Anaesthesia 2021, 76, 270–276 doi:10.1111/anae.15163

Review Article

# A systematic review and trial sequential analysis of intravenous vs. oral peri-operative paracetamol

**M. Mallama,**[1] **A. Valencia,**[1] **K. Rijs,**[2] **W. J. R. Rietdijk,**[3] **M. Klimek**[4] and **J. A. Calvache**[5]

1 Resident, 2 Department of Anaesthesiology, 3 Department of Intensive Care, 4 Sub-Head, Department of Anaesthesiology, Erasmus University Medical Centre, Rotterdam, The Netherlands, 5 Consultant, Department of Anaesthesiology, Universidad del Cauca, Popayan, Colombia

## Summary

Postoperative pain might be different after intravenous vs. oral paracetamol. We systematically reviewed randomised controlled trials in patients >15 years that compared intravenous with oral paracetamol for postoperative pain. We identified 14 trials with 1695 participants. There was inconclusive evidence for an effect of route of paracetamol administration on postoperative pain at 0–2 h (734 participants), 2–6 h (766 participants), 6–24 h (1115 participants) and >24 h (248 participants), with differences in standardised mean (95%CI) pain scores for intravenous vs. oral of −0.17 (−0.45 to 0.10), −0.09 (−0.24 to 0.06), 0.06 (−0.12 to 0.23) and 0.03 (−0.22 to 0.28), respectively. Trial sequential analyses suggested that a total of 3948 participants would be needed to demonstrate a meaningful difference in pain or its absence at 0–2 h. There were no differences in secondary outcomes. Intravenous paracetamol is more expensive than oral paracetamol. Substitution of oral paracetamol in half the patients given intravenous paracetamol in our hospital would save around £ 38,711 (€ 43,960 or US$ 47,498) per annum.

Correspondence to: J. A. Calvache
Email: jacalvache@unicauca.edu.co; j.calvache@erasmusmc.nl
Accepted: 25 May 2020
Keywords: acetaminophen; paracetamol; postoperative pain; meta-analysis; systematic review; cost-benefit analysis
Twitter: @jacalvache

## Introduction

Postoperative pain management aims to facilitate optimal recovery and patient satisfaction [1]. Good postoperative analgesia is associated with shorter hospital stay, fewer re-admissions after same-day surgery and fewer postoperative complications, including chronic pain conditions and myocardial ischaemia [2–4].

Paracetamol is a synthetic, non-opioid, centrally-acting analgesic [5]. It is one of the most used and safest drugs available [6, 7], and may avoid the use and undesirable side-effects of opioids [5, 8–10]. Adverse events caused by paracetamol are usually mild, transient and comparable in frequency with placebo [11]. The onset and duration of the analgesic action of paracetamol varies with the route of administration. However, despite several differences in peak plasma concentration after intravenous and oral administration, pain relief is usually similar after 45 min and subsequently could be superior after oral administration [12]. Intravenous paracetamol is more expensive than a bioequivalent dose of oral paracetamol [13, 14].

We aimed to systematically review whether there is a difference in the efficacy, safety and costs of intravenous vs. oral peri-operative paracetamol in adults.

## Methods

We searched MEDLINE, Epub, Embase, CENTRAL, Web of Science, LILACs and Google Scholar to February 2020 for trials that compared intravenous with oral peri-operative paracetamol, published in any language (online Supporting Information, Appendix S1). We scanned clinical trial


© 2020 The Authors. Anaesthesia published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

