A SYSTEMATIC REVIEW AND TRIAL SEQUENTIAL ANALYSIS OF INTRAVENOUS VS. ORAL PERI-OPERATIVE PARACETAMOL

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ACCEPTANCE NOTE

Dr. Jose Andres Calvache, professor of the Department of Anesthesiology, Faculty of Health Sciences of the University of Cauca, in his capacity as academic advisor of the degree project "**A SYSTEMATIC REVIEW AND TRIAL SEQUENTIAL ANALYSIS OF INTRAVENOUS VS. ORAL PERI-OPERATIVE PARACETAMOL**", by the specialization student in Anesthesiology **Mario Fernando Mallama Quetama**; states that he is APPROVED in the conceptual and methodological integrity of his presentation.

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Dr. Jose Andres Calvache España

DEDICATION

This work is dedicated to my family for having been my support throughout my university career and throughout my life. To all the special people who accompanied me in this stage, contributing to my training both professionally and as a human being.

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.

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ABSTRACT

Background: Differences in efficacy (i.e., effectiveness, safety, and cost-benefit) of intravenous versus oral administration of paracetamol for postoperative pain management in adult surgical patients are largely unknown.

***Methods and data*:** We performed a systematic review, meta-analysis, and cost-benefit analysis of randomized controlled trials (RCTs) in adult patients that compared intravenous versus oral paracetamol for postoperative pain. We applied trial sequential analysis (TSA) to assess the risks of type I and II error, and the GRADE scheme was used to evaluate the available evidence.

Results: 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.

Conclusions: There is no increased efficacy of intravenous versus oral administration of paracetamol, though the quality of evidence is low. Our cost-benefit analyses showed that considerable cost reductions are possible by switching to oral paracetamol.

PROSPERO registration number: CRD42019125241.

Keywords: Acetaminophen, paracetamol, postoperative pain, meta-analysis, systematic review, cost-benefit analysis

INTRODUCTION

In the postoperative period, effective acute pain control is essential for optimal recovery and patient satisfaction. Postsurgical pain is associated with more than patient discomfort; it is also the most common cause of unanticipated readmissions for same-day surgery. Adequate postoperative pain control provides advantages to patients beyond immediate clinical benefits, such as increased satisfaction, improved sleep, less time in the post anaesthesia care unit, shorter hospital stays and lower risks of postoperative complications [1], such as the development of chronic pain conditions, neuroendocrine side effects of surgical injury, deep vein thrombosis, pulmonary complications and myocardial ischaemia [2-3].

Postoperative pain management have focused on balancing effective analgesia with patient safety by optimizing analgesic strategies and refining multimodal analgesia techniques [1].

Paracetamol is a synthetic, non-opioid, centrally acting analgesic. It is one the mostly used and safest analgesic drugs available in the recommended dose. It has not been related with a decrease in platelet function, increase in surgical bleeding or affect kidney function. Therefore, paracetamol is an appropriate drug for use at any time during the perioperative period, especially in high-risk populations such as children and elderly patients. Adverse events related with paracetamol are usually mild and transient and studies have shown similar frequency of adverse events between paracetamol and placebo [5].

The onset and duration of paracetamol's analgesic action is determined to a large extent by the route of administration. Intravenous administration will achieve therapeutic plasma concentrations within 20 min of an initial dose, and concentrations remain therapeutic for around 2 h post dose. While oral bioavailability is good (63–89%), early plasma concentrations following oral administration may vary, and in some cases, concentrations may remain subtherapeutic (less than 10 mcg/ml) for a significant period. Peak plasma concentration (Cmax) is achieved approximately 45 min after 1 g orally, and approximately 25 min after a 1 g intravenous infusion [4].

PROBLEM STATEMENT

Intravenous paracetamol (1 gr IV) results in a 70% higher Cmax compared to a bioequivalent oral dose (1 gr PO) (28.4mcg/mL vs. 15.1mcg/mL) [5]. However, 45 min after administration of equivalent doses of oral and intravenous paracetamol, pain relief was equal for both treatments, and after 2 h, pain relief was superior in the oral group. In clinical practice, this difference has been shown to lead to a faster onset of analgesia when paracetamol is given intravenously [4]. Also, intravenous administration could be suited for settings where quick analgesia is required and oral or rectal administration is difficult or impossible, such as the perioperative period [6]. In addition, rectal route presents some limitations for perioperative period like impracticality for usage and less predictable pharmacokinetics (providing longer analgesic effect than intravenous route) [5].

The use of intravenous paracetamol has shown numerous benefits in many studies including good quality analgesia, decreased opioid consumption, decreased hospital length of stay, earlier discharge from the post anesthesia care unit, and earlier extubating time [5]. Those benefits have been reported in surgeries associated with varying levels of pain, including cesarean section [7], total abdominal hysterectomy [8], tonsillectomy [9], lumbar discectomy [10], coronary artery bypass grafting [11], thyroidectomy [12], hip or knee replacement [13], breast cancer [14] and laparoscopic cholecystectomy procedures [15].

On the other hand, oral paracetamol also has a good clinical profile. Its effect depends on absorption which itself depends on the circumstances of administration. Although overall bioavailability is quoted as 69–84% of the administered dose, area under the absorption/time curve in healthy subjects is equivalent to intravenous paracetamol [16]. Despite the theoretical pharmacokinetic benefits of intravenous paracetamol, research has shown that the number need to treat (NNT) for a 50% reduction in postoperative pain is 5.3 for intravenous paracetamol compared with 3.8 for oral when both are dosed at 1000 mg every six hours [17-18]. Certain direct comparisons have showed no significant differences in intraoperative or postoperative pain measures between 1000 mg of oral versus intravenous paracetamol [16]. There is unknown whether a rapid reachment of Cmax -per se-, confers a long-lasting analgesic advantage to intravenous paracetamol over oral route. A question that remains is: how safe and effective is the route of administration with respect to patient parameters of safety and pain relief?

Another factor that contributes to the comparison of paracetamol administered orally or intravenous are the costs. The cost of intravenous paracetamol is greater than bioequivalent dosed oral paracetamol. This may affect the decision to administer

paracetamol orally or intravenous, especially to budget-conscious healthcare providers or in limited resources settings [19]. However, no structurally investigation into this matter has been done yet.

JUSTIFICATION

A major advantage of oral paracetamol over intravenous paracetamol is cost. The cost of intravenous paracetamol is 400-fold greater than bioequivalent dosed oral paracetamol tablets, making it less attractive to budget-conscious healthcare providers or limited resources settings [4]. Perioperative interventions aimed at decreasing costs and improving outcomes. The relative efficacy of intravenous versus oral paracetamol for postoperative pain control has been in controversy and there is no a single study about cost-effectiveness.

Taken together, the effectiveness and efficiency of intravenous versus oral administration of paracetamol requires further investigation. For this reason, we aim to systematically evaluate in adult postoperative patients the efficacy, safety, and costs associated with intravenous versus oral administration of paracetamol as analgesic drug. We do so by conducting a systematic review, meta-analysis, trial sequential analysis, and cost-benefit analysis.

RESEARCH QUESTION

What is the efficacy and safety of intravenous versus oral paracetamol administration in the control of postoperative pain in adults undergoing all types of surgery?

OBJECTIVES

GENERAL OBJECTIVE

- To evaluate in adult participants undergoing all types of surgery, the efficacy and safety of intravenous versus oral administration of paracetamol in postoperative pain.

