperative hemodynamic monitoring with transesophageal Doppler technology. *Anesth Analg* 2009; **109**: 340–53
- 9 Critchley LA, Lee A, Ho AM. A critical review of the ability of continuous cardiac output monitors to measure trends in cardiac output. *Anesth Analg* 2010; **111**: 1180–92
- 10 Peyton PJ, Chong SW. Minimally invasive measurement of cardiac output during surgery and critical care: a meta-analysis of accuracy and precision. *Anesthesiology* 2010; **113**: 1220–35
- 11 Squara P, Cecconi M, Rhodes A, Singer M, Chiche JD. Tracking changes in cardiac output: methodological considerations for the validation of monitoring devices. *Intensive Care Med* 2009; **35**: 1801–8
- 12 Challand C, Struthers R, Sneyd JR, et al. Randomized controlled trial of intraoperative goal-directed fluid therapy in aerobically fit and unfit patients having major colorectal surgery. *Br J Anaesth* 2012; **108**: 53–62
- 13 NICE. CardioQ-ODM oesophageal Doppler monitor. 2011. Available from <http://guidance.nice.org.uk/MTG3/Guidance/pdf/English>
- 14 Corcoran T, Emma Joy Rhodes J, Clarke S, Myles PS, Ho KM. Perioperative fluid management strategies in major surgery: a stratified meta-analysis. *Anesth Analg* 2012; **114**: 640–51
- 15 Kiefer N, Theis J, Putensen-Himmer G, Hoeft A, Zenker S. Peristaltic pneumatic compression of the legs reduces fluid demand and improves hemodynamic stability during surgery: a randomized, prospective study. *Anesthesiology* 2011; **114**: 536–44
- 16 Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med* 2009; **37**: 2642–7
- 17 Cansson M, Le Manach Y, Hofer CK, et al. Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a 'gray zone' approach. *Anesthesiology* 2011; **115**: 231–41
- 18 Metzelder S, Coburn M, Fries M, et al. Performance of cardiac output measurement derived from arterial pressure waveform analysis in patients requiring high-dose vasopressor therapy. *Br J Anaesth* 2011; **106**: 776–84
- 19 Lansdorp B, Lemson J, van Putten MJ, de Keijzer A, van der Hoeven JG, Pickkers P. Dynamic indices do not predict volume responsiveness in routine clinical practice. *Br J Anaesth* 2012; **108**: 395–401
- 20 De Hert SG. Assessment of fluid responsiveness: insights in a 'gray zone'. *Anesthesiology* 2011; **115**: 229–30
- 21 Gelman S. Venous function and central venous pressure: a physiologic story. *Anesthesiology* 2008; **108**: 735–48
- 22 Jansen JR, Maas JJ, Pinsky MR. Bedside assessment of mean systemic filling pressure. *Curr Opin Crit Care* 2010; **16**: 231–6
- 23 Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, Jansen JR. Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. *Crit Care Med* 2009; **37**: 912–8
- 24 Geerts BF, Aarts LP, Groeneveld AB, Jansen JR. Predicting cardiac output responses to passive leg raising by a PEEP-induced increase in central venous pressure, in cardiac surgery patients. *Br J Anaesth* 2011; **107**: 150–6
- 25 Chikhani M, Moppett IK. Minimally invasive cardiac output monitoring: what evidence do we need. *Br J Anaesth* 2011; **106**: 451–3