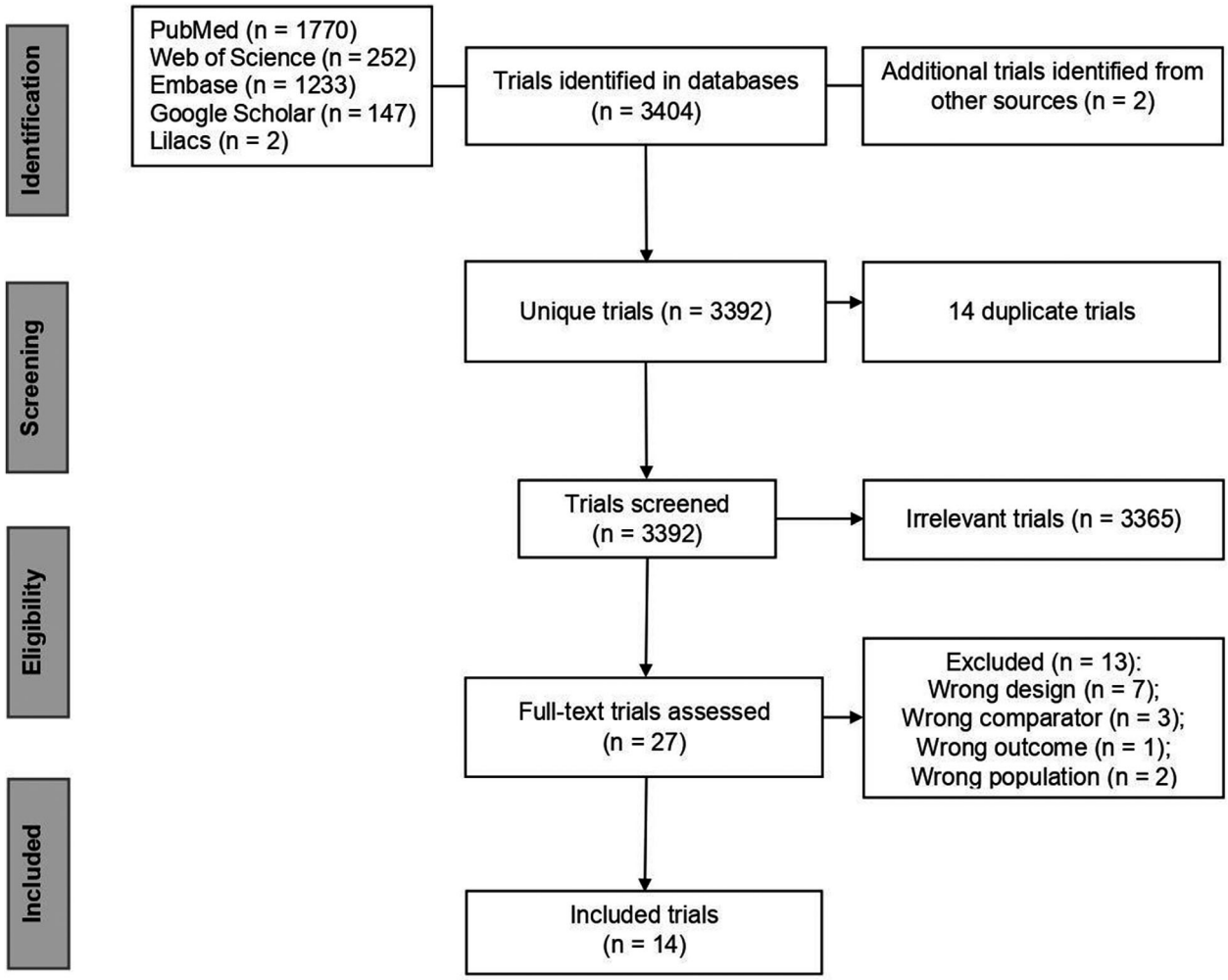


**Figure 1** Flow chart of the literature search.

registries (http://www.who.int/ictrp and clinicaltrials.gov) and the reference lists and citations of included trials and relevant systematic reviews for further trials. When necessary, we contacted trial authors for additional information. Two authors (MM and AV) independently determined trials eligible for inclusion and extracted data, with disagreements resolved by consensus with the help of a third author (JC).

We included parallel group, randomised controlled trials of intravenous vs. oral paracetamol for any operation. Paracetamol could be given before, during or after surgery, as one or multiple doses. We excluded trials with <10 participants or with any participants <15 years old. We chose postoperative pain as the primary outcome, measured by a validated pain scale. We categorised pain measured: during 0–2 postoperative hours; 2–6 postoperative hours; 6–24 postoperative hours; and after 24 postoperative hours. We used the latest available estimate in each time period. Secondary outcomes were: opioid consumption during the first 24 h; time to first analgesic request or rescue dosage; participant satisfaction; time to discharge from the recovery unit and the hospital; nausea or vomiting; pruritus; sedation; and plasma paracetamol concentration (online Supporting Information, Table S1).

Two authors (MM and AV) independently assessed risk of bias in each methodological domain as low, unclear or high [15, 16]. We downgraded the strength of evidence for pooled data from trials at risk of bias and with heterogeneous results, particularly when imprecise. We derived the standard deviations for mean values from standard errors, confidence intervals and p values where necessary and we transformed median (range or interquartile range) to mean (SD) [17–23]. We converted postoperative opioid consumption to intravenous

© 2020 The Authors. Anaesthesia published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists 