SPECIFIC OBJECTIVES

- To evaluate the intensity of postoperative pain measured by a validated pain scale. We classify pain measured during: 0-2 postoperative hours; 2-6 hours postoperative; 6-24 hours postoperative; and after 24 postoperative hours in both groups.

- To evaluate opioid consumption during the first 24 postoperative hours in the two groups.

- To evaluate the time to the first analgesic dose or rescue dose in the two groups.

- To evaluate the satisfaction of the participants in the two groups.

- To evaluate the discharge time from the postanaesthetic care unit and from the hospital in the two groups.

- To evaluate adverse events such as nausea or vomiting; pruritus; sedation in both groups.

- To evaluate the plasma concentration of paracetamol in the two groups.

METHODS

RESEARCH DESIGN

Systematic Review, Meta-Analysis, Trial sequential analysis and Cost-Benefit Analysis.

Our systematic review was registered with PROSPERO of the National Institute for Health Research (www.crd.york.ac.uk), registration number CRD42019125241. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed.

LITERATURE SEARCH

We performed a systematic electronic literature search in the databases MEDLINE, Epub, Embase.com (Embase plus MEDLINE), Cochrane Central, Web of Science, LILACs and Google Scholar to February 2020 in order to identify trials that compared intravenous with oral paracetamol in the perioperative setting. We scanned the following trials registries for ongoing and unpublished trials: World Health Organization International Clinical Trials Registry Platform (http://www.who.int/ictrp/en) and ClinicalTrials.gov (clinicaltrials.gov). We scanned the reference lists and citations of included trials and any relevant systematic reviews identified for further references to additional trials. When necessary, we contacted trial authors for additional information. No language restriction was applied to the search for studies. After removing duplicate citations, two authors (MM and AV) independently screened the search results for eligible trials. Used search strategies are provided in the Supplementary data 1.

INCLUSION AND EXCLUSION CRITERIA

We defined inclusion and exclusion criteria a priori. We included parallel group, randomized controlled trials (RCTs) only. For inclusion, studies had to have followed the PICO characteristics:

- Patients: adults (at least 15 years) undergoing any type of surgery.

- Intervention: intravenous paracetamol for the treatment of postoperative pain.

- Comparator: oral paracetamol for the treatment of postoperative pain.

- Outcomes: Primary outcome – Postoperative pain by using validated pain scales (pain intensity and pain relief in the form of visual analogue scales, categorical scales, or both). We used four-time frames to assess pain during the postoperative period: 1) from end-of-surgery up to two hours (0 – 2 hours), 2) from two hours until six hours (2 – 6 hours), 3) from six hours up to 24 hours (6 – 24 hours), and 4) beyond 24 hours (> 24 hours). Secondary outcomes were opioid consumption during the first 24 hours or as reported by the studies, time to first analgesic request or rescue dosage (minutes), patient satisfaction, length of stay at post-anaesthesia care unit (PACU) or at hospital, presence of nausea and vomiting, presence of pruritus, sedation (measured on a continuous scale such as the Ramsay Sedation Scale 0 to 6 with sedation defined as 3 or more (yes/no)) and plasma paracetamol concentrations.

Inclusion criteria:

1. Blinded or unblinded RCTs.

2. Studies that evaluated the analgesic efficacy of intravenous versus oral forms of paracetamol for the treatment of postoperative pain, following any type of surgery.

3. Studies with at least ten participants randomly allocated to each treatment group.

4. Studies with a single dose or multiple-doses.

5. Studies in which the interventions were administered preoperatively, intraoperatively or postoperatively alone or in combination with other analgesic treatment.

6. Studies in which participants self-reported pain relief or pain intensity.

Exclusion criteria:

1. The following were excluded: review articles, case reports, clinical observations, and studies of experimental pain or studies without

randomization.

No language restriction was applied to the search for studies.

DATA EXTRACTION AND DATA COLLECTION

We extracted data onto an electronic database using standardized data extraction forms. Two review authors performed this independently (MM and AV), and resolved any disagreements by consensus. If disagreement still exists, we consulted a third review author (JAC). We translated non-English language studies and extracted data following translation. If data were not contained within the original research report, we contacted the corresponding author, irrespective of the age of publication.

We report the primary outcome of each study included into our meta-analysis. The primary outcome was the outcome explicitly mentioned as primary in the text or the variable for which a sample size calculation was done or the variable that was first reported in the results section of the study.

If two or more groups using different routes of administration of paracetamol were studied, we used only data from intravenous and oral routes. Combining dichotomous data was by simple addition; for the combination of continuous data we used mean and standard deviations when available. Calculator tool of RevMan® was used to obtain standard deviations from standard errors, confidence intervals and p-values for primary outcomes in 3 studies [20-22]. Data from median and range or interquartile range was transformed to mean and standard deviation by using the method reported by Wan X. et al [23] for two studies providing data for the primary outcome [24, 25]. Finally, raw data was obtained in one study by contacting directly their authors [26] and if needed, other original authors were contacted. For secondary outcomes, calculator tool including in RevMan® was used to obtain standard deviations from standard errors, confidence intervals and p values in 4 studies [16, 20, 21, 26]. Data from median and range or interquartile range was transformed to mean and standard deviation by using the method reported by Wan X. et al [23] (Wan X) for two studies [22, 25].

Postoperative consumption of morphine milligram equivalents (MMEs) were calculated from other opioids using the website: http://opioidcalculator.practicalpainmanagement.com/conversion.php ("Opioid Conversions and Opioid Dosing Calculator").

ASSESSMENT OF RISKS OF BIAS

Two review authors (MM and AV) independently assessed risk of bias in the included studies using standard Cochrane methods and using the tool for assessing risk of bias [27]. Each major domain was assessed as low-, unclear- or high-risk of bias and presented in both a “Risk of bias” summary and a “Risk of bias” graph.

CONVENTIONAL META-ANALYSIS AND ASSESSMENT OF PUBLICATION BIAS

We decided a priori to perform meta-analyses when at least two studies were identified. Review Manager (RevMan®, version 5.3) was used for meta-analysis. We applied the random effects model as clinical and methodological heterogeneity across studies was expected. We calculated risk ratio (RR) and 95% confidence interval (95% CI); the I^2 statistic was used to assess heterogeneity. For all analyses, a p-value <0.05 was considered statistically significant. For our primary outcome we performed funnel plots to explore the risk of publication bias.

TRIAL SEQUENTIAL ANALYSIS

Trial sequential analysis (TSA) was performed for the primary outcome. TSA aims to reduce the risk of type-1 (false positive results) and type-2 (false negative results) errors which have been shown to affect meta-analyses [28]. A cumulative Z-curve was calculated with corresponding monitoring and futility boundaries. We calculated the required information size allowing for type 1 error of 0.05, and type 2 error of 0.20. We used the mean difference from the effect estimate of the conventional random effects model as well as variance and heterogeneity. If the cumulative Z-curve crosses the TSA monitoring or futility boundary, sufficient evidence is present and no additional studies are needed. If not, more studies are needed to make conclusions. Calculations were performed using Trial Sequential Analysis software (version 0.9.5.10 Beta, Copenhagen Trial Unit, Copenhagen, Denmark).

