## References


1. Mukai A, Suheiro K, Watanabe R, et al. Impact of intraoperative goal-directed therapy on major morbidity and mortality after transthoracic oesophagectomy: a multicentre, randomized controlled trial. *Br J Anaesth* 2020; **125**: 953–61
2. Asombang AK, Chishinga N, Nkhoma A, et al. Systematic review and meta-analysis of esophageal cancer in Africa: epidemiology, risk factors, management and outcomes. *World J Gastroenterol* 2019; **25**: 4512–33
3. Parise P, Elmore U, Fumagalli U, et al. Esophageal surgery in Italy. Criteria to identify the hospital units and tertiary referral centers entitled to perform it. *Updates Surg* 2016; **68**: 129–33
4. Low DE, Allum W, De Manzoni G, et al. Guidelines for perioperative care in esophagectomy: Enhanced Recovery After Surgery (ERAS®) society recommendations. *World J Surg* 2019; **43**: 299–330
5. Bahlmann H, Halldestam I, Nilsson N. Goal-directed therapy during transthoracic oesophageal resection does not improve outcome: randomised controlled trial. *Eur J Anaesthesiol* 2019; **36**: 153–61
6. Piccioni F, Bernasconi F, Tramontano GTA, Langer M. A systematic review of pulse pressure variation and stroke volume variation to predict fluid responsiveness during cardiac and thoracic surgery. *J Clin Monit Comput* 2017; **31**: 677–84
7. Veelo DP, van Berge Henegouwen M, Ouwehand KS, et al. Effect of goal-directed therapy on outcome after esophageal surgery: a quality improvement study. *PLoS One* 2017; **12**, e0172806


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# Increasing intraoperative hydromorphone does not decrease postoperative pain: a retrospective observational study

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**Keywords:** acute hyperalgesia; acute tolerance; hip surgery; hydromorphone; knee surgery; opioid-induced hyperalgesia; orthopaedic surgery; postoperative pain

Editor—Recent evidence suggests that intraoperative opioids have inconsistent effects on nociception and pain in the immediate postoperative period.[1–6] Potent shorter acting opioids, most consistently remifentanil but also sufentanil and fentanyl,[1,2] have been shown to produce dose-related increases in pain scores and opioid consumption in the immediate postoperative recovery period. This may represent either acute opioid tolerance, opioid-induced hyperalgesia, or both.[3] Conversely intraoperative doses of longer acting opiates such as morphine[4,5] and methadone[6] have been shown to reduce pain scores and opioid requirements in the immediate postoperative period.

Hydromorphone is being used increasingly in perioperative settings.[7] It has a greater potency and shorter onset time than morphine but a similar duration of effect, and may decrease pain in the immediate postoperative period when given intraoperatively. The goal of this retrospective cohort study was to test the hypothesis that intraoperative hydromorphone reduces pain scores and opioid consumption in the immediate postoperative period in a dose-dependent manner. Our primary outcome was immediate postoperative pain scores and our secondary outcome was opioid consumption in the PACU.

All patients who underwent a first total hip (THA) or knee arthroplasty (TKA) under general anaesthesia at our institution between December 3, 2012 and May 1, 2017 and who received both intraoperative fentanyl and hydromorphone were eligible for inclusion. We excluded patients with preoperative opioid use, those with missing key demographic or outcome data, and data from any subsequent arthroplasties within the study's time period. Pain scores were assessed in the PACU using a 0–10 numeric rating score (NRS); PACU opioid doses were converted to morphine equivalents. Patients were grouped by quartiles of intraoperative hydromorphone dose (mg $kg^{-1}$). We examined the relationships of maximum PACU NRS and PACU opioid consumption with intraoperative hydromorphone quartile, using ordinal regression (with a logit linking function) and analysis of covariance, respectively. In both cases, we adjusted for covariates that were associated with the independent variable ($P<0.1$) in bivariate analyses. For maximum pain scores, odds ratios represent the odds of having NRS=10 *vs* the odds of NRS=0–9. Morphine equivalent data were log transformed before analysis and adjusted geometric mean values were calculated as the base 10 exponent of the estimated marginal mean. All