**Table 1** Details of 14 randomised controlled trials of intravenous vs. oral peri-operative paracetamol.

| Trial | Number of patients | | Surgery | Paracetamol dose and timing | | Primary outcome | Peri-operative analgesia |
|---|---|---|---|---|---|---|---|
| | i.v. | p.o. | | i.v. | p.o. | | |
| Brett et al. [18] | 10 | 20 | Knee arthroscopy | 1 g just before surgery | 1 g up to 60 min before surgery | Plasma concentration | Intra-operative fentanyl |
| Politi et al. [19] | 63 | 57 | Hip and knee arthroplasty | 1 g before surgery and 6-hourly for 24 h | 1 g before surgery and 6-hourly for 24 h | Opioid dose<br>Pain (10 cm VAS) 4-hourly for 24 h | Pre-operative celecoxib and oxycodone. Intra-operative bupivacaine. Postoperative hydromorphone, oxycodone, oxycontin and celecoxib |
| Plunkett et al. [20] | 32 | 28 | Cholecystectomy | 1 g 1 h before surgery and 4 h later | 1 g 1 h before surgery and 4 h later | Pain scores differences from baseline first 24 h (NRS) | Intra-operative fentanyl and hydromorphone and subsequent narcotic doses |
| Fenlon et al. [21] | 63 | 65 | Third molar | 1 g after induction of anaesthesia | 1 g 45 min before surgery | Pain (10 cm VAS) at 1 h after surgery | Intra-operative fentanyl. Postoperative rescue diclofenac |
| Westrich et al. [22] | 77 | 77 | Total hip arthroplasty | 1 g 30 min after admission to the PACU | 1 g 30 min after admission to the PACU | Pain scores (NRS) with activity POD 1<br>Cumulative opioid between POD 0–3<br>Opioid-related side effects POD 1 | Intra-operative ketorolac. Postoperative ketorolac, meloxicam and patient-controlled epidural analgesia with bupivacaine and clonidine |
| Bhoja et al. [23] | 50 | 51 | Endoscopic sinus surgery | 1 g 1 h before surgery end | 1 g 1 h before anaesthesia start | Pain scores (10 cm VAS) 1 h postoperative | Pre-operative celecoxib |
| Pettersson et al. [25] | 40 | 40 | Coronary artery bypass graft | 1 g 6-hourly after extubation until 0900 next morning | 1 g 6-hourly after extubation until 0900 next morning | Opioid dose<br>Nausea, vomiting<br>Pain (10 cm VAS) | Pre-operative morphine or ketobemidone. Intra-operative fentanyl. Postoperative ketobemidone and aspirin |
| Wilson et al. [26] | 47 | 47 | Elective caesarean section | 1 g postoperative and 8-hourly × 2 | 1 g postoperative and 8-hourly × 2 | Opioid dose to 24 h | Intra-operative spinal bupivacaine with fentanyl and morphine. Postoperative ketorolac, oxycodone and morphine |
| Hickman et al. [27] | 245 | 241 | Knee or hip arthroplasty | 1 g intra-operative | 1 g 80 min pre-operative | Opioid dose to 24 h postoperative | Pre-operative celecoxib, pregabalin paracetamol (1 g). Postoperative paracetamol (1 g), methocarbamol, tramadol, oxycodone and hydromorphone |
| Van der Westhuizen et al. [28] | 54 | 52 | Ear, nose and throat or orthopaedic | 1 g on induction of anaesthesia | 1 g 30 min before surgery | Plasma concentration every 30 min for 240 min | Not specified |
| Mahajan et al. [29] | 50 | 50 | Elective caesarean section | 10–15 $mg.kg^{-1}$ 20 min before surgery end | 650 mg 20 min before surgery | Analgesia duration<br>Pain (10 cm VAS) 2-hourly to 24 h postoperative | Spinal bupivacaine. Rescue diclofenac |
| O'Neal et al. [30] | 57 | 58 | Knee arthroplasty | 1 g at the end of surgery | 1 g at the end of surgery | Pain scores (NRS 11 point) every 15 min for up to 4 h | Pre-operative celecoxib and oxycodone. Intra-operative pericapsular ropivacaine, ketorolac, clonidine |
| Pettersson et al. [31] | 7 | 14 | Varicose vein, hernia, knee arthroscopy | 2 g propacetamol postoperative | 1 and 2 g postoperative | Plasma concentration at 80 min | Lornoxicam |
| Patel et al. [32] | 44 | 56 | Laparoscopic unilateral hernia repair surgery | 1 g after induction of anaesthesia | 975 mg 15 min before entering the operating room | Pain scores (NRS 0-10) at rest and 1 h on PACU, and 6 h postoperative<br>Opioid use intra-operatively and in the PACU | Intra-operative opioids and bupivacaine for infiltration prior and on closure of the incision sites. Postoperative oxycodone and fentanyl; in some cases, used hydromorphone |

i.v., intravenous; p.o., oral; VAS, visual analogue scale; NRS, numerical rating scale; PACU, post-anaesthesia care unit; POD, postoperative days.

morphine milligram equivalents (http://opioidcalculator.practicalpainmanagement.com).