GRADING OF RECOMMENDATIONS ASSESSMENT, DEVELOPMENT, AND EVALUATION SYSTEM (GRADE)

We presented these using the GRADE approach [29]. We downgraded the quality of evidence from high-quality to moderate-, low- or very low-quality. Downgrading was undertaken independently by two review authors (MM and AV) and agreement

reached by consensus. Characteristics of the evidence that caused downgrading include: 1. limitations in the design and implementation of available studies, suggesting a high likelihood of bias (for example, studies not using a double dummy placebo design); 2. indirectness of evidence (indirect population, intervention, control or outcomes); 3. inconsistency of results; 4. imprecision of results (wide confidence intervals). When one of the above items was assessed as a risk, the evidence was downgraded by two levels (very serious risk) or one level (serious risk). We used the following interpretations of this assessment of quality of evidence for our primary outcome: 1) High quality: Further research is very unlikely to alter the confidence in the estimate of the effect; 2) Moderate quality: Further research is likely to alter the confidence in the estimate of the effect; 3) Low quality: Further research is very likely to alter the confidence in the estimate of the effect; 4) Very low quality: The confidence in the effect estimate is very little.

ETHICAL CONSIDERATIONS

This project consists of a systematic review considered a type of secondary study; whose methodology is based on the review of articles already published, mainly clinical trials. Since there will be no contact with patients or access to information from medical records or any other data that may affect the confidentiality of the study subjects, or generate any risk or have legal implications, no institutional ethical endorsement is required for its execution.

Ethical principles

The fundamental principles of bioethics will be complied with: Principles of Beneficence and Non-Maleficence, having the obligation to act for the benefit of others, promoting their legitimate interests and suppressing prejudices, as well as refraining from taking actions that may cause harm or harm others. Another of the ethical principles that will be complied with will be the Principle of Confidentiality, not revealing the identity of the patients or their particularities noted in the medical records.

The international bioethical norms currently in force have been taken into account, such as the Nuremberg code, a series of principles that govern experimentation with human beings; the Declaration of Helsinki, a document created by the World Medical Association on ethical principles for medical research on human beings; and the Belmont report, a document created by the United States Department of Health, Education and Welfare.

RESULTS

Figure 1 shows the flow chart of our study selection. Of the 3,404 studies retrieved, 14 were potentially eligible to be included and were subjected to an assessment of the methodological quality. Table 1 contains the details of the included studies [16, 20-22, 24-26, 30-36]. All included studies were reviewed in full text. Authors of three studies were contacted by email to supplement information regarding outcomes [22, 26, 31]. We derived standard deviations for three trials [20-22] and mean (SD) for two trials [24, 25]. Supplementary data (Table S1) provides exact definitions of the outcomes analysed in the included studies.

The methodological quality of the studies is given in Figure 2. Most methodological domains were poorly reported by most trials, whereas the provided information revealed high risks of bias for three trials.

Primary outcome:

Postoperative pain

Figure 3 shows the conventional meta-analysis for the primary outcome for 0 - 2 hours [16, 20, 21, 24, 26, 31, 34, 36], 2 - 6 hours [21, 25, 26, 36], 6 - 24 hours [21, 22, 25, 26, 30, 31, 36], and > 24 hours [22, 30] respectively. When comparing oral paracetamol versus intravenous, the mean pain scores difference at 0 - 2 hours was -0.17 with a 95% confidence interval -0.45 to 0.10. Pain scores at 2 - 6 hours, 6 - 24 hours and > 24 hours showed mean differences of -0.09, 0.06 and 0.13 respectively (Figure 3).

Secondary outcomes:

Opioid consumption during the first 24 hours

Ten studies reported the opioid consumption [20-22, 24-26, 30, 31, 34, 36], standardized to equivalents of intravenous morphine. When comparing the opioid consumption for intravenous versus oral paracetamol, the mean difference estimated was -0.13 with a 95% confidence interval of -1.75 to 1.49. Forest plot is shown in Supplementary Figure S2.

Time to first analgesic request or rescue dosage

This outcome was reported in 6 studies [16, 22, 25, 31, 33, 34]. The mean difference was -0.19 minutes with a 95% confidence interval of -4.20 to 3.82. Forest plot is shown in Supplementary Figure S2.

Figure 1. Flow chart of the literature search.