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## EDITORIAL II



# Prevention of opioid-induced hyperalgesia in surgical patients: does it really matter?

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In a recent issue of the *British Journal of Anaesthesia*, Echevarría and colleagues<sup>1</sup> reported that nitrous oxide (N<sub>2</sub>O) reduced postoperative opioid-induced hyperalgesia (OIH) after remifentanyl-propofol anaesthesia. In their study, 50

adult ASA I–II patients undergoing elective open septorhinoplasty under general anaesthesia were assigned to receive N<sub>2</sub>O (70%) or 100% oxygen. Mechanical pain thresholds were measured before surgery and 2 and 12–18 h after

surgery. Pain measurements were performed on the arm using hand-held von Frey filaments. Baseline pain thresholds to mechanical stimuli were similar in both groups, with the mean values of 69 [95% confidence interval (CI): 50.2, 95.1] g in the group without N<sub>2</sub>O and 71 (95% CI: 45.7, 112.1) g in the group with N<sub>2</sub>O. Postoperative pain scores and cumulative morphine consumption were similar between the groups. The analysis revealed a decrease in the threshold value in both groups. However, *post hoc* comparisons showed that at 12–18 h after surgery, the decrease in mechanical threshold was greater in the group without N<sub>2</sub>O than the group with N<sub>2</sub>O.

OIH has been clearly identified in animal models<sup>2</sup> and in human volunteers.<sup>3</sup> Opioids which are potentially responsible for OIH in these experimental conditions include remifentanyl and fentanyl. The neurobiology of OIH is complex and likely to involve more than one system, with probable differences between acute and chronic settings at both pre- and post-synaptic levels, affecting *N*-methyl-D-aspartate receptor activity, G-proteins, and intracellular systems.<sup>4</sup> The cumulative dose of remifentanyl and the rapid withdrawal may be factors in remifentanyl-induced hyperalgesia.<sup>5,6</sup> In a model of incisional pain in mice, remifentanyl induced pro-nociceptive effects, which were dose-dependent but unaltered by the duration of administration.<sup>5</sup> The importance of the cumulative dose of opioid appears to be confirmed by clinical studies of remifentanyl-induced hyperalgesia in surgical patients. In negative studies, the cumulative dose range used was 20–30 µg kg<sup>-1</sup>,<sup>6–10</sup> in contrast to a range of 80–120 µg kg<sup>-1</sup> used in positive studies.<sup>11–15</sup> An *in vitro* study showed that abrupt withdrawal of opioid agonists induced long-term potentiation at the first synapse in pain pathways.<sup>16</sup> This provides a previously unrecognized target for selectively combating pro-nociceptive effects of opioids without compromising opioid analgesia. The importance of tapered withdrawal to reduce the expression of remifentanyl-induced hyperalgesia has not been investigated in humans.

How is OIH defined in the surgical patient? The International Association of the Study of Pain defines hyperalgesia as 'Increased pain from a stimulus that normally provokes pain'. Therefore, the increased perception of pain after opioid-based anaesthesia could be the key factor associated with OIH. In addition, tolerance with the increased use of opioid after surgery is another potential, coexisting aspect of OIH. The mechanisms of opioid tolerance were recently addressed in an editorial accompanying a study of the role of β-arrestin 2 in a rodent model of opioid tolerance.<sup>17,18</sup> These two phenomena may be interrelated by common neural substrates.<sup>19</sup> In surgical patients, OIH, tolerance, or both have been identified mainly after remifentanyl-based anaesthesia.<sup>11–15,20</sup> However, of these studies, only two have tested pain sensitivity to clearly identify OIH.<sup>12,20</sup>

Although OIH is an interesting concept, does its prevention matter for surgical patients? Different methods to prevent OIH have been tested, including perioperative ketamine,<sup>12</sup> magnesium,<sup>15</sup> propofol,<sup>14</sup> and nitrous oxide.<sup>1</sup> In

these clinical studies aimed at preventing OIH, the clinical benefit in the immediate postoperative period is either absent,<sup>1</sup> limited to a moderate opioid-sparing effect,<sup>12,14</sup> or a slight reduction in pain scores.<sup>14,15</sup> None of these studies found that the morphine-sparing effect had any impact on the opioid-related side-effects. Finally, these studies were not powered to adequately estimate the side-effects related to the prevention technique. Therefore, the clinical benefit–tolerance ratio of OIH prevention in the immediate postoperative period needs further evaluation.