We pooled outcomes reported by two or more trials with a random effects model. We calculated the $I^2$ statistic to assess trial heterogeneity. We considered a p value $< 0.05$ statistically significant. We used trial sequential analysis and a funnel plot for the primary outcome (TSA; version 0.9.5.10 Beta, Copenhagen Trial Unit, Copenhagen, Denmark) [24]. We calculated the required information size allowing for a type-1 error of 0.05 and type-2 error of 0.20.


© 2020 The Authors. Anaesthesia published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists

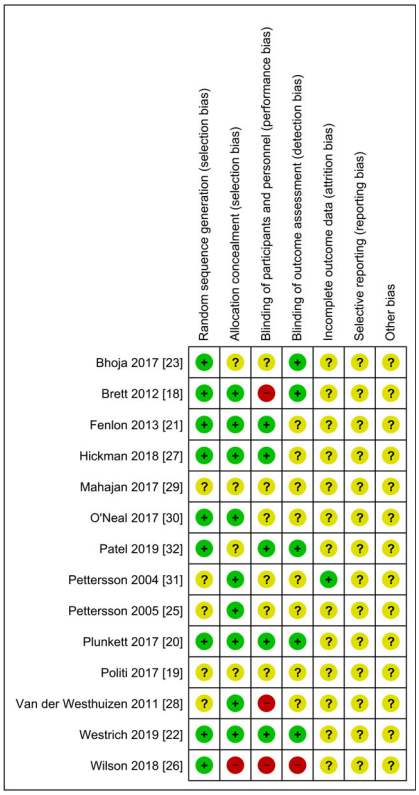


**Figure 2** Risk of bias assessment of included trials using the Cochrane risk of bias tool. ?, unclear risk; −, high risk; +, low risk.

## Results

We included 14 trials (Fig. 1; Table 1) [18–23, 25–32]. We asked authors of three trials to supply additional information [20, 23, 26]. We derived standard deviations for three trials [18, 19, 26] and mean (SD) for two trials [25, 27]. Most methodological domains were poorly reported by most trials, whereas the provided information revealed high risks of bias for three trials (Fig. 2).

Route of paracetamol administration did not affect postoperative pain (Figs. 3 and 4). There were insufficient trials to interrogate small studies effects (online Supporting Information, Figure S1). Route of paracetamol administration did not affect any of the secondary outcomes (online Supporting Information, Figure S2). We graded the quality of evidence as 'low' for an effect of route of paracetamol administration on postoperative pain.

We did not pool plasma paracetamol concentrations, which were reported at different times and in different units by three trials [18, 28, 31]. Intravenous paracetamol administration may increase plasma concentration more than oral administration 20–240 min later, although one trial reported higher plasma concentration 80 min after oral administration [28].

Intravenous paracetamol is approximately 10 times more expensive than an equivalent oral dose, for instance, £1.95 (€2.21, US$2.39) vs. £0.19 (€0.22, US$0.23). We estimate that we spend £85,910 (€97,558, US$120,420) on intravenous paracetamol per annum in our hospital. We would save around £38,711 (€43,960, US$47,498) per annum if we used oral instead of intravenous paracetamol for half of these patients (online Supporting Information, Table S2).

## Discussion

We found that the peri-operative route of paracetamol administration, intravenous vs. oral, did not affect pain or any other postoperative outcome. There was insufficient evidence to exclude important clinical effects and overall, the quality of evidence was poor.

Two systematic reviews similarly reported no effect of paracetamol administration route on clinical and pharmacokinetic outcomes [33, 34]. The conclusions of both reviews were limited by the poor methodological or reporting quality of the included trials. This is consistent with large observational studies [35]. Important differences between administration routes could not be excluded.

Most of the included trials gave paracetamol prophylactically and some did not clearly describe whether paracetamol was given as prophylaxis or treatment [22, 25, 26, 30, 31]. We excluded one trial that gave paracetamol as treatment [36].

Previous trials have shown bioequivalence of paracetamol 1 g and propacetamol 2 g [6, 37]. Head-to-head trials of intravenous paracetamol vs. intravenous propacetamol have shown no differences in the proportion of participants achieving at least 50% pain relief during 4 postoperative hours [6, 36, 38, 39]. Only one included trial gave propacetamol compared with five doses of oral paracetamol [31]. This study did not report any clinical outcomes that we could analyse.