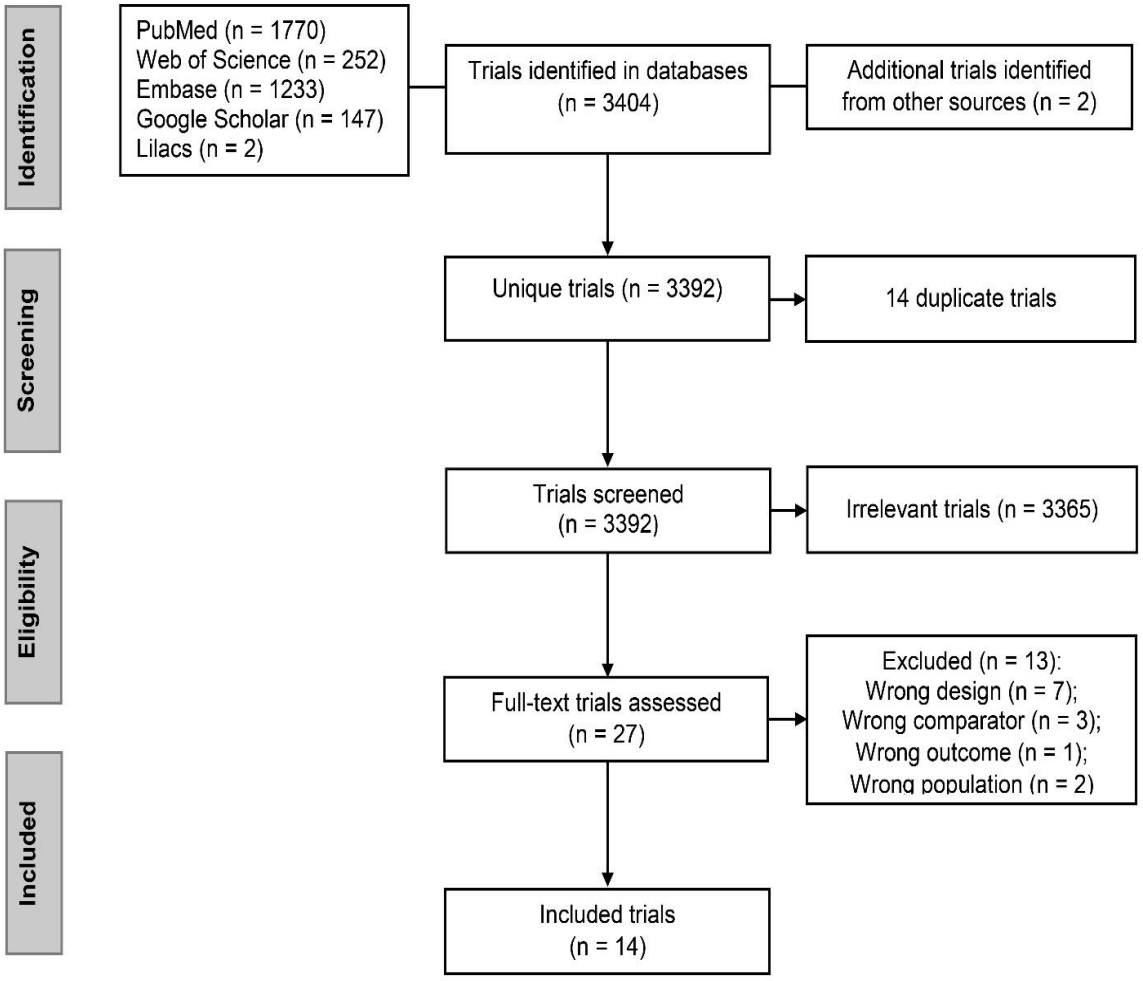
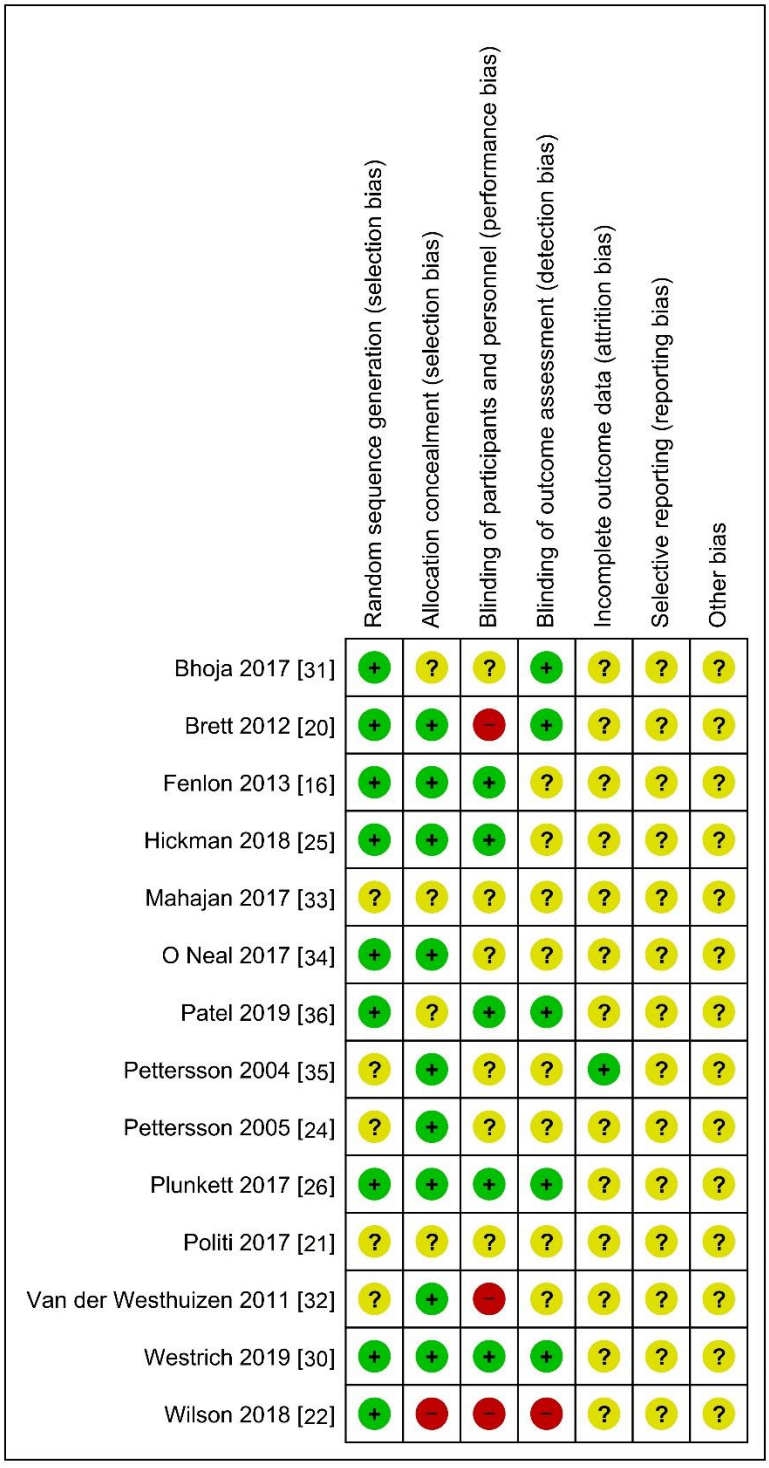


Table 1. Details of 14 randomised controlled trials of intravenous vs. oral peri-operative paracetamol.

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. [20]	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. [21]	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 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. [26]	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. [16]	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. [30]	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 Cumulative opioid between POD 0–3 Opioid-related side effects POD 1	Intra-operative ketorolac. Postoperative ketorolac, meloxicam and patient-controlled epidural analgesia with bupivacaine and clonidine
Bhoja et al. [31]	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. [24]	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 Nausea, vomiting Pain (10 cm VAS)	Pre-operative morphine or ketobemidone. Intra-operative fentanyl. Postoperative ketobemidone and aspirin
Wilson et al. [22]	47	47	Elective caesarean section	1 g postoperative and 8-hourly x 2	1 g postoperative and 8-hourly x 2	Opioid dose to 24 h	Intra-operative spinal bupivacaine with fentanyl and morphine. Postoperative ketorolac, oxycodone and morphine
Hickman et al. [25]	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. [32]	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. [33]	50	50	Elective caesarean section	10–15 mg.kg^{-1} 20 min before surgery end	650 mg 20 min before surgery	Analgesia duration Pain (10 cm VAS) 2-hourly to 24 h postoperative	Spinal bupivacaine. Rescue diclofenac
O'Neal et al. [34]	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. [35]	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. [36]	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 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

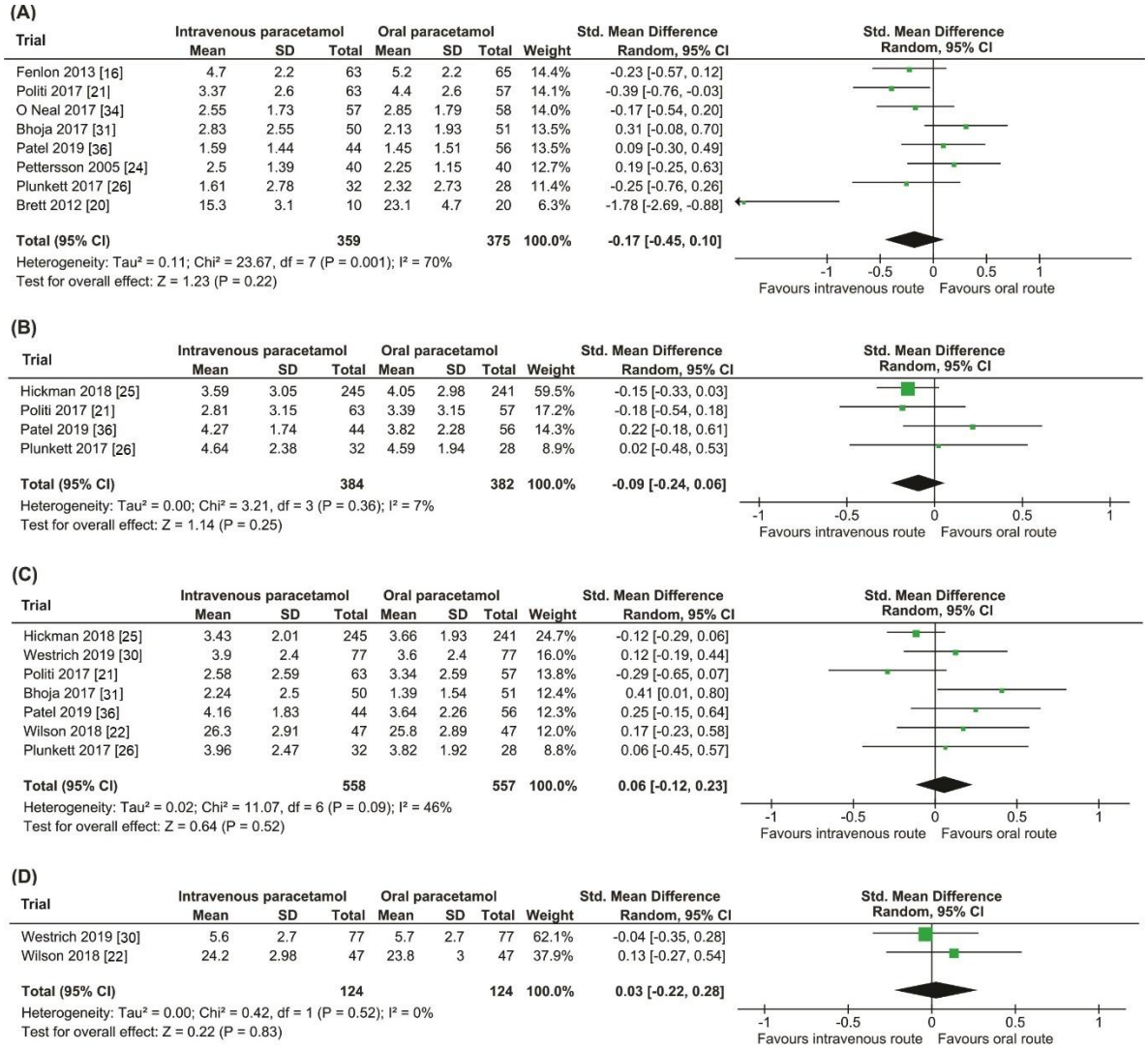
i.v., intravenous; p.o., oral; VAS, visual analogue scale; NRS, numerical rating scale; PACU, post-anaesthesia care unit; POD, postoperative days.