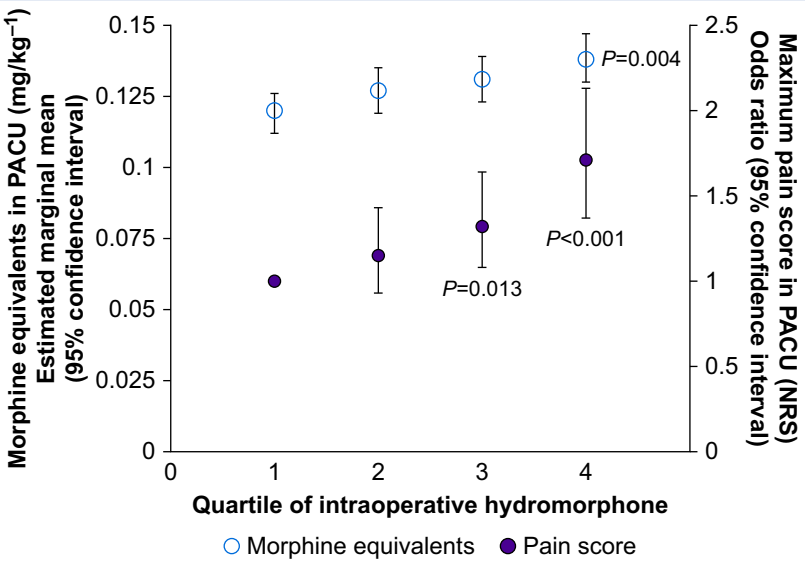


Fig 1. Adjusted relationships of maximum pain score* and total morphine equivalents† in PACU with intraoperative hydromorphone dose. NRS, numerical rating scale. *Odds ratios, calculated by ordinal logistic regression, were adjusted for age, sex, length of surgery, joint replaced (hip, knee), intraoperative fentanyl dose, and last NRS score before anaesthesia. N=2132 subjects had complete data for all covariates and were included the analysis; n=494, 514, 539, and 587 in quartiles 1, 2, 3, and 4, respectively. †Morphine equivalent data were adjusted for sex, BMI, length of surgery, joint replaced (hip, knee), intraoperative fentanyl dose, and last NRS score before anaesthesia using analysis of covariance. N=1861 subjects had complete data for all covariates and were included in the analysis; n=406, 442, 478, and 535 in quartiles 1, 2, 3, and 4, respectively.

analyses were performed using SPSS statistical software, version 25 (IBM SPSS Inc., Armonk, NY, USA).

Of 6200 cases identified, 3519 (56.8%) were eligible for inclusion, with 880, 880, 903, and 856 patients in intraoperative hydromorphone dose quartiles 1–4, respectively. Overall, 1590 (45.2%) of patients were male; mean (range) age was 65.1 (25–93) yr; mean (standard deviation) BMI was 30.0 (6.2) kg $m^{-2}$; 2496 (70.9%) underwent THA (*vs* TKA); and median (range) length of surgery was 69.0 (36–208) min. Intraoperative hydromorphone dose, median (range), was 4.0 (0.0–5.5), 6.9 (5.6–8.3), 9.7 (8.3–11.0), and 13.0 (11.1–34.4) μg $kg^{-1}$ in quartiles 1–4, and median (inter-quartile range) intraoperative fentanyl dose was 1.1 (0.8–1.5), 1.2 (0.9–1.6), 1.3 (1.0–1.4), and 1.6 (1.2–2.3) μg $kg^{-1}$, in quartiles 1–4, respectively.

Figure 1 displays maximum PACU pain score (adjusted odds ratio) and total PACU opioid dose (adjusted geometric mean) for each quartile of intraoperative hydromorphone. Maximum pain scores increased monotonically with intraoperative hydromorphone quartile. Unadjusted odds ratios (mean [95% confidence interval]) were 1.0 (reference); 1.42 (1.20–1.67), P<0.001; 1.61 (1.36–1.89), P<0.001; and 2.48 (2.10–2.93), P<0.001) at quartiles 1–4 of intraoperative hydromorphone dose, respectively. The equivalent adjusted odds ratios were 1.0 (reference); 1.15 (0.93–1.43), P=0.20; 1.32 (1.08–1.64), P=0.013; and 1.71 (1.37–2.13), P<0.001, respectively. Adjusted PACU opioid consumption also showed a monotonic increase by quartile of intraoperative hydromorphone dose, and this was significant (P=0.005) at the fourth quartile. Unadjusted geometric means (95% confidence interval) were 0.11 (0.10–0.1.2) (reference); 0.12 (0.12–0.13), P<0.001; 0.12 (0.12–0.13), P<0.001; and 0.15 (0.15–0.16), P<0.001) morphine equivalents (mg $kg^{-1}$) at quartiles 1–4 of intraoperative hydromorphone dose, respectively. The equivalent adjusted geometric means were 0.12 (0.12–0.14) (reference); 0.13 (0.12–0.14), P=0.24; 0.13 (0.12–0.14), P=0.063; and 0.14 (0.13–0.15) P=0.005, respectively.