All systematic reviews are limited by the trials they observe. Most trials incompletely reported their methods and outcomes were often different. We had to transform some results that were reported as median (range or interquartile range) or as mean without variance. We had to standardise pain scores, limiting their direct clinical interpretation. Our cost analysis is specific to our hospital in the Netherlands, but we believe it is generally applicable [40]. We did not compare the rectal route with others, nor pharmacokinetic profiles of included routes, which remain uncertain. We decided not to extend the pooling of results

© 2020 The Authors. Anaesthesia published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists 

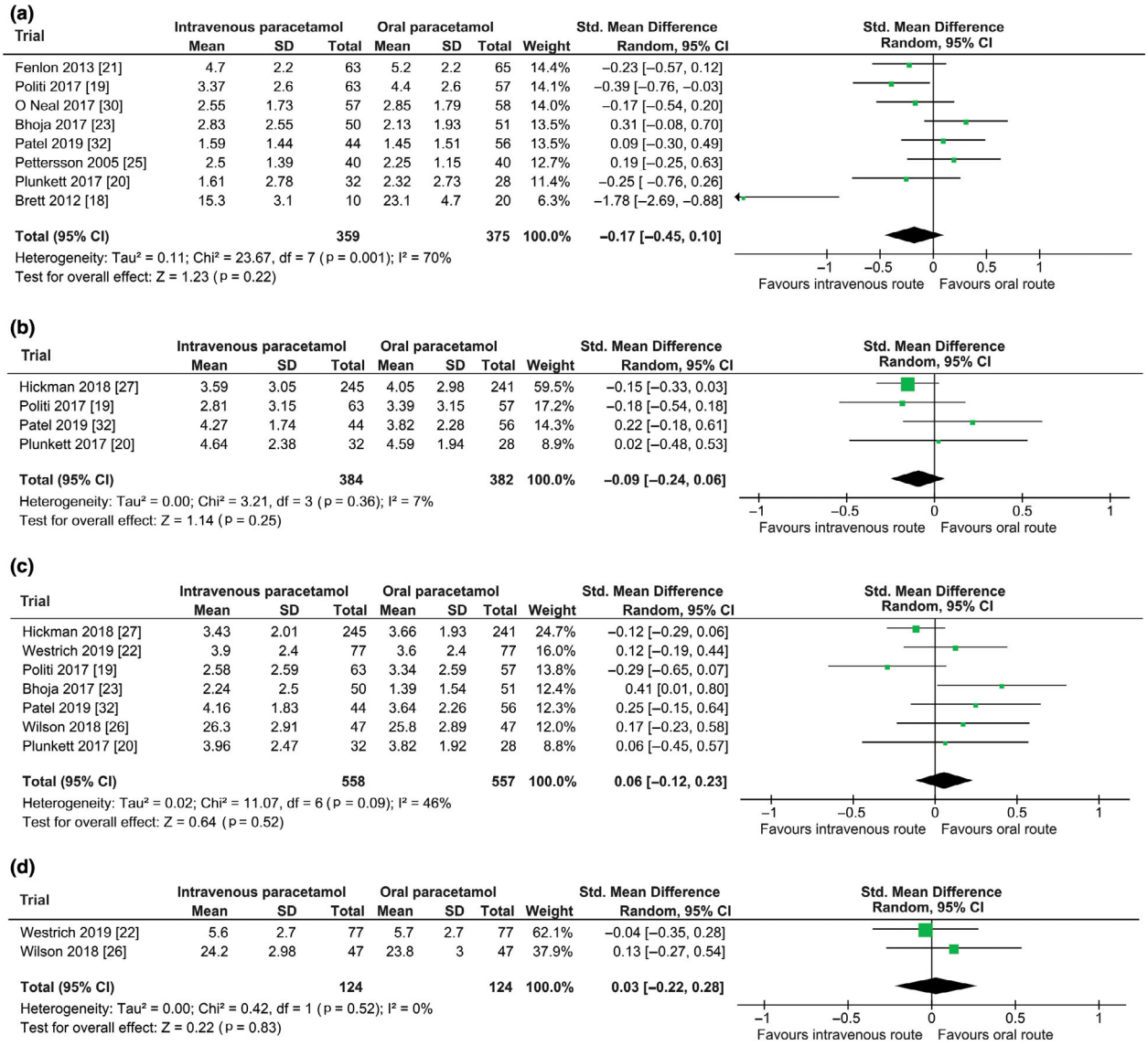


**Figure 3** Forest plots of postoperative pain after intravenous vs. oral peri-operative paracetamol: (a) 0–2 h; (b) 2–6 h; (c) 6–24 h; (d) >24 h.

with network meta-analyses, given the heterogeneity of trials and the variability of plasma concentrations [41].