Figure 2. Risk of bias assessment of included trials using the Cochrane risk of bias tool.



?, unclear risk; -, high risk; +, low risk.

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.

Length of stay in recovery area or hospital

The stay in recovery area was only reported by 5 studies [20, 25, 26, 34, 36], where there was a mean difference of -1.56 minutes in favour of intravenous paracetamol, with a confidence interval of -14.49 to 11.38. On the other side, the hospital stay was reported in 3 studies [22, 25, 30] and its mean difference was 1.14 hours in favour of oral paracetamol, with a confidence interval -0.54 to 2.83. Forest plot is shown in

Supplementary Figure S2.

Patient satisfaction

Patient satisfaction was reported only in two study [22, 30], the mean difference estimated was 0.01 with a 95% confidence interval of -0.24 to 0.26. Forest plot is shown in Supplementary Figure S2.

Presence of nausea and vomiting

Postoperative nausea and vomiting were reported in five studies [22, 24, 25, 31, 33]. The outcome under study was presented in 124 out of 427 patients in the oral group vs 123 out of 431 patients in the intravenous group (Odds Ratio 0.98 with a 95% confidence interval of 0.72 to 1.33). Forest plot is shown in Supplementary Figure S2.

Presence of pruritus

The pruritus was reported only in one study [22]. It was present in 14 out of 47 patients in the oral group vs 8 out of 47 patients in the intravenous group.

Sedation

There were no studies reporting this outcome.

Plasma paracetamol concentrations

Plasma paracetamol concentrations were reported in three studies [20, 32, 35]. Because of different measurement units and different time-points, we could not synthesize data in a meta-analysis. Brett et al. [20] found higher plasma paracetamol concentrations 30 minutes after patient's arrival in the recovery room in the intravenous group. Another study [35] reported a significantly higher plasma paracetamol concentrations 20 minutes after administration of 2-g of paracetamol in the intravenous group, at 40 minutes after administration of this same dose significant difference was not observed between the two groups, however, 80

minutes later, paracetamol concentrations were significantly higher in the oral group. On the other side, Van der Westhuizen [32] reported higher values in plasma paracetamol concentration up to 240 minutes after administration of equivalent doses of paracetamol in the intravenous group.

Funnel plots

The funnel plots for the analysis of primary outcome are shown in Supplementary Figure S1. The plots are symmetric and do not suggest publication bias.

Trial sequential analysis

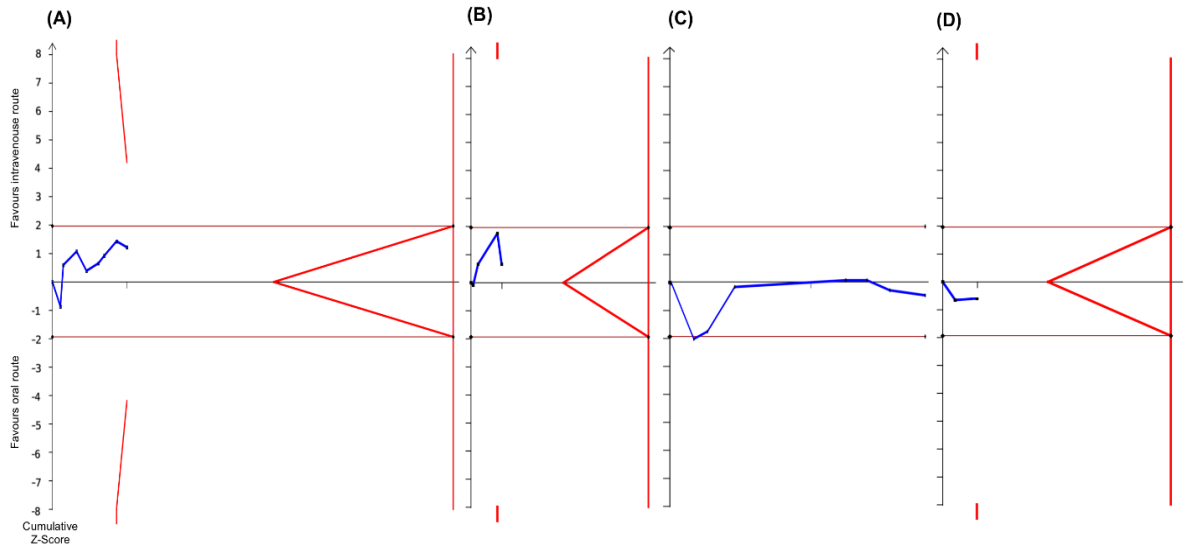
Trial sequential analysis was applied for the primary outcome, postoperative pain for the first four time periods. As with the conventional meta-analysis, we included all trials providing data at each period. The cumulative Z-curve (blue line) do not cross both the trial sequential monitoring boundary and the futility boundary for each time frame (Figure 4), indicating that the meta-analysis was not sufficiently powered to answer the clinical question defined by the assumptions used.

Grading of Recommendations Assessment, Development and Evaluation - Grade

We assigned the GRADE level of “low quality” to our primary outcome “postoperative pain”. This assessment was based on 1) the risk of bias, demonstrated with an “unclear risk of bias” for the most of domains and 2) imprecision due to large confidence intervals. There was, in our assessment, no increased risk from the remaining GRADE criteria: inconsistency, indirectness and publication bias.