Increasing intraoperative hydromorphone dose was independently associated with increased pain score and opioid dosing in the PACU. This effect may be related to intraoperative dosing of hydromorphone based on other known variables associated with higher PACU pain scores and opioid requirements such as age, sex, BMI, duration of surgery, type of surgery, and preoperative pain scores. To examine the independent effect of hydromorphone, these were included as covariates in the multivariate analysis. Although the magnitude of the relationship between intraoperative hydromorphone dose and pain score and opioid dosing in the PACU was small, it was the opposite of the postoperative analgesic effect seen previously with intraoperative morphine[4,5] and methadone.[6]

This paradoxical effect could represent acute tolerance or opioid-induced hyperalgesia. Each phenomenon is associated with higher than expected pain levels and opioid requirements after acute opioid administration. They can only be distinguished by the additional finding of hyperalgesia on experimental nociceptive testing which was not performed in our patients.[3] Prior studies have described hyperalgesia in the setting of high-dose hydromorphone in cancer patients,[8] but no such studies have described this after intraoperative use. The doses of hydromorphone observed in this study were relatively low, and most reports suggest that opioid-induced hyperalgesia or acute tolerance occur only after larger opioid doses.[9] A study in healthy volunteers did find evidence of opioid-induced hyperalgesia using cold-pressor pain thresholds and tolerance with hydromorphone i.v. at doses of 2 mg per 70 kg body

weight.[10] This dose is only slightly higher than the doses administered in our study. While the absolute effect and the immediate clinical impact observed in these patients was small, if related to opioid-induced hyperalgesia, this may contribute to development of chronic postsurgical pain syndromes.[6]

The study is limited by its retrospective, observational nature and single-centre setting, but strengthened by the consistent findings in both pain scores and opioid consumption in a large number of patients undergoing similar orthopaedic surgical trauma.

In summary, we found increasing intraoperative doses of hydromorphone were associated with increasing pain scores and opioid requirements in the immediate postoperative period. Our data suggest a lack of intended benefit and possibly development of acute tolerance or opioid-induced hyperalgesia.

## Authors' contributions

Conceived and designed the study, interpreted the data: CSC
Analysed and interpreted the data: WYC, DSW
Worked to acquire and manage the study data: JMR
Drafted and revised the manuscript, has final approval of the version submitted, and is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors

## Declarations of interest

The authors declare that they have no conflicts of interest.

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## References

1. Aubrun F, Amour J, Rosenthal D, et al. Effects of a loading dose of morphine before i.v. morphine titration for postoperative pain relief: a randomized, double-blind, placebo-control study. *Br J Anaesth* 2007; **98**: 124–30
2. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br J Anaesth* 2014; **112**: 991–1004
3. Lavand'homme P, Steyaert A. Opioid-free anesthesia opioid side effects: tolerance and hyperalgesia. *Best Pract Res Clin Anaesthesiol* 2017; **31**: 487–98
4. Murphy GS, Szokol JW, Avram MJ, et al. Clinical effectiveness and safety of intraoperative methadone in patients undergoing posterior spinal fusion surgery: a randomized, double-blinded, controlled trial. *Anesthesiology* 2017; **126**: 822–33
5. Pico L, Hernot S, Negre I, et al. Peroperative titration of morphine improves immediate postoperative analgesia after total hip arthroplasty. *Can J Anaesth* 2000; **47**: 309–14
6. Weber L, Yeomans DC, Tzabazis A. Opioid-induced hyperalgesia in clinical anesthesia practice: what has remained from theoretical concepts and experimental studies? *Curr Opin Anaesthesiol* 2017; **30**: 458–65
7. Gulur P, Koury K, Arnstein P, et al. Morphine versus hydromorphone: does choice of opioid influence outcomes? *Pain Res Treat* 2015; **2015**: 482081
8. Lee M, Silverman SM, Hansen H, et al. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician* 2011; **14**: 145–61
9. Angst MS. Intraoperative use of remifentanil for TIVA: postoperative pain, acute tolerance, and opioid-induced hyperalgesia. *J Cardiothorac Vasc Anesth* 2015; **29**(Suppl 1): S16–22
10. Compton P, Athanasos P, Elashoff D. Withdrawal hyperalgesia after acute opioid physical dependence in non-addicted humans: a preliminary study. *J Pain* 2003; **4**: 511–9

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# The importance of perfusion pressure in estimating oxygen delivery and extraction. Comment on *Br J Anaesth* 2020; 124: 395–402

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**Keywords:** cardiac output; extracorporeal circulation; mean arterial pressure; oxygen delivery; oxygen extraction; perfusion pressure

Editor—The study recently published by Bojan and colleagues[1] in the *British Journal of Anaesthesia* may have two additional limitations. Firstly, the authors describe the optimisation of cellular respiration by improving oxygen delivery ($DO_2$) but did not consider the primary parameter for transmembrane delivery: perfusion pressure. Secondly, in the absence of an