In which conditions may the prevention of OIH have more clinical significance? In certain groups of patients, OIH prevention might be more beneficial. Genetic factors and preoperative use of opioids are potential influences on the benefit related to OIH prevention. A clinical study of 43 healthy volunteers using a painful thermal stimulus found that individuals homozygous for the met (158) polymorphism of the catechol *O*-methyl transferase gene had greater hyperalgesia after remifentanyl.<sup>21</sup> Preoperative screening of genetic factors is not feasible on a daily basis but may in the future help to define a prevention strategy. In the situation of preoperative use of opioid to treat existing pain, this chronic administration of opioid can increase the risk of hyperalgesia.<sup>22</sup> The additional impact of preoperative opioid might increase the severity of OIH. In a study of the intraoperative use of ketamine in surgical patients treated before operation with opioids, the benefit in the prevention of OIH was sustained, with a morphine-sparing effect for 6 weeks after surgery.<sup>23</sup>

The immediate postoperative period may not be the optimal period to detect the benefit of OIH prevention. One study has suggested that a higher dose of remifentanyl may be predictive of a higher incidence of persistent post-surgical pain after thoracotomy.<sup>20</sup> In this study, a high dose of remifentanyl (effect-site concentration 5.6 ng ml<sup>-1</sup>) was compared with a low dose of remifentanyl (effect-site concentration 2 ng ml<sup>-1</sup>). There was an incidence of persistent post-surgical pain of 70% in the high-dose group compared with 16.7% in the low-dose group. Although the methodology of this study had some potential bias as epidural analgesia timing was different in the two groups, the potential connection between OIH and the development of persistent post-surgical pain is interesting. The incidence of persistent post-surgical pain 6 months after surgery has been previously shown correlated to the area of peri-incisional punctuate mechanical allodynia after colorectal surgery.<sup>24</sup> A recent study also observed that the intraoperative use of nitrous oxide reduced the risk of persistent post-surgical pain after thoracotomy by more than half.<sup>25</sup> This may suggest that Echevarría and colleagues<sup>1</sup> did not observe the potential clinical benefit related to preoperative nitrous oxide as their study focused on the immediate postoperative period. Overall, these clinical studies suggest that in the prevention of hyperalgesia related to opioid or surgical inflammation-induced hyperalgesia, it may be of interest to limit the incidence of persistent post-surgical pain rather than to improve immediate postoperative pain control. However, this hypothesis will need additional clinical data to confirm it before it could be included in guidelines.

In conclusion, it is not clear yet whether using strategies to prevent OIH in the surgical patient is clinically worthwhile. In the immediate postoperative period, the benefit is not clinically significant. Clinical studies with prolonged follow-up of persistent post-surgical pain or OIH prevention in selected populations may help to determine the value of this prevention.

## Declaration of interest

None declared.