In summary, route of paracetamol administration did not affect postoperative pain (Figs. 3 and 4). There were insufficient trials to interrogate small studies effects. Route of paracetamol administration did not affect any of the secondary outcomes. We graded the quality of evidence as ‘low’ for an effect of route of paracetamol administration on postoperative pain.

Figure 4. Trial sequence analysis (TSA) for intravenous vs. oral peri-operative paracetamol for postoperative pain.



(A) 0–2 h (734participants); (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 4514participants (>24 h), assuming alpha 0.05 and beta 0.20.

Cost-benefit analysis

A pragmatic approach to a cost-benefit analyses was performed as all included studies did not consistently report important clinical factors (e.g., opioid medication, complications). Number of readmissions or follow up meetings was not reported in studies. This made a realistic cost-benefit analyses not possible, but we do want take costs into account.

Individual level costs

We looked at the bare cost difference between intravenous and oral medication in

several Western countries. These results show that costs associated with intravenous and oral administration are between £ 1,92 - 1,95 (€ 2,18-2,21/US$ 2,36-2,39) and £ 0,15 - 0,19 (€ 0,17-0,22/US$ 0,18-0,23) for 500mg and 1000mg dosage, respectively. At an individual level, the cost differences between intravenous versus oral administration does not make a huge difference, especially taken into account the total costs of a total admission (e.g., surgery, length of stay in recovery area and hospital, additional medication, follow-up). We are aware that these prices may only be representative for Western European countries, but not generalizable for the rest of the world.

Hospital level costs

To provide more information, we requested the inventory data for intravenous paracetamol dosages in our university medical center. Our academic hospital has 525 single person rooms with around 31 023 admissions each year. We found that in 2018 around 1 542 and 46 623 paracetamol dosages of 500mg and 1000mg are given intravenously to patients, respectively. Till November 13th 2019, these numbers to be 956 and 53 546 of 500mg and 1000mg, respectively. Costs of only intravenous administration of paracetamol for both dosages are in the range of £ 86 075,49 - 106 250,22 (€ 97 558 - 120 420/US$ 105411,31 - 130 113,68). Assuming we can switch form intravenous to oral administration in 50% of the patients - which is quite a careful assumption, as there are only very few contraindications to oral paracetamol and even less strong indications for the intravenous route - this would already yield a cost reduction of around £ 38 872,91 - 47 966,54 (€ 43 959,60 - 54 239,05/US$ 47498,30 – 58 605,24) per year for a large teaching hospital, only concerning paracetamol. If 25%, 75%, or even 100% of patients would be switched to oral administration the cost reductions would be in the range between £ 19 436,46 - 94 240,96 (€ 21 979,80 - 106 556,54/US$ 24 379,47-117 706,91), respectively. In Supplementary Table S2 presents the total costs, costs reductions for each dosage, and for cost reductions for the different percentages of switching to oral administration.

DISCUSSION

Using conventional meta-analysis, the primary outcome under analysis postoperative pain showed that when comparing oral paracetamol versus intravenous at 0 - 2 hours, 2 - 6 hours, 6 - 24 hours and > 24 hours the mean pain scores were not significantly different. TSA indicated that the required information size was not reached to draw clear conclusions to answer the clinical question defined by the assumptions used regarding postoperative pain (which in prospective trials would be equal to an underpowered study). We also observed that opioid consumption during the first 24 hours, time to first analgesic request, length of stay at recovery area and at hospital and presence of nausea and vomiting, in the studies that were reported, did not show statistically significant differences. Patient satisfaction and presence of pruritus were rarely reported. Plasma paracetamol concentrations was highly variable because of different doses and measurement times, with plasma peaks at different times in both routes of administration (intravenous versus oral), without being able to draw a concrete conclusion. Overall, the quality of the available evidence was low.

In 2015, a systematic review was published comparing intravenous versus oral paracetamol for pain in general patients, not specifically in the perioperative setting [19]. Its included studies were randomized trials in adults that reported at least one clinical or pharmacokinetic outcome. In agreement with our results, those authors did not find significant differences in efficacy between the two routes of administration and there was no evidence to suggest that increased bioavailability of the intravenous route enhances efficacy outcomes. In addition, risk of bias assessment was unclear for a large number of domains in that study.

The only meta-analysis comparing intravenous and oral paracetamol for pain in the perioperative period was published in 2018, but was limited to patients undergoing total knee and hip replacement surgery [37]. They included only two studies with 236 patients and demonstrated that there were no significant differences between groups regarding postoperative pain scores and opioid requirements at 12, 24, or 48 hours, with a not negligible risk of bias. These findings and also those related to postoperative opioid consumption are in accordance with our results using different time periods of assessment and including a wide range of surgical procedures. Despite the differences in population, both meta-analyses found similar results for our primary outcome: there were no major differences in terms of pain control with low quality of the summarized evidence.

A recent observational study evaluating the effectiveness of oral versus intravenous paracetamol, with more than one million patients in hip and knee arthroplasties

surgery, found no superior benefit of intravenous administration, neither in terms of opioid administration, opioid-related complication risk, length of hospital stays, nor cost of hospitalization [38]. Considering this background, we argue that currently there is no direct evidence of superiority of the intravenous versus oral route for postoperative pain. However, TSA indicates that the number of patients included in the meta-analysis is not enough to allow a definitive conclusion regarding postoperative pain control.

Based on the above, the question arises if these findings are clinically relevant? Using pain assessment methods based on VAS, despite its power as a measurement and research tool, it can be tempting to overestimate the clinical importance of small differences in scores just because they reach statistical significance. Some authors argue that minimum clinically significant differences in VAS pain scores may be as low as 0.9 cm [39]. Considering none of our results exceeded this minimum difference, we can conclude that there were no clinically significant differences.

Embracing this uncertainty, we did our best to add the cost dimension into the analyses. The analysis is limited due to the availability of public data and therefore we focused on our own hospital and prices for The Netherlands. Nevertheless, our pragmatic analysis showed that there is a huge difference in costs between intravenous and oral administration of paracetamol. In a large academic hospital switching from intravenous to oral administration may yield a significant decrease in costs, this for paracetamol alone. For future research it would be relevant to study whether these cost differences are generalizable to other than Western European countries. In addition, taking a more macro-economic perspective on this issue [40].

The World Health Organization defines quality of care as the medical care that focuses on being safe, minimizing the risks to the patient to the maximum and effective on the basis of scientific evidence. This definition also considers equity and people-centeredness [41]. Finally, but not less important, any treatment should be “efficient” in terms that maximize the use of resources and minimizing costs of supplies and medicines. Surely, this definition applies to hospitalized and also perioperative patients. To the best of our knowledge and based on the results of this meta-analysis, the current practice of a broad routine use of intravenous paracetamol in the perioperative period is not in line with this statement. The use of intravenous route does not justify the elevated cost in all patients.

There are limitations in our study. First, most of the trials presented incomplete reporting and incomplete outcome data. Fourteen trials were included in our systematic review and twelve of them were included in at least one quantitative

analysis. Overall, available evidence was classified as “low quality”. Second, we have to deal with high uncertainty (due to very high confidence intervals) from the original outcome data, as well as, some outcome data transformation from the original articles. As a consequence, some trials with large sample size presented a relatively low weighted average contribution to meta-analysis. Third, the pragmatic cost analysis was performed might have limited generalizability as the data are taken just from one major teaching hospital in The Netherlands. Although, there are reports of small community hospitals in United States, in which they analysed the high costs of intravenous paracetamol and decided to limit its wide use [42].