Our review summarises the lack of evidence to justify the expense of peri-operative intravenous paracetamol. It remains possible that there might be an important clinical difference for the route of paracetamol administration. We believe that intravenous paracetamol should only be used in clinical trials or when the oral route is contra-indicated.

## Acknowledgements

We thank N. Hunfeld for data on the use of paracetamol in our hospital. We prospectively registered this systematic review (PROSPERO CRD42019125241). This study was funded by the Department of Anesthesiology, Erasmus Medical Center Rotterdam, The Netherlands and the Departamento de Anestesiología, Universidad del Cauca, Popayán, Colombia. No other external funding or competing interests declared.

 © 2020 The Authors. Anaesthesia published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists

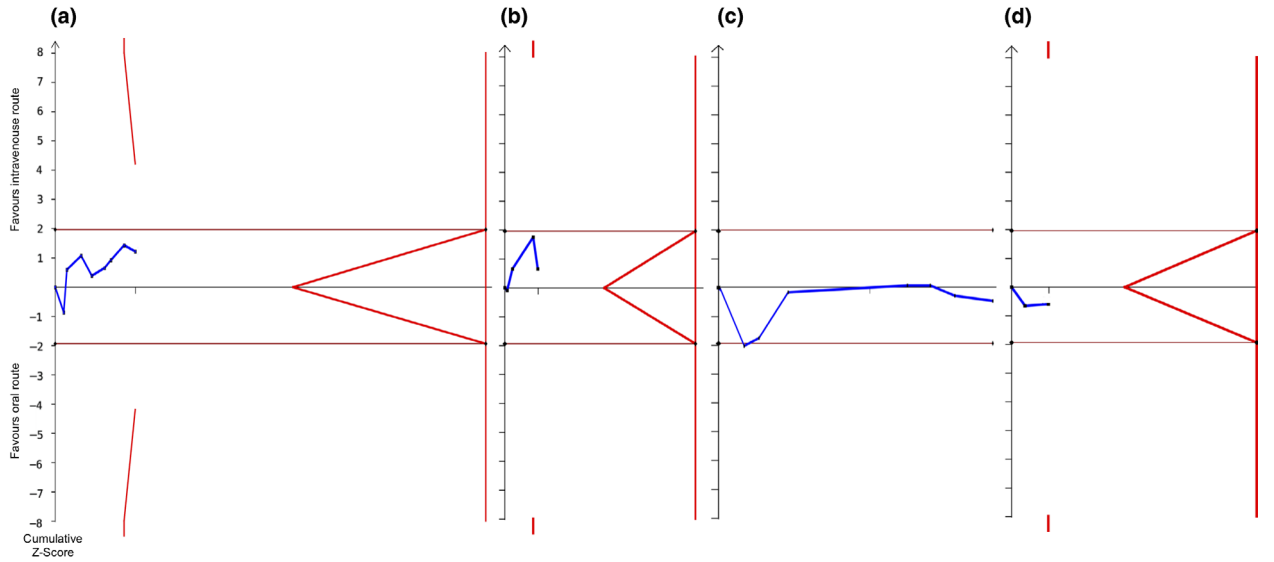


**Figure 4** Trial sequence analysis (TSA) for intravenous vs. oral peri-operative paracetamol for postoperative pain: (a) 0–2 h (734 participants); (b) 2–6 h (766 participants); (c) 6–24 h (1115 participants); (d) >24 h (248 participants). The point of interest is whether the cumulative evidence for an effect (Z-curve, blue line) breaches the TSA boundaries (red line) in favour of intravenous paracetamol (above the top red line) or in favour of oral paracetamol (below the bottom red line). The cumulative evidence favours neither route. Additional evidence might breach a boundary for effect, or it might breach the boundaries for clinical futility, set at a Z-score <1.96 (wedged red lines to the right). At this limit definitive answers could be expected after studying a total of 3948 participants (0–2 h), 14,336 participants (2–6 h), an undetermined number of participants (6–24 h), and 4514 participants (>24 h), assuming alpha 0.05 and beta 0.20.