## References

- Echevarría G, Elgueta F, Fierro C, et al. Nitrous oxide (N<sub>2</sub>O) reduces postoperative opioid-induced hyperalgesia after remifentanil-propofol anaesthesia in humans. *Br J Anaesth* 2011; **107**: 959–65
- Minville V, Fourcade O, Girolami JP, Tack I. Opioid-induced hyperalgesia in a mice model of orthopaedic pain: preventive effect of ketamine. *Br J Anaesth* 2010; **104**: 231–8
- Vinik HR, Kissin I. Rapid development of tolerance to analgesia during remifentanil infusion in humans. *Anesth Analg* 1998; **86**: 1307–11
- Colvin LA, Fallon MT. Opioid-induced hyperalgesia: a clinical challenge. *Br J Anaesth* 2010; **104**: 125–7
- Cabanero D, Campillo A, Celerier E, Romero A, Puig MM. Pronociceptive effects of remifentanil in a mouse model of postsurgical pain: effect of a second surgery. *Anesthesiology* 2009; **111**: 1334–45
- Schraag S, Checketts MR, Kenny GN. Lack of rapid development of opioid tolerance during alfentanil and remifentanil infusions for postoperative pain. *Anesth Analg* 1999; **89**: 753–7
- Cortinez LI, Brandes V, Munoz HR, Guerrero ME, Mur M. No clinical evidence of acute opioid tolerance after remifentanil-based anaesthesia. *Br J Anaesth* 2001; **87**: 866–9
- Engelhardt T, Zaarour C, Naser B, et al. Intraoperative low-dose ketamine does not prevent a remifentanil-induced increase in morphine requirement after pediatric scoliosis surgery. *Anesth Analg* 2008; **107**: 1170–5
- Lee JR, Jung CW, Lee YH. Reduction of pain during induction with target-controlled propofol and remifentanil. *Br J Anaesth* 2007; **99**: 876–80
- Lahtinen P, Kokki H, Hynynen M. Remifentanil infusion does not induce opioid tolerance after cardiac surgery. *J Cardiothorac Vasc Anesth* 2008; **22**: 225–9
- Guignard B, Bossard AE, Coste C, et al. Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. *Anesthesiology* 2000; **93**: 409–17
- Joly V, Richebe P, Guignard B, et al. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology* 2005; **103**: 147–55
- Crawford MW, Hickey C, Zaarour C, Howard A, Naser B. Development of acute opioid tolerance during infusion of remifentanil for pediatric scoliosis surgery. *Anesth Analg* 2006; **102**: 1662–7
- Shin SW, Cho AR, Lee HJ, et al. Maintenance anaesthetics during remifentanil-based anaesthesia might affect postoperative pain control after breast cancer surgery. *Br J Anaesth* 2010; **105**: 661–7
- Song JW, Lee YW, Yoon KB, Park SJ, Shim YH. Magnesium sulfate prevents remifentanil-induced postoperative hyperalgesia in patients undergoing thyroidectomy. *Anesth Analg* 2011; **113**: 390–7
- Drdla R, Gassner M, Gingl E, Sandkuhler J. Induction of synaptic long-term potentiation after opioid withdrawal. *Science* 2009; **325**: 207–10
- Hales TG. Arresting the development of morphine tolerance and dependence. *Br J Anaesth* 2011; **107**: 653–5
- Yang CH, Huang HW, Chen KH, et al. Antinociceptive potentiation and attenuation of tolerance by intrathecal  $\beta$ -arrestin 2 small interfering RNA in rats. *Br J Anaesth* 2011; **107**: 774–81
- Mao J, Price DD, Mayer DJ. Mechanisms of hyperalgesia and morphine tolerance: a current view of their possible interactions. *Pain* 1995; **62**: 259–74
- Salengros JC, Huybrechts I, Ducart A, et al. Different anesthetic techniques associated with different incidences of chronic post-thoracotomy pain: low-dose remifentanil plus presurgical epidural analgesia is preferable to high-dose remifentanil with post-surgical epidural analgesia. *J Cardiothorac Vasc Anesth* 2010; **24**: 610–16
- Jensen KB, Lonsdorf TB, Schalling M, Kosek E, Ingvar M. Increased sensitivity to thermal pain following a single opiate dose is influenced by the COMT val(158)met polymorphism. *PLoS One* 2009; **4**: e6016
- Chen L, Malarick C, Seefeld L, et al. Altered quantitative sensory testing outcome in subjects with opioid therapy. *Pain* 2009; **143**: 65–70
- Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. *Anesthesiology* 2010; **113**: 639–46
- Eisenach JC. Preventing chronic pain after surgery: who, how, and when? *Reg Anesth Pain Med* 2006; **31**: 1–3
- Chan MT, Wan AC, Gin T, Leslie K, Myles PS. Chronic postsurgical pain after nitrous oxide anaesthesia. *Pain* 2011; **152**: 2514–20