CONCLUSIONS

Our study summarizes the lack of supportive evidence justifying the use of intravenous above oral paracetamol for postoperative pain management. In line with previous studies focusing on non-operated patients or only one type of surgery, we were able to demonstrate for all types of surgery, that there is no convincing clinical or statistical difference. However, uncertainty about the efficacy when comparing both routes does remain, because the available studies provide only low-quality evidence and TSA indicates that the current evidence is not yet enough to provide a definitive conclusion. Our cost-benefit analyses showed that considerable cost reductions are possible by switching to oral paracetamol. With these findings in mind, we believe that intravenous paracetamol should only be used in clinical trials or when the oral route is contra-indicated.

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SUPPLEMENTARY INFORMATION

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

Embase.com (Embase plus MEDLINE)

'surgery'/exp AND ('paracetamol'/exp OR 'intravenous drug administration'/exp) AND ('oral drug administration'/exp OR 'administration, oral' OR 'drug administration, oral' OR 'oral administration' OR 'oral drug administration' OR 'oral drug intake' OR 'p.o. administration' OR 'p.o. dosage' OR 'p.o. dose' OR 'p.o. drug administration' OR 'p.o. drug intake' OR 'per os drug administration') AND ('pain'/exp OR 'postoperative pain'/exp OR 'pain, postoperative' OR 'post operation pain' OR 'postoperative pain') AND 'randomized controlled trial'/exp

MEDLINE Epub (Ovid)

(Acetaminophen OR Paracetamol OR "Acetaminophen"[Mesh]) AND (Intravenous [tiab] OR Intra-venous [tiab] OR IV [tiab] OR oral [tiab] OR PO[tiab]) AND (((((Pain) OR Postoperative Pain) OR "Pain, Postoperative"[Mesh]) OR Surgery) OR postsurgical pain) OR "Surgical Procedures, Operative"[Mesh]) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] not (humans [mh] and animals [mh]))

Cochrane Central

((Acetaminophen * OR Paracetamol*) (administrat* OR inject*))):ab,ti) AND ((Intravenous* OR intrav* OR PO* OR oral OR):ab,ti) AND ((Postoperative* OR pain* OR postsurgical*):ab,ti))

Web of Science

(Ti= Pain OR Postoperative Pain OR Postoper* OR Surgery OR postsurgical pain OR Surg*) AND (Ti=intravenous OR intra-veno* OR IV OR oral OR PO) AND

(Ti=Acetaminop* OR Paracet*)

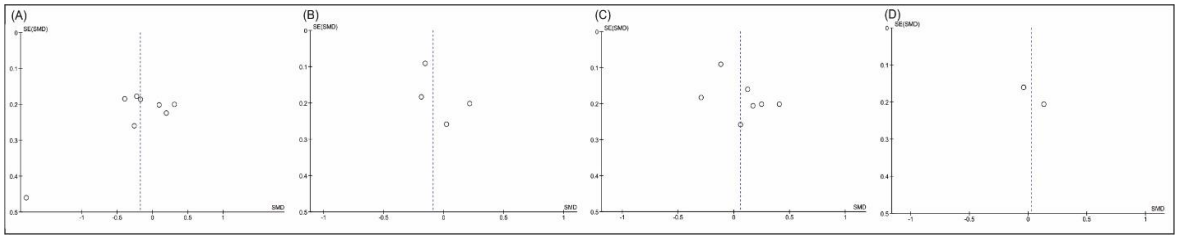
Google Scholar (relevance)

“cirugia | quirurgi* | posquir* | perioperat* | surger*”,
“acetamin* | paracetamol | intraveno*”,
“(((acetamin* oral | intravenous*) | (cirugia | surgery)) | (ensay* | aleatori*))”

LILACs

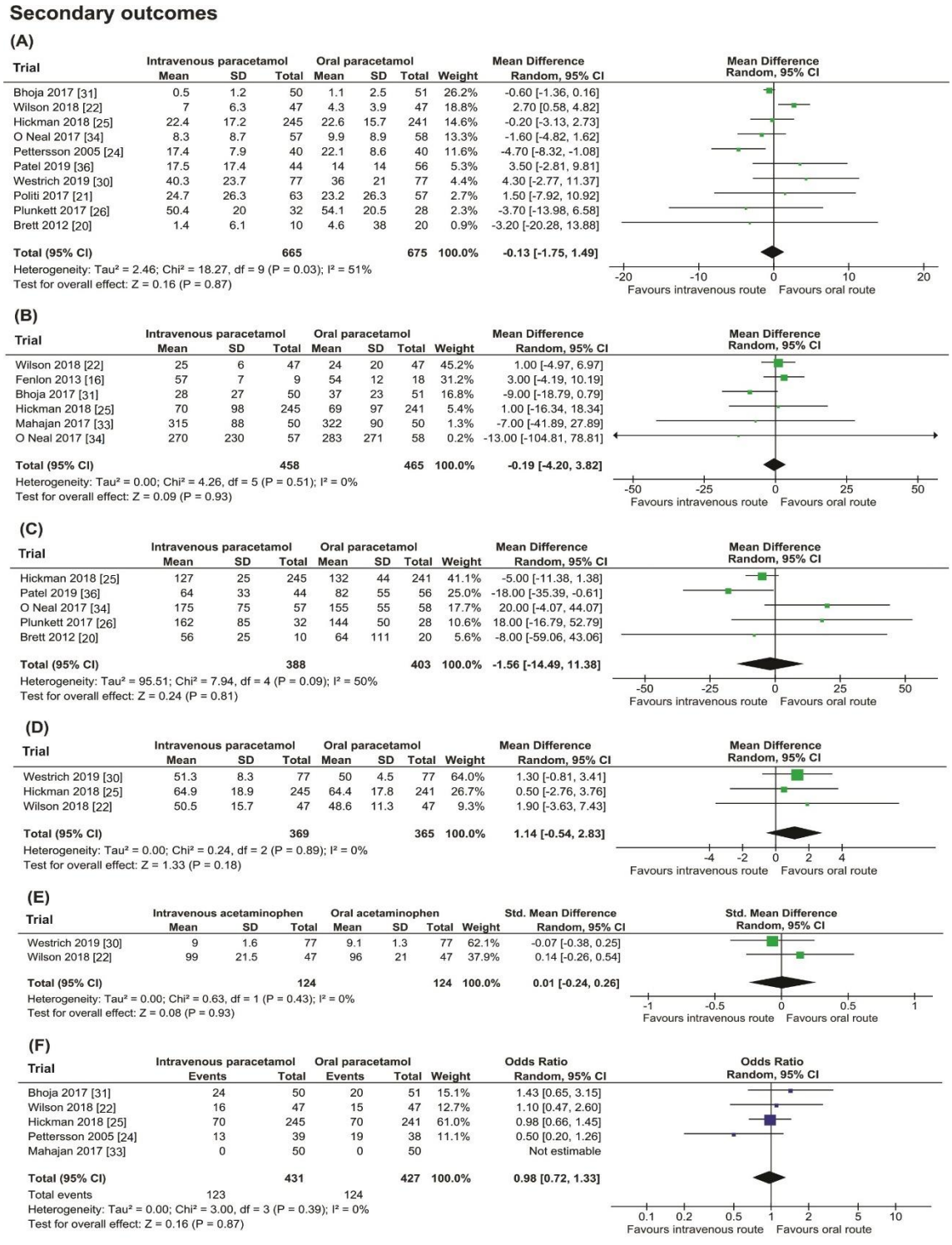
Acetaminofen [Palabras] AND Oral [Palabras] AND Intravenoso [Palabras] AND Cirugia [Palabras]

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.