## References


1. American Society of Anesthesiologists Task Force on Acute Pain Management: Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology* 2012; **116**: 248–73.
2. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesthesia and Analgesia* 2003; **97**: 534–40.
3. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. *Anesthesiology* 2000; **93**: 1123–33.
4. Nimmo WS, Duthie DJ. Pain relief after surgery. *Anaesthesia and Intensive Care* 1987; **15**: 68–71.
5. Jahr J, Lee V. Intravenous acetaminophen. *Anesthesiology Clinics* 2010; **28**: 619–45.
6. McNicol ED, Ferguson MC, Haroutounian S, Carr DB, Schumann R. Single dose intravenous paracetamol or intravenous propacetamol for postoperative pain. *Cochrane Database of Systematic Reviews* 2016; **5**: CD007126.
7. Murat I, Baujard C, Foussat C, et al. Tolerance and analgesic efficacy of a new i.v. paracetamol solution in children after inguinal hernia repair. *Pediatric Anesthesia* 2005; **15**: 663–70.
8. Atef A, Fawaz A. Intravenous paracetamol is highly effective in pain treatment after tonsillectomy in adults. *European Archives of Oto-Rhino-Laryngology* 2008; **265**: 351–5.
9. Hong JY, Kim WO, Chung WY, Yun JS, Kil HK. Paracetamol reduces postoperative pain and rescue analgesic demand after robot-assisted endoscopic thyroidectomy by the transaxillary approach. *World Journal of Surgery* 2010; **34**: 521–6.
10. Salihoglu Z, Yildirim M, Demiroluk S, et al. Evaluation of intravenous paracetamol administration on postoperative pain and recovery characteristics in patients undergoing laparoscopic cholecystetomy. *Surgical Laparoscopy Endoscopy and Percutaneous Techniques* 2009; **19**: 321–3.
11. Jahr JS, Filocamo P, Singh S. Intravenous acetaminophen: a review of pharmacoeconomic science for perioperative use. *American Journal of Therapeutics* 2013; **20**: 189–99.
12. Oscier CD, Milner QJW. Peri-operative use of paracetamol. *Anaesthesia* 2009; **64**: 65–72.
13. Gollamudi J, Marks S. Oral versus intravenous acetaminophen #302. *Journal of Palliative Medicine* 2016; **19**: 231–2.
14. Yeh YC, Reddy P. Clinical and economic evidence for intravenous acetaminophen. *Pharmacotherapy* 2012; **32**: 559–79.
15. Higgins JPT, Thomas J, Chandler J, et al. (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019). Cochrane, 2019.
16. Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation – determinants of a recommendation's direction and strength. *Journal of Clinical Epidemiology* 2013; **66**: 726–35.
17. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology* 2014; **14**: 135.
18. Brett CN, Barnett SG, Pearson J. Postoperative plasma paracetamol levels following oral or intravenous paracetamol administration: a double-blind randomised controlled trial. *Anaesthesia and Intensive Care* 2012; **40**: 166–71.
19. Politi JR, Davis RL, Matrka AK. Randomized prospective trial comparing the use of intravenous versus oral acetaminophen in total joint arthroplasty. *Journal of Arthroplasty* 2017; **32**: 1125–7.
20. Plunkett A, Haley C, McCoart A, et al. A preliminary examination of the comparative efficacy of intravenous vs oral


© 2020 The Authors. Anaesthesia published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists 