Author	Pain scores after surgery	Opioid requirements	Time to first analgesic request or rescue dosage	Patient satisfaction	Length of stay at PACU or at hospital	Presence of PONV	Plasma concentrations of paracetamol
Brett 2012 [18]	VAS (0-100mm scale) for pain at 10-minute intervals until discharge from the recovery area.	Total fentanyl requirements prescribed as 20 μg increments and given by a blinded recovery nurse if the visual analogue scale exceeded 30 mm.			Length of stay was calculated for each patient (minutes).		Plasma paracetamol level 30 minutes after each patient's arrival in the recovery room from the arm contralateral to the intravenous line. Unit: μmol/l.
Politi 2017 [19]	VAS (0-10 scale) for pain at 0, 4, 8, 12, 16, 20 and 24 h.	Opioid requirements were calculated in hydromorphone equivalents at 0, 4, 8, 12, 16, 20 and 24 h.					

Plunkett 2017 [20]	NRS (0-10 scale). Pain scores were assessed pre-operative, first post-operative, discharge from PACU, and at 6, 12, 18 and 24 h. Primary outcome: the time-weighted sum of pain intensity differences from baseline over the initial 24 h following surgery.	Opioid requirements were converted to OME: perioperative, operative, PACU periods and at home.			Time in PACU (h) for each group.		
Fenlon 2013 [21]	VAS (0-100mm scale). 1 h from the end of surgery.		Time (minutes) to request for rescue analgesia if applicable.				
Westric h 2019 [22]	NRS (0-10 scale) with activity on POD 1 (patient reported pain during physical therapy).	Opioid requirements between POD 0 and POD 3 (OME).		APS-POQ-R (POD 2) that includes satisfaction.	Time to hospital discharge (h) median (Q1, Q3)	APS-POQ-R (POD 2) that includes nausea.	

Bhoja 2017 [23]	VAS (0-10 scale) 1 h and 24 h postoperatively.	Opioid requirements at PACU and 24 h following surgery (MME).	Time (minutes) to request for rescue analgesia if applicable.			The occurrence of PONV at PACU and 24 h following surgery. n (%)	
Petterss on 2005 [25]	VAS (0-10 scale). Pain during deep breathing or coughing was evaluated with VAS at 0, 20, 80, and 120 minutes after the first dose of paracetamol.	Opioid requirements during the postoperative from the first paracetamol administered until the next morning in the ICU (Ketomebidone).				The occurrence of PONV. n (%)	
Wilson 2018 ** [26]	VAS (0-100mm scale) at 24 and 48 h postoperatively at rest and with ambulation.	Opioid requirements at 24 h (MME).	Time to first opiate rescue (h).	Patient satisfaction at 24 and 48 h with 0-100mm scale: 0mm, very unsatisfied; 100mm, very satisfied.	Time to discharge criteria in h.	Total number of patients with PONV. n (%)	

Hickman 2018 [27]	VAS (0-10 scale) in the first 24 h postoperatively. If the patient is not alert and responsive, the nurse identifies pain via observation of grimacing, agitation, and restlessness using the same 0–10 scale.	Opioid requirements at 24 h (MME).	Time (minutes) from PACU admission to first use of postoperative pain medication.		Length of PACU stay and hospital stay (h).	Documented PONV. n (%)	
Van der Westhuizen 2011 [28]							Blood sample was collected 30 minutes after the dose was given in the oral group and 30 minutes after the IV dose was administered in the IV group, then at intervals of 30 minutes for 240 minutes after the initial dose. Unit: mg/l.

Mahajan 2017 [29]	VAS (0-10 scale) immediately in recovery room then 2 hourly till 24 h postoperative in the ward.		Time of first rescue analgesia (minutes). Rescue analgesia was given for pain score ≥ 4.			Documented PONV. n (%)	
O Neal 2017 [30]	NRS (0-10 scale) every 15 minutes in the PACU for up to 4 h.	Opioid requirements (converted to IV hydromorphone equivalents in milligrams) within 6 and 24 h of surgery.	Time to rescue analgesia (minutes).		Time until ready for PACU discharge (minutes) defined by resolution of spinal anaesthetic.		
Petterss on 2004 [31]							Blood samples were taken prior to paracetamol administration (baseline) and at 20, 40 and 80min after the administration. Plasma paracetamol concentrations were determined by fluorescent polarization immunoassay. Unit: µmol/l.

Patel 2019 [32]	NRS (0-10 scale) at rest on PACU arrival, 1 h after PACU arrival, at discharge from PACU, 6 and 24 h postoperative.	Opioid requirements (MME) during the first 24 h.		Patient satisfaction scores, with overall pain management, from 0 to 10.	Time in PACU (minutes) for each group.		

*** Wilson 2018 also collected data about pruritus as total number of patients with occurrence of pruritus.*

NRS, numeric rating scale; VAS, visual analogue scale; IV, intravenously; PACU, post-anaesthesia care unit; PO, oral; h, hours; PONV, postoperative nausea and vomiting; APS POQ, American Pain Society Patient Outcome Questionnaire; POD, postoperative days; OME, oral morphine equivalents; MME; morphine milligram equivalent.

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

Intravenous administration	Quantity 2018	Quantity 2019 (till November 13th, 2019)	Price Intravenous	Projected Price Oral
Paracetamol (500mg)	1542	956	1,92	0,15
Paracetamol (1000mg)	42623	53546	1,95	0,19

Intravenous administration, current costs	**2018**	**2019**
Costs 500mg	£ 2.960,64	£ 1.835,52
Costs 1000mg	£ 83.114,85	£ 104.414,70
Total current costs	£ 86.075,49	£ 106.250,22
Projected price oral, 25% switching	£ 2.018,00	£ 2.019,00
Costs 500mg	£ 2.278,31	£ 1.412,49
Costs 1000mg	£ 64.360,73	£ 80.854,46
Total projected costs	£ 66.639,04	£ 80.854,46
COST REDUCTION	£ 19.436,46	£ 25.395,76

* Cost if 25% of the dosages are switched from intravenous to oral administration.

Projected price oral, 50% switching	**2018**	**2019**
Costs 500mg	£ 1.595,97	£ 989,46
Costs 1000mg	£ 45.606,61	£ 57.294,22
Total projected costs	£ 47.202,58	£ 58.283,68
COST REDUCTION	£ 38.872,91	£ 47.966,54

* Cost if 50% of the dosages are switched from intravenous to oral administration.

Projected price oral, 75% switching	**2018**	**2019**
Costs 500mg	£ 913,64	£ 566,43
Costs 1000mg	£ 26.852,49	£ 33.733,98
Total projected costs	£ 27.766,13	£ 34.300,41
COST REDUCTION	£ 58.309,36	£ 71.949,81

* Cost if 75% of the dosages are swtiched from intravenous to oral administration.

Projected price oral, 100% switching	**2018**	**2019**
Costs 500mg	£ 231,30	£ 1.835,52
Costs 1000mg	£ 8.098,37	£ 10.173,74

Total projected costs	£ 8.329,67	£ 12.009,26
COST REDUCTION	£ 77.745,82	£ 94.240,96

* Cost if 100% of the dosages are swtiched from intravenous to oral administration.