acetaminophen in the treatment of perioperative pain. *Pain Medicine* 2017; **18**: 2466–73.
21. Fenlon S, Collyer J, Giles J, et al. Oral vs intravenous paracetamol for lower third molar extractions under general anaesthesia: is oral administration inferior? *British Journal of Anaesthesia* 2013; **110**: 432–7.
22. Westrich G, Birch GA, Muskat AR, et al. Intravenous vs oral acetaminophen as a component of multimodal analgesia after total hip arthroplasty: a randomized, blinded trial. *Journal of Arthroplasty* 2019; **34**: S215–20.
23. Bhoja R, Ryan MW, Klein K, et al. Intravenous vs oral acetaminophen in sinus surgery: a randomized clinical trial. *Laryngoscope Investigative Otolaryngology* 2020; 1–6. http://dx.doi.org/10.1002/lio2.375.
24. Imberger G, Thorlund K, Gluud C, Wetterslev J. False-positive findings in Cochrane meta-analyses with and without application of trial sequential analysis: an empirical review. *British Medical Journal Open* 2016; **6**: e011890.
25. Pettersson PH, Jakobsson J, Owall A. Intravenous acetaminophen reduced the use of opioids compared with oral administration after coronary artery bypass grafting. *Journal of Cardiothoracic and Vascular Anesthesia* 2005; **19**: 306–9.
26. Wilson SH, Wolf BJ, Robinson SM, Nelson C, Hebbar L. Intravenous vs oral acetaminophen for analgesia after cesarean delivery: a randomized trial. *Pain Medicine* 2019; **20**: 1584–91.
27. Hickman SR, Mathieson KM, Bradford LM, Garman CD, Gregg RW, Lukens DW. Randomized trial of oral versus intravenous acetaminophen for postoperative pain control. *American Journal of Health-System Pharmacy* 2018; **75**: 367–75.
28. Van der Westhuizen J, Kuo P, Reed PW, Holder K. Randomised controlled trial comparing oral and intravenous paracetamol (acetaminophen) plasma levels when given as preoperative analgesia. *Anaesthesia and Intensive Care* 2011; **39**: 242–6.
29. Mahajan L, Mittal V, Gupta R, Chhabra H, Vidhan J, Kaur A. Study to compare the effect of oral, rectal, and intravenous infusion of paracetamol for postoperative analgesia in women undergoing cesarean section under spinal anesthesia. *Anesthesia Essays and Researches* 2017; **11**: 594–8.
30. O'Neal JB, Freiberg AA, Yelle MD, et al. Intravenous vs oral acetaminophen as an adjunct to multimodal analgesia after total knee arthroplasty: a prospective, randomized, double-blind clinical trial. *Journal of Arthroplasty* 2017; **32**: 3029–33.
31. Pettersson PH, Öwall A, Jakobsson J. Early bioavailability of paracetamol after oral or intravenous administration. *Acta Anaesthesiologica Scandinavica* 2004; **48**: 867–70.
32. Patel A, Pai BHP, Diskina D, et al. Comparison of clinical outcomes of acetaminophen IV vs PO in the perioperative setting for laparoscopic inguinal hernia repair surgeries: A triple blinded, randomized controlled trial. *Journal of Clinical Anesthesia* 2019; **61**: 109628.
33. Jibril F, Sharaby S, Mohamed A, Wilby KJ. Intravenous versus oral acetaminophen for pain: systematic review of current evidence to support clinical decision-making. *Canadian Journal of Hospital Pharmacy* 2015; **68**: 238–47.
34. Sun L, Zhu X, Zou J, Li Y, Han W. Comparison of intravenous and oral acetaminophen for pain control after total knee and hip arthroplasty: a systematic review and meta-analysis. *Medicine* 2018; **97**: 1–8.
35. Stundner O, Poeran J, Ladenhauf HN, et al. Effectiveness of intravenous acetaminophen for postoperative pain management in hip and knee arthroplasties: a population-based study. *Regional Anesthesia and Pain Medicine* 2019; **44**: 565–72.
36. Moller PL, Sindet-Pedersen S, Petersen CT, Juhl GI, Dillenschneider A, Skoglund LA. Onset of acetaminophen analgesia: comparison of oral and intravenous routes after third molar surgery. *British Journal of Anaesthesia* 2005; **94**: 642–8.
37. Flouvat B, Leneveu A, Fitoussi S, Delhotal-Landes B, Gendron A. Bioequivalence study comparing a new paracetamol solution for injection and propacetamol after single intravenous infusion in healthy subjects. *International Journal of Clinical Pharmacology and Therapeutics* 2004; **42**: 50–7.
38. Marty J, Benhamou D, Chassard D, et al. Effects of single-dose injectable paracetamol versus propacetamol in pain management after minor gynecologic surgery: a multicenter, randomized, double-blind, active-controlled, two-parallel-group study. *Current Therapeutic Research* 2005; **66**: 294–306.
39. Sinatra RS, Jahr JS, Reynolds LW, Viscusi ER, Groudine SB, Payen-Champenois C. Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. *Anesthesiology* 2005; **102**: 822–31.
40. Prince JS, Dungy D. When IV acetaminophen costs skyrocketed, one health system did some new math. *Drug Topics* 2015. https://www.drugtopics.com/health-system-news/when-iv-acetaminophen-costs-skyrocketed-one-health-system-did-some-new-math (accessed 18/01/2020).
41. Mian P, van Esdonk MJ, Olkkola KT, et al. Population pharmacokinetic modelling of intravenous paracetamol in fit older people displays extensive unexplained variability. *British Journal of Clinical Pharmacology* 2019; **85**: 126–35.

## Supporting Information

Additional supporting information may be found online via the journal website.

**Figure S1.** Funnel plot for small studies effects on postoperative pain: (a) 0–2 h; (b) 2–6 h; (c) 6–24 h; (d) >24 h.

**Figure S2.** Forest plots for secondary postoperative outcomes: (a) opioid consumption; (b) time to first analgesic request or rescue; (c) length of stay in the recovery area (min); (d) length of hospital stay (hours); (e) satisfaction; (f) nausea or vomiting.

**Table S1.** Definitions for outcomes extracted from included randomised controlled trials.

**Table S2.** Economic analysis for intravenous vs. oral paracetamol.

**Appendix S1.** Search strategy for randomised controlled trials of peri-operative intravenous vs. oral paracetamol.


© 2020 The Authors. Anaesthesia published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists