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REVIEW ARTICLE

Single-dose intravenous paracetamol or propacetamol for prevention or treatment of postoperative pain: a systematic review and meta-analysis

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Editor's key points

- Meta-analysis of efficacy and adverse event of single-dose paracetamol or propacetamol in postoperative pain.
- Similar efficacy, with number needed to treat around 4 for 50% reduction in pain at 4 h.
- Pain on infusion in 23% of patients receiving propacetamol.
- Both provide a reduction in opioid use but not in opioid-related side-effects.

Summary. Paracetamol is the most commonly prescribed analgesic for the treatment of acute pain. The efficacy and safety of i.v. formulations of paracetamol is unclear. We performed a systematic search (multiple databases, bibliographies, any language, to May 2010) for single-dose, randomized, controlled clinical trials of propacetamol or i.v. paracetamol for acute postoperative pain in adults or children. Thirty-six studies involving 3896 patients were included. For the primary outcome, 37% of patients (240/367) receiving propacetamol or i.v. paracetamol experienced at least 50% pain relief over 4 h compared with 16% (68/527) receiving placebo (number needed to treat=4.0; 95% confidence interval, 3.5–4.8). The proportion of patients in propacetamol or i.v. paracetamol groups experiencing at least 50% pain relief diminished over 6 h. Patients receiving propacetamol or paracetamol required 30% less opioid over 4 h and 16% less opioid over 6 h than those receiving placebo. However, this did not translate to a reduction in opioid-induced adverse events (AEs). Similar comparisons between propacetamol or i.v. paracetamol and active comparators were either not statistically significant, not clinically significant, or both. AEs occurred at similar rates with propacetamol or i.v. paracetamol and placebo. However, pain on infusion occurred more frequently in those receiving propacetamol compared with placebo (23% *vs* 1%). A single dose of either propacetamol or i.v. paracetamol provides around 4 h of effective analgesia for about 37% of patients with acute postoperative pain. Both formulations are associated with few AEs, although patients receiving propacetamol have a higher incidence of pain on infusion.

Keywords: acetaminophen; analgesia, postoperative; analgesic techniques; analgesics non-narcotic, pain, postoperative

Paracetamol, known as acetaminophen in North America, is the most commonly prescribed analgesic for the treatment of acute pain.[1] Its major advantages over non-steroidal anti-inflammatory drugs (NSAIDs) are its lack of interference with platelet function and safe administration in patients with a history of peptic ulcers or asthma.[2] Systematic reviews of randomized controlled trials (RCTs) confirm the efficacy of oral paracetamol for acute pain.[3 4] One out of four patients who receives 1 g of paracetamol achieves at least 50% pain relief.[2] However, oral paracetamol has a slow onset of analgesia and the non-availability of the oral route immediately after surgery limits its value in treating immediate postoperative pain. Currently, there are two formulations of i.v. paracetamol: propacetamol, a prodrug of paracetamol; and the recently approved i.v. paracetamol. Propacetamol is hydrolysed by plasma esterases to paracetamol within 7 min after administration. A dose of 2 g of propacetamol is hydrolysed to 1 g of paracetamol.[5 6] Propacetamol requires reconstitution, and contact dermatitis in health personnel who have handled the drug has been observed.[7 8] Additionally, it causes pain at the site of injection. This discomfort can be reduced if it is injected by slow infusion.[9] Conversely, i.v. paracetamol is presented as a ready-to-use solution. No incidences of contact dermatitis have been reported, nor have there been reports of its infusion causing discomfort.[10–12]

Although many clinical trials have evaluated i.v. formulations of paracetamol, published systematic reviews are either outdated[13] or have analysed only selected outcomes.[14] The objectives of this systematic review were to assess the efficacy and safety of a single dose of paracetamol i.v. for

the treatment of postoperative pain in both adults and children.

Methods

Literature search

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, 2nd Quarter 2010), MEDLINE using the OVID platform (1950 to May 2010), EMBASE (1980–2010, Week 18), and LILACS (1992 to May 2010) by combining terms for RCTs with those for paracetamol/acetaminophen, i.v. administration, and postoperative pain. We also checked the clinical trials registry http://www.clinicaltrials.gov and reference lists of retrieved articles. We did not apply any language restriction.

We included blinded or unblinded, placebo- or active-controlled, single-dose RCTs that evaluated children or adults with postoperative pain after any kind of surgery, who were able to self-report pain intensity or pain relief. The time period of interest was 4–6 h post-intervention. Multiple-dose studies that provided separate data for the first dose were also included. We excluded crossover studies, because the intensity of postoperative pain changes over time, and studies with $<$4 h of follow-up post-intervention. Interventions had to be given within the last 30 min of surgery, in the immediate postoperative period or at any time within the first three postoperative days. Two independent review authors screened all articles identified in the electronic searches.

Data extraction and analysis were also performed in duplicate. When studies did not provide sufficient data, we contacted study authors where possible. Continuous outcomes were extracted as means and standard deviations. Dichotomous outcomes [e.g. number of patients with at least 50% pain relief, adverse events (AEs)] were extracted as the presence or absence of the effect, and expressed as odds ratios (ORs). If data were only presented graphically, we extracted them using xyExtract Graph Digitizer software (v 3.1, Wilton Pereira da Silva, Brazil).

Primary outcomes included pain relief and pain intensity assessed by any categorical or numerical pain intensity or pain relief scales. Secondary outcomes included: number of participants requiring rescue medication; time to rescue medication; opioid consumption; patients' global evaluation of therapy [provided they were patient reported and measured on a four- or five-point categorical scale or visual analogue scale (VAS)]; and AEs.

Two reviewers independently assessed the risk of bias of all included studies by making critical assessments for each of the following different domains: sequence generation (randomization), allocation concealment, and blinding, with answers 'Yes' indicating low risk of bias, 'No' indicating high risk of bias, and 'Unclear' indicating either lack of information or uncertainty over the potential for bias.[15]

Meta-analysis

Our primary analysis was the proportion of patients with 50% or greater pain relief in each treatment arm over both the 4 and 6 h periods post-intervention. If not reported, we calculated the theoretical proportion of participants achieving at least 50% pain relief by extracting or calculating total pain relief (TOTPAR) or summed pain intensity difference (SPID) and using formulas derived by Cooper and Moore and colleagues.[16–18] In turn, we calculated the number needed to treat to benefit (NNTB) for at least 50% pain relief over the 4 or 6 h period.

Secondary analyses included:

(i) The proportion of patients in each arm receiving additional analgesia during the 4–6 h post-study drug administration and the number needed to treat to prevent (NNTp) re-medication.
(ii) Time to next medication in each treatment arm and the mean time difference between the groups.
(iii) Opioid consumption in studies in which co-administration of opioids [including patient-controlled analgesia (PCA)] was allowed. We converted opioid requirements into i.v. morphine-equivalents (mg), using widely accepted opioid conversion tables.[19] To determine the opioid-sparing effect of an intervention, we calculated the mean difference in opioid requirements between treatment arms.
(iv) Patients' global evaluation of therapy. Dichotomous information was derived from categorical evaluations (number of patients reporting the top two categories, e.g. 'good/satisfied' or 'excellent/very satisfied'). For VAS ratings, we compared means of each intervention.
(v) AEs: We assessed both the total number of AEs and the reporting of individual AEs, for example, nausea. In addition, we extracted the number of patients reporting pain due to infusion of the study medication. Withdrawals or dropouts were noted when adequately described. Validated scales were noted when used.

All meta-analyses were performed using RevMan 5.0 software.[20] Results are expressed as ORs for dichotomous data or weighted mean differences for continuous data, both with 95% confidence intervals (CIs). We assessed statistical heterogeneity by visually examining the forest plots and quantified it by using the I^2 statistic. An I^2 value of $>$50% is considered to indicate substantial heterogeneity.[21] Sensitivity analyses were performed to investigate the effect of various study characteristics on the primary efficacy outcome: placebo- and active-controlled trials were analysed separately; propacetamol and i.v. paracetamol were analysed both separately and together; and non-blinded studies were included then removed.

Results

Retrieved trials

Our searches produced 1231 references (Fig. 1). Review of the abstracts identified 56 potentially relevant studies. Nineteen studies did not meet inclusion criteria.[12 22–39] For one study, we were unable to retrieve the full article from any source.[40]

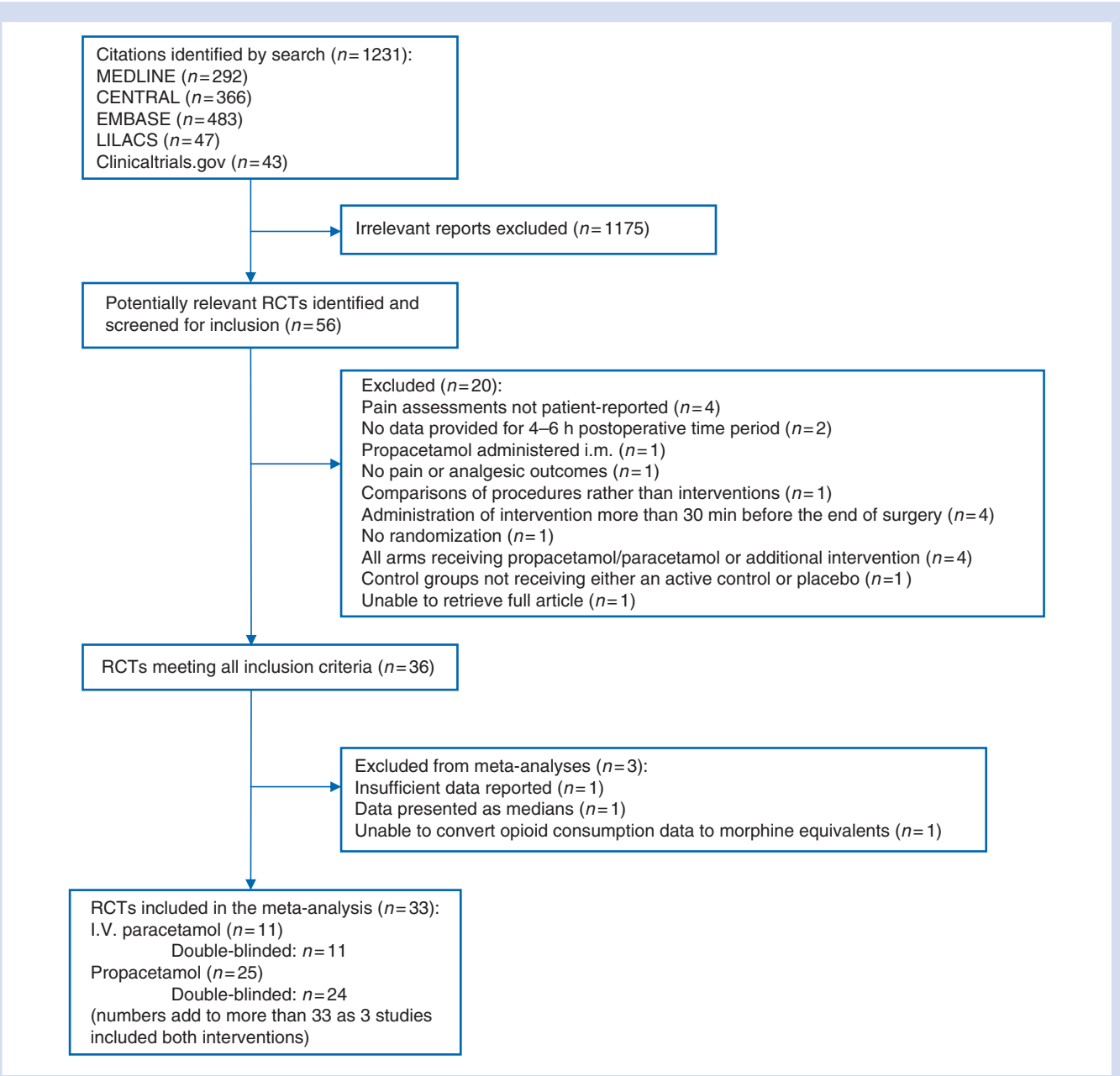

Fig 1 Flow chart of retrieved, excluded, and analysed trials. I.V., intravenous; RCT, randomized controlled trial.

Therefore, 36 studies were included in the review. In the included studies, enrolment ranged from 30[41] to 550 patients.[42] In total, 712 patients were treated with i.v. paracetamol, 1431 with propacetamol, 1048 with placebo, and 705 with an active comparator (either opioid or NSAID). Paracetamol i.v. was used in 13 studies[11 43–54] and 26 gave propacetamol.[11 41 42 51 53 55–75] Three studies administered both.[11 51 53] All but three studies used the equivalent of paracetamol 1 g. The remaining studies administered 30 mg kg^{-1} propacetamol,[74] 10, 20, or 40 mg kg^{-1} propacetamol,[59] or 2 g paracetamol in addition to 1 g.[48] The surgery performed included orthopaedic;[53 56 62 63 70 75] obstetric/gynaecologic;[43 51 59 71 73] eye/ear/nose and throat;[44 49 50 61 66] back;[45 58 60] cardiovascular;[47 57 65] dental;[11 48 69 72] general;[46 52 54 55 64 68] transplant;[41] and mixed.[42 67 74] Three studies evaluated adults and adolescents together, with the youngest patient being 13 yr of age.[44 61 72] The remainder evaluated only adults. No studies performed exclusively in children met inclusion criteria, primarily because pain was not patient-reported.

Studies fell broadly into two designs: those in which the intervention was automatically administered shortly before or after the end of surgery and the primary outcome was opioid consumption (usually PCA, but occasionally as on-demand injections); or those in which the intervention was administered only after a patient reported

moderate-to-severe pain post-surgically, in which case the primary outcome was pain relief/pain intensity difference. From the latter studies, we were able to calculate the number of patients with at least 50% pain relief over either 4 or 6 h, or both.[11 48 51 53 57 62 63 67 69 72 75]

Four studies did not present efficacy data in a format that we were able to meta-analyse, for example, presenting data without standard deviations.[41 43 44 61] In three studies, we were unable to analyse either efficacy or safety data for similar reasons.[47 52 59]

Risk of bias in included studies

Twenty-one studies described adequate randomization methods, either by using tables of random numbers or by computer-generated randomization. In 15 studies, the method of randomization was unclear, usually because there was no description of the methods used. Fewer studies described attempts at allocation concealment. In 21 studies, concealment was unclear as there was no description of any method used. Nine studies did use adequate concealment methods. One study made no attempt at allocation concealment.[68] On the basis of the descriptions in each paper, 24 studies used adequate methods to ensure blinding. Interventions were prepared by a party not directly involved in the study. Papers either stated that the interventions appeared identical or where that was not possible, a double- or triple-dummy technique was used. For the 11 studies in which the adequacy of blinding was unclear, most made some description of their method, for example, a third party prepared the interventions, but did not give enough information that we could be certain, for example, no mention of whether treatments appeared identical. One study was an open trial.[68]

Pain outcomes

Propacetamol or i.v. paracetamol compared with placebo

Propacetamol and i.v. paracetamol were superior to placebo for all meta-analysed efficacy outcomes at all measured time points (Table 1). Nine studies provided data on the first time period of the primary outcome, number of patients achieving at least 50% pain relief over 4 h (Fig. 2). The proportion of patients experiencing at least 50% pain relief over 4 h with propacetamol was 40% (166/415) and with i.v. paracetamol was 32% (74/232). The proportion of patients experiencing at least 50% pain relief over 4 h with placebo was 16% (66/425). The derived NNTB for at least 50% pain relief over 4 h was 4.3 (3.5–5.6), 3.4 (2.8–4.5), and 4.0 (3.5–4.8) for propacetamol, paracetamol, and the combined data, respectively. That is, for every four patients treated with propacetamol or paracetamol, one would experience at least 50% pain relief who would not have done so with placebo. Outcomes measured over 6 h produced similar results to those measured over 4 h, but with some diminution of analgesic effect. The proportion of patients experiencing at least 50% pain relief over 6 h with propacetamol was 26% (91/344) and with paracetamol was 27% (63/232). The NNT for at least 50% pain relief over 6 h was 5.9 (4.5–9.1), 3.8 (3.1–5.3), and 5.3 (4.2–6.7) for propacetamol, paracetamol, and their data combined, respectively.

Six studies reported the numbers of participants requiring rescue medication. For combined propacetamol or paracetamol data, the proportion of patients using rescue medication was 59% (188/319) *vs* 77% for those given placebo. This gives a number needed to treat to prevent (NNTp) rescue medication of 3.7 (2.9–5.0). In those patients who required rescue medication, the weighted mean difference of time to use of rescue medication was 28 min (19–37) longer for patients receiving either propacetamol or paracetamol *vs* placebo.

Opioid consumption data were available for the time periods 0–4 and 0–6 h. Over 0–4 h, three studies reported data on propacetamol or paracetamol, with 56 patients receiving propacetamol, 20 paracetamol, and 78 placebo. Patients receiving placebo required an average of 4.4 mg of morphine, which was a mean of 1.3 mg more than those receiving propacetamol or paracetamol, and this translates to a 30% reduction in opioid requirements. For the time period 0–6 h, reductions in morphine equivalents translate to a 16% reduction in opioid requirements.

Patients' global evaluation was predominately assessed using categorical scales. Ten studies provided data on categorical rating of global evaluation *vs* placebo. Overall, 66% (526/798) of patients receiving propacetamol or paracetamol rated therapy as 'good/satisfied' or better *vs* 54% (327/606) receiving placebo. The overall NNT for a global evaluation of 'good/satisfied' or better was 5.3 (4.3–7.1). Two studies used 0–10 VAS for global evaluation. Overall, there was a 1.6 (1.0–2.2) point superiority for patients receiving propacetamol.

Propacetamol compared with i.v. paracetamol

Three studies presented a direct comparison,[11 51 53] with a total of 181 patients receiving propacetamol and 180 receiving i.v. paracetamol. The pain outcomes did not demonstrate a statistically significant difference between propacetamol and i.v. paracetamol for any outcome. Meta-analyses of the number of patients achieving at least 50% pain relief gave ORs of 1.0 (0.6–1.5) and 0.9 (0.6–1.4) over 0–4 and 0–6 h, respectively. Only single studies were available for number of patients requiring rescue medication and for opioid consumption—neither demonstrated a statistically significant difference between arms. For global evaluation, meta-analysis provided an OR of 0.9 (0.5–1.6).

Propacetamol or i.v. paracetamol compared with active comparators

Limited data described the analysed pain outcomes for propacetamol or i.v. paracetamol *vs* NSAIDs or opioids. For some outcomes, there were no head-to-head studies of i.v. paracetamol and active comparators. None of the analyses demonstrated a statistically significant difference between treatment arms, with the exception of opioid consumption,

Table 1 Meta-analyses of pain outcomes: propacetamol or i.v. paracetamol *vs* placebo. *Combined numbers may be less than individual totals due to studies including both propacetamol and i.v. paracetamol arms

Outcome	Statistical method	Intervention	Number of studies, total patients enrolled*	Overall estimate (95% CI)
At least 50% pain relief over 4 h (*n*/*N*)	Odds ratios	Propacetamol	8, 807	4.6 (3.1, 6.8)
		Paracetamol	3, 367	17.2 (5.6, 53.2)
		Combined data	9, 1072	5.8 (4.1, 8.4)
At least 50% pain relief over 6 h (*n*/*N*)	Odds ratios	Propacetamol	6, 662	4.2 (2.6, 7.0)
		Paracetamol	3, 367	22.0 (5.3, 91.2)
		Combined data	7, 927	6.0 (3.8, 9.6)
Requirement for additional analgesia (*n*/*N*)	Odds ratios	Propacetamol	3, 204	0.28 (0.16, 0.50)
		Paracetamol	3, 340	0.12 (0.05, 0.30)
		Combined data	6, 544	0.21 (0.13, 0.33)
Time to additional analgesia (min)	Mean difference	Propacetamol	3, 316	23.7 (13.8, 33.6)
		Paracetamol	1, 74	56.0 (30.2, 81.8)
		Combined data	4, 390	27.9 (18.6, 37.2)
Opioid consumption over 4 h (i.v. morphine equivalents, mg)	Mean difference	Propacetamol	2, 114	−2.0 (−3.2, −1.0)
		Paracetamol	1, 40	−1.2 (−1.6, −0.8)
		Combined data	3, 154	−1.3 (−1.7, −0.9)
Opioid consumption over 6 h (i.v. morphine equivalents, mg)	Mean difference	Propacetamol	6, 399	−2.9 (−4.4, −1.4)
		Paracetamol	2, 141	−2.0 (−2.6, −1.4)
		Combined data	7, 488	−2.1 (−2.6, −1.6)
Global evaluation: ('good/satisfied' or better, *n*/*N*)	Odds ratio	Propacetamol	8, 1114	2.4 (1.8, 3.1)
		Paracetamol	4, 392	3.7 (2.1, 6.7)
		Combined data	10, 1404	2.6 (2.0, 3.3)
Global evaluation: VAS (0–10)	Mean difference	Propacetamol	2, 282	1.6 (1.0, 2.2)

where two studies supplied data for the time period 0–4 h. Those receiving propacetamol or paracetamol required 0.2 mg (0.0–0.4 mg) less i.v. morphine than those receiving an NSAID.

Adverse events

The time over which AE data were collected varied from 4 h to 7 days, with the majority of studies reporting data at 24 h. In only eight studies, it was clear that AE data collection was confined to the 4–6 h postoperative period, that is, the same period over which we assessed efficacy.[46 49 51 57 63 67 74 75] No studies reported whether AE data continued to be collected after rescue medication.

Propacetamol or paracetamol compared with placebo

Thirteen studies reported the number of patients reporting any AE.[11 42 44 48 49 53 56 62 63 69 70 72 75] Meta-analysis of those studies comparing propacetamol and placebo demonstrated an increase in AEs in the propacetamol group, with 38% (278/740) of patients receiving propacetamol reporting an AE compared with 31% (220/720) of those receiving placebo. This translates to an OR of 1.4 (1.1–1.7) and a number needed to treat to harm (NNTH) of 16.7 (10.0, 100.0). There was no statistical difference in the rate of AEs in those patients receiving i.v. paracetamol (47%, 144/306) *vs* those receiving placebo (40%, 84/211), translating to an OR of 1.1 (0.8–1.7).

We also analysed reports of individual AEs. Of the 19 different AEs reported (nausea; vomiting; nausea/vomiting; headache; pruritus; respiratory depression; sedation; vertigo/dizziness; fatigue; fever; gastrointestinal disorders; urinary retention; allergy/skin rash/local reaction; heart rate disorders; malaise; bleeding; liver function test abnormalities; hypotension; or AEs causing a patient to withdraw from a study) only the incidence of fever demonstrated a statistically significant difference between propacetamol or paracetamol (2%, 2/99) and placebo (12%, 6/52).[53]

Propacetamol compared with i.v. paracetamol

Propacetamol is reported to cause more pain on infusion than i.v. paracetamol. We analysed data from propacetamol/placebo studies, i.v. paracetamol/placebo studies, and any studies that performed direct comparisons of propacetamol and paracetamol.[11 51 53] Our analysis of propacetamol/placebo demonstrated that 23% (75/333) of patients reported pain on infusion with propacetamol compared with 1% (4/312) of those receiving placebo. Conversely,

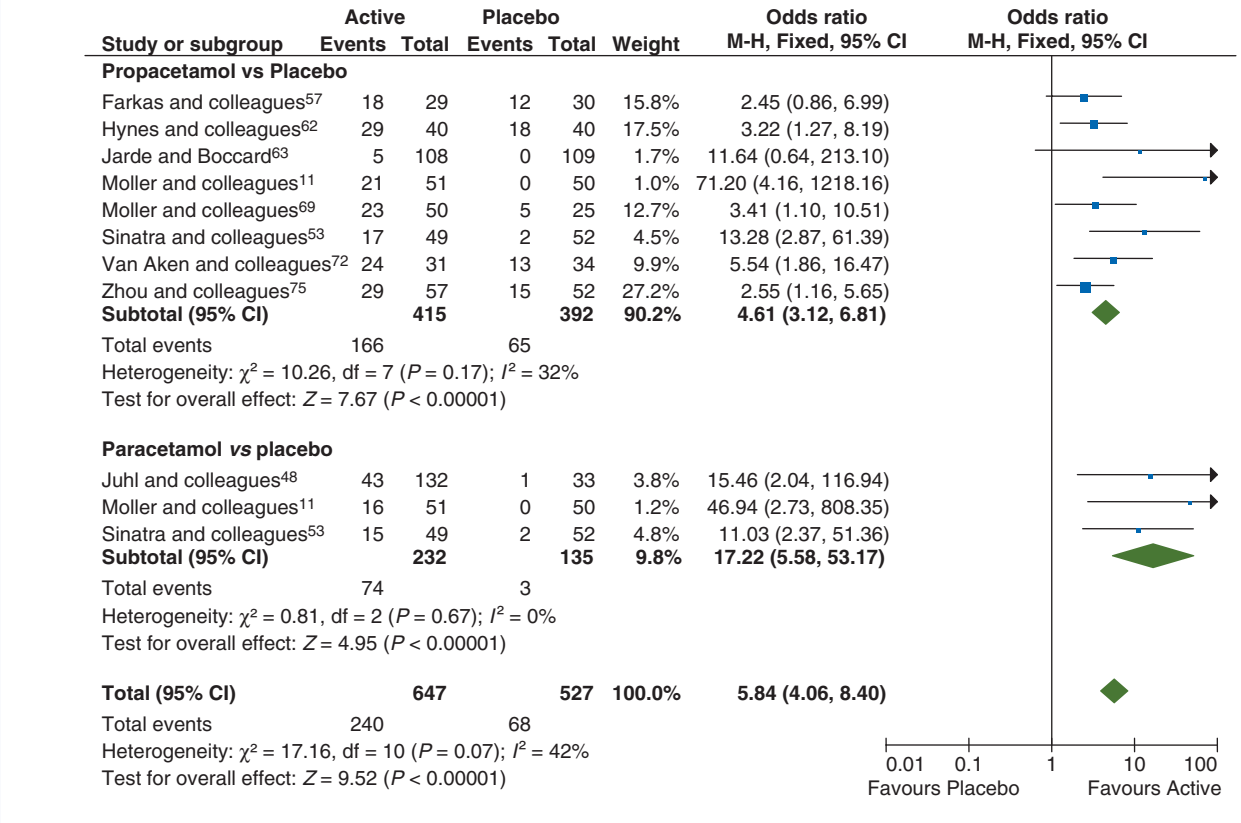

Fig 2 Number of patients with at least 50% pain relief from 0 to 4 h: propacetamol or i.v. paracetamol *vs* placebo. CI, confidence interval.

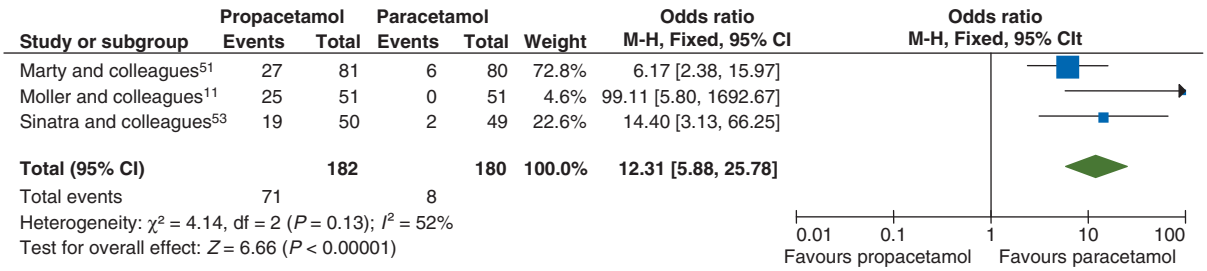

Fig 3 Number of patients reporting pain on infusion: propacetamol *vs* i.v. paracetamol. CI, confidence interval.

comparison of paracetamol and placebo showed similarly low rates of pain on infusion, with 2% (3/181) of patients receiving paracetamol and 1% (1/85) of patients receiving placebo reporting pain. In direct comparisons of propacetamol and paracetamol, more patients reported pain on infusion when receiving propacetamol (39%, 71/182) than those receiving paracetamol (4%, 8/180) (Fig. 3).

Propacetamol or i.v. paracetamol compared with active comparators

Three studies provided data comparing propacetamol with NSAIDs[57 62 75] and one propacetamol with opioids[72] for patients reporting any AE. Neither the meta-analysis of the NSAID studies, nor the single-opioid study demonstrated a statistically significant difference between propacetamol and active comparator. We were able to include data for 14 different individual AEs when comparing propacetamol or paracetamol with an NSAID. Of these, only the incidence of hypotension demonstrated a statistically significant difference. One per cent (1/101) of patients receiving propacetamol or paracetamol suffered an incidence of hypotension compared with 10% (10/103) of those receiving an NSAID (P=0.02). There were data reporting incidences of six different AEs when comparing propacetamol with opioids. Of these comparisons, only the incidence of gastrointestinal

Table 2 Risk of bias: adequacy of sequence generation, allocation concealment, and blinding in each included study. +, methods adequate; ?, methods unclear; X, methods inadequate

Adequate?	Sequence generation	Allocation concealment	Blinding
Arici and colleagues[43]	?	?	?
Atef and Fawaz[44]	+	?	+
Aubrun and colleagues[42]	?	?	+
Beaussier and colleagues[55]	+	+	+
Cakan and colleagues[45]	+	+	+
Dejonckheere and colleagues[46]	?	?	?
Delbos and Boccard[56]	?	?	?
Eremenko and Kuslieva[47]	+	?	?
Farkas and colleagues[57]	+	?	?
Fletcher and colleagues[58]	+	?	+
Hahn and colleagues[59]	+	+	+
Hans and colleagues[60]	?	?	?
Hiller and colleagues[61]	?	+	+
Hynes and colleagues[62]	+	?	+
Jarde and Boccard[63]	?	?	?
Juhl and colleagues[48]	+	?	+
Kampe and colleagues[64]	+	+	+
Kemppainen and colleagues[49]	+	+	+
Khajavi and colleagues[41]	?	?	?
Lahtinen and colleagues[65]	+	+	+
Landwehr and colleagues[50]	+	+	+
Leykin and colleagues[66]	+	?	+
Ma and colleagues[67]	?	?	+
Marty and colleagues[51]	+	?	+
Mimoz and colleagues[68]	?	X	X
Moller and colleagues[11]	+	?	+
Moller and colleagues[69]	+	?	+
Ohnesorge and colleagues[52]	?	?	+
Peduto and colleagues[70]	+	?	+
Siddik and colleagues[71]	+	?	+
Sinatra and colleagues[53]	?	?	+
Tiippana and colleagues[54]	?	?	?
Van Aken and colleagues[72]	?	?	+
Varrassi and colleagues[73]	+	?	?
Vuilleumier and colleagues[74]	?	?	?
Zhou and colleagues[75]	+	?	+

disorders (constipation,[41] unspecified)[72] demonstrated a statistically significant difference between propacetamol (11%, 5/46) and opioids (42%, 19/45).

Discussion

Our meta-analyses demonstrated that propacetamol and i.v. paracetamol were statistically superior to placebo for each of the measured efficacy outcomes. The primary measure of efficacy was the proportion of patients achieving at least 50% pain relief over 4 or 6 h—estimates of clinically important reductions in acute pain vary between 30% and 50%, with larger absolute reductions required when baseline pain is more severe.[4 76 77] While propacetamol and paracetamol were superior to placebo over both 4 and 6 h, the proportion of patients with at least 50% pain relief appears to decrease at 6 h in both active groups (and in the placebo groups). Direct comparisons of propacetamol and i.v. paracetamol demonstrated similar efficacy at either 4 or 6 h. However, indirect comparisons (Table 1) demonstrated differences in the estimated overall ORs (and derived NNTs) for propacetamol/placebo (OR=4.6 at 4 h and 4.2 at 6 h) and i.v. paracetamol/placebo (OR=17.2 at 4 h and 22.0 at 6 h), suggesting that i.v. paracetamol may be more effective than propacetamol. This may be explained by the different surgery performed. Placebo rates in dental surgery have been shown to be lower than in other types of surgery.[78] Two of the three studies comparing i.v.

paracetamol with placebo were performed in dental surgery patients and indeed, placebo rates were very low in both.[11 48] This may account for the apparently superior efficacy of i.v. paracetamol over propacetamol in the indirect comparisons. As the meta-analysis of i.v. paracetamol studies was based on lower overall number of patients, the best point estimate may be less accurate, as reflected in a wider CI than that seen for the propacetamol meta-analysis. In contrast, the overall OR and derived NNT appear to be robust under the sensitivity analysis of study design. For example, two studies[53 75] enrolled patients on the first postoperative days and allowed them to use PCA. All other studies were started at first report of moderate-to-severe pain and patients had to request rescue analgesia (one study also enrolled patients on the first postoperative day, but patients had to request analgesia).[62] Although not part of our planned sensitivity analysis, *post hoc* analysis with removal of the data from these two studies resulted in minimal changes in the derived NNT at both 4 and 6 h.

Our analysis of risk of bias demonstrated that the majority of studies attempted to minimize the potential for bias by using accepted methods of randomization, allocation concealment, and double-blinding. In only one case, the single non-blinded study included in our review, allocation concealment and blinding was clearly inadequate.[68] However, this study did not provide data for the primary outcome, and sensitivity analysis where data from it were removed made no difference to either the direction or the statistical significance of any other efficacy or safety outcome. All other studies were described as randomized and double-blinded. However, published studies do not routinely adequately describe methods used to reduce risk of bias. All of the studies included in our primary outcome analysis (Table 2) inadequately described at least one aspect, either sequence generation (randomization), allocation concealment, or blinding. While this lack of information is common when performing meta-analysis, we cannot assume that the studies adequately reduced the potential for bias. Therefore, the possibility of over- or underestimation of effect exists.

When assessing the clinical significance of the above findings, it is possible to indirectly compare the NNT for a single dose of propacetamol or i.v. paracetamol with that of a single dose of other analgesics.[79] The NNTs for combined propacetamol and paracetamol data are similar to those seen with various doses of oral paracetamol,[4] but inferior to most orally or parenterally administered opioids. Although these indirect comparisons are not surprising, the data should be interpreted with caution. The efficacy of the other analgesics in this 'league table' is measured over 4–6 h, rather than discretely at 4 and 6 h as in our analyses. As demonstrated above, NNTs may increase if measured over 6 h. Although NNTs for i.v. and oral paracetamol are similar, the studies would almost certainly have enrolled different populations. First, patients in the oral studies would have to be capable of taking oral medication immediately after operation. Oral administration after operation is problematic, in that patients may have nausea or vomiting or may have delayed absorption, such as postoperative ileus. Secondly, patients in the oral studies may have had lower baseline pain. When baseline pain is low, a smaller absolute reduction in intensity is required to effect a clinically important change.[77]

Among secondary outcomes, data related to rescue medication demonstrated that fewer patients receiving propacetamol or paracetamol required rescue analgesia in the 4–6 h time period than those receiving placebo, and those that did require rescue analgesia waited longer before requesting it than those receiving placebo. In the majority of studies comparing opioid consumption, a PCA was used. A meta-analysis[14] of PCA opioid consumption in patients receiving multiple doses of i.v. or oral paracetamol over 24 h found an overall reduction in morphine consumption of 20%, but this made no significant difference to the incidence of opioid-related side-effects. In our larger analysis, we compared the incidence of AEs that could be considered to be opioid-induced and found no difference in side-effects, despite the reported reduction in opioid requirements. In contrast, meta-analyses of NSAIDs used in combination with PCA demonstrate a relative reduction in postoperative nausea and vomiting by 30%, nausea alone by 12%, vomiting alone by 32%, and sedation by 29%.[80 81] Finally, the modest superiority in patients' global evaluation in our analysis may in part be due to the high proportion of patients receiving placebo who expressed satisfaction with their intervention (54%), which in turn could be due to the placebo group having access to rescue medication, or simply that inclusion in a trial may lead to patients being more closely monitored.

Meta-analyses did not demonstrate a difference between either test drug and NSAIDs or opioids for any pain outcome, with the exception of a clinically insignificant reduction in opioid consumption. There were fewer subjects in each comparison than in the placebo-controlled studies, which suggests that rather than demonstrating lack of difference there may be insufficient data to demonstrate a difference. Also, the nature of comparators, even within the same class of drugs, may vary considerably. For example, in one comparison, three different NSAIDs were used as comparators at doses that may not be equivalent.

Reported AEs in a postoperative pain study may reflect a number of factors. The AEs may be residual effects of anaesthesia and surgery. They may be due to side-effects of postoperative opioids, in which case you may expect to see a reduction in their incidence when an effective analgesic that lowers opioid consumption is administered. As discussed above, despite demonstrating a reduction in morphine consumption at 4 and 6 h, paracetamol did not reduce opioid-induced AEs. Reported AEs could be an indication of an intervention's safety profile, and propacetamol and i.v. paracetamol appear to be as well tolerated as placebo. The only difference between propacetamol or i.v. paracetamol and placebo in our analyses was a reduced incidence of fever, which is to be expected. For the incidence of individual events, both the total number of patients in each comparison

and those reporting an AE tended to be lower than the overall numbers included in our efficacy analyses, reflecting the relative rarity of AEs compared with efficacy events and the under-reporting of AEs in general. Therefore, our findings should be interpreted with caution.

The direct comparison studies[11 51 53] demonstrate that propacetamol and i.v. paracetamol have similar efficacy and safety, with the exception of the incidence of pain with propacetamol infusion. Although most studies do not report the intensity of pain on infusion, it appears to be in the moderate-to-severe range[63] and may lead to interruption of the infusion.[11] As propacetamol requires reconstitution (and has potential issues of contact dermatitis), i.v. paracetamol would appear preferable, assuming cost is not an issue.

There were few differences in the proportion of patients with individual AEs when propacetamol or paracetamol were compared with active comparators. While our analyses showed little difference between i.v. formulations of paracetamol and NSAIDs or opioids, it is generally acknowledged that paracetamol has a superior safety profile.[82] Other than in situations of accidental overdose where hepatotoxicity may occur, AEs with oral paracetamol are rare ($>$1/10 000 to $<$1/1000 for malaise, hypotension, and increased hepatic transaminases) or very rare ($<$1/10 000 for hypersensitivity, thrombocytopenia, leucopoenia, and neutropenia).[83] This illustrates that AE data from RCTs should be interpreted with caution. Studies are routinely underpowered to detect differences in AEs, and do not capture rare, but potentially catastrophic events. One of the included studies tested a dose of 2 g of i.v. paracetamol and demonstrated superior analgesic efficacy to 1 g.[48] Further studies at this higher dose may provide evidence that i.v. paracetamol reduces opioid consumption to an extent that opioid-induced AEs are reduced. Equally, they may show an increase in paracetamol-induced AEs.

The efficacy data were analysed over 4 or 6 h, but most safety analyses used data for $\geq$24 h. As with all quantitative systematic reviews, meta-analyses are only as good as the data that are reported and the description of methods in each study. As previously mentioned, studies fell broadly into two designs: those in which the intervention was administered shortly before or after the end of surgery (prevention of pain) and the primary outcome was opioid consumption; or those in which the intervention was administered only if the patient reported moderate-to-severe pain after operation (treatment of pain), and the primary outcome was pain relief/pain intensity difference. The former may not accurately reflect a drug's efficacy, in that some patients may never have developed moderate-to-severe pain. The latter studies offer proof of concept and allow us to make direct or indirect comparisons with other analgesics. However, they do not necessarily reflect practice, as it is unlikely that paracetamol alone would provide sufficient analgesia in moderate-to-severe pain for the majority of patients.

In conclusion, our analyses suggest that propacetamol or i.v. paracetamol are effective analgesics with a safety profile similar to placebo. Given alone, they are unlikely to provide sufficient analgesia in surgery which produces moderate-to-severe pain. If used in combination with opioids, they reduce opioid consumption, but this reduction does not appear sufficient to reduce opioid-induced AEs. Larger trials are required. I.V. paracetamol may be a better option than propacetamol, in that reconstitution is not required and the incidence of pain on infusion is reduced. Finally, studies that assess patient-reported pain in paediatric patients are required.

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Conflict of interest

E.D.M. has consulted for Javelin Pharmaceuticals, Wyeth, and Ortho-McNeil-Janssen Pharmaceuticals. M.S.C. is an employee of Johnson & Johnson Pharmaceutical Research & Development. Johnson & Johnson Pharmaceutical Research & Development is an affiliate of Ortho-McNeil-Janssen Pharmaceuticals, Inc., which markets several analgesic drug products including opioids and over-the-counter analgesics such as acetaminophen. She participated in the design of the study, before she joined Johnson & Johnson Pharmaceutical Research & Development.

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References

1 Sachs CJ. Oral analgesics for acute nonspecific pain. *Am Fam Phys* 2005; **71**: 913–8

2 Hyllested M, Jones S, Pedersen JL, Kehlet H. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. *Br J Anaesth* 2002; **88**: 199–214

3 Perrott DA, Piira T, Goodenough B, Champion GD. Efficacy and safety of acetaminophen versus ibuprofen for treating children's pain or fever: a meta-analysis. *Arch Pediatr Adolesc Med* 2004; **158**: 521–6

4 Toms L, McQuay HJ, Derry S, Moore RA. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. *Cochrane Database Syst Rev* 2008

5 Anderson BJ, Pons G, Autret-Leca E, Allegaert K, Boccard E. Pediatric intravenous paracetamol (propacetamol) pharmacokinetics: a population analysis. *Paediatr Anaesth* 2005; **15**: 282–92

6 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. *Int J Clin Pharmacol Ther* 2004; **42**: 50–7

7 Barbaud A, Trechot P, Bertrand O, Schmutz JL. Occupational allergy to propacetamol. *Lancet* 1995; **346**: 902

8 Gielen K, Goossens A. Occupational allergic contact dermatitis from drugs in healthcare workers. *Cont Derm* 2001; **45**: 273–9

9 Depre M, van Hecken A, Verbesselt R, Tjandra-Maga TB, Gerin M, de Schepper PJ. Tolerance and pharmacokinetics of propacetamol, a paracetamol formulation for intravenous use. *Fund Clin Pharmacol* 1992; **6**: 259–62

10 Berl V, Barbaud A, Lepoittevin JP. Mechanism of allergic contact dermatitis from propacetamol: sensitization to activated N,N-diethylglycine. *Contact Dermatitis* 1998; **38**: 185–8

11 Moller PL, Juhl GI, Payen-Champenois C, Skoglund LA. Intravenous acetaminophen (paracetamol): comparable analgesic efficacy, but better local safety than its prodrug, propacetamol, for postoperative pain after third molar surgery. *Anesth Analg* 2005; **101**: 90–6

12 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. *Paediatr Anaesth* 2005; **15**: 663–70

13 Romsing J, Moiniche S, Dahl JB. Rectal and parenteral paracetamol, and paracetamol in combination with NSAIDs, for postoperative analgesia. *Br J Anaesth* 2002; **88**: 215–26

14 Remy C, Marret E, Bonnet F. Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. *Br J Anaesth* 2005; **94**: 505–13

15 Higgins JPT, Altman DG. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.0.0. The Cochrane Collaboration, *2008*. Available from www.cochrane-handbook.org (updated February 2008)

16 Cooper SA. Single dose analgesic studies: the upside and downside of assay sensitivity. In: Max MB, Portenoy RK, Laska EM, eds. *The Design of Analgesic Clinical Trials. Advances in Pain Research and Therapy*, Vol. 18. New York: Raven Press, 1991; 117–24

17 Moore A, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: verification from independent data. *Pain* 1997; **69**: 127–30

18 Moore A, Moore O, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: use of pain intensity and visual analogue scales. *Pain* 1997; **69**: 311–5

19 Jacox AK, Carr DB, Payne R, Berde CB. *Management of Cancer Pain. Clinical Practice Guidelines*. Rockville: Agency for Health Care Policy and Research, 1994 [AHCPR publication No 94-0595]

20 *Review Manager (RevMan) [Computer program]*. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008

21 Deeks JJ, Higgins JPT, Altman DG. Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, Deeks JJ, Higgins JPT, Altman DG, eds. *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.0.0. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org (updated February 2008)

22 Alhashemi JA, Daghistani MF. Effect of intraoperative intravenous acetaminophen vs. intramuscular meperidine on pain and discharge time after paediatric dental restoration. *Eur J Anaesthesiol* 2007; **24**: 128–33

23 Alhashemi JA, Daghistani MF. Effects of intraoperative i.v. acetaminophen *vs* i.m. meperidine on post-tonsillectomy pain in children. *Br J Anaesth* 2006; **96**: 790–5

24 Ang ET, Goldfarb G, Boccard E. Analgesic efficacy of propacetamol hydrochlorate 2 g versus pentazocine 30 mg after orthopedic surgery. *Eur J Pain* 1990; **11**: 137–42

25 Aydogan H, Dogru K, Erdem S, Bicer C, Aksu R, Boyaci A. The effect of IV paracetamol on the hemodynamic indices, liver functions and the postoperative analgesia in the patients underwent major orthopaedic surgery. *Erciyes Tip Dergisi [Erciyes Medical J]* 2008; **30**: 71–7

26 Fijalkowska A, Trela-Stachurska K, Rechberger T. Efficacy of intravenous paracetamol for early postoperative analgesia after gynaecological surgery. *Anaesth Int Ther* 2006; **38**: 66–8

27 Fourcade O, Sanchez P, Kern D, Mazoit JX, Minville V, Samii K. Propacetamol and ketoprofen after thyroidectomy. *Eur J Anaesthesiol* 2005; **22**: 373–7

28 Garcia F, Rodriguez-Huertas F, Gutierrez M, Bustos A, Sariego M, Garcia-Baquero A. Preoperative propacetamol and postoperative pain after laparoscopic surgery for tubal blockage. *Revis Soc Espana Dolor* 1999; **6**: 83–7

29 Granry JC, Rod B, Monrigal JP, *et al.* The analgesic efficacy of an injectable prodrug of acetaminophen in children after orthopaedic surgery. *Paediatr Anaesth* 1997; **7**: 445–9

30 Grundmann U, Wornle C, Biedler A, Kreuer S, Wrobel M, Wilhelm W. The efficacy of the non-opioid analgesics parecoxib, paracetamol and metamizol for postoperative pain relief after lumbar microdiscectomy. *Anesth Analg* 2006; **103**: 217–22

31 Hernandez-Palazon J, Tortosa JA, Martinez-Lage JF, Perez-Flores D. Intravenous administration of propacetamol reduces morphine consumption after spinal fusion surgery. *Anesth Analg* 2001; **92**: 1473–6

32 Nikoda VV, Makarova VV, Maiachkin RB, Bondarenko AV. Clinical aspects of analgesia with intravenous paracetamol in the early postoperative period. *Anestez Reanimatol* 2006; **6**: 54–8

33 Pernia A, Torres LM, Calderon E. Management of postoperative pain through intravenous patient controlled analgesia (iv PCA) versus propacetamol and metamizol. *Revis Soc Espanola Dolor* 2000; **7**: 354–60

34 Salonen A, Silvola J, Kokki H. Does 1 or 2 g paracetamol added to ketoprofen enhance analgesia in adult tonsillectomy patients? *Acta Anaesthesiol Scand* 2009; **53**: 1200–6

35 Silvanto M, Munsterhjelm E, Savolainen S, *et al.* Effect of 3 g of intravenous paracetamol on post-operative analgesia, platelet function and liver enzymes in patients undergoing tonsillectomy under local anaesthesia. *Acta Anaesthesiol Scand* 2007; **51**: 1147–54

36 Topal A, Erol A, Tuncer S, Tavlan A, Kilicaslan A, Otelcioglu S. The effect of intravenous paracetamol on postoperative analgesia and morphine consumption. *Anestezi Dergisi* 2009; **17**: 29–32

37 Uvarov DN, Orlov MM, Levin AV, Sokolov AV, Nedashkovskii EV. Role of paracetamol in a balanced postoperative analgesia scheme after thoracotomy. *Anesteziol Reanimatol* 2008; **4**: 46–9

38 Verchere E, Grenier B, Mesli A, Siao D, Sesay M, Maurette P. Postoperative pain management after supratentorial craniotomy. *J Neurosurg Anesth* 2002; **14**: 96–101

39 Ziolkowski R, Srebrzynski A, Kaczka K, Butwicka A, Kuzdak K, Pomorski L. Assessment of postoperative analgesia using intravenous paracetamol during first day following thyroid surgery for goiter. *Clin Exper Med Lett* 2008; **49**: 41–6

40 Rasheed A, Aqil M, Haq A, Usman SK. Comparative study of tramadol and propacetamol for postoperative pain management in patients undergoing nasal surgeries. *Med For Monthly* 2007; **18**: 21–5

41 Khajavi MR, Najafi A, PanahKhahi M, Moharari RS. Propacetamol and morphine in postoperative pain therapy after renal transplantation. *Int J Pharmacol* 2007; **3**: 183–6

42 Aubrun F, Kalfon F, Mottet P, *et al.* Adjunctive analgesia with intravenous propacetamol does not reduce morphine-related adverse effects. *Br J Anaesth* 2003; **90**: 314–9

43 Arici S, Gurbet A, Turker G, Yavascaoglu B, Sahin S. Preemptive analgesic effects of intravenous paracetamol in total abdominal hysterectomy. *Agri Dergisi* 2009; **21**: 54–61

44 Atef A, Fawaz AA. Intravenous paracetamol is highly effective in pain treatment after tonsillectomy in adults. *Eur Arch Oto-Rhino-Laryng* 2008; **265**: 351–5

45 Cakan T, Inan N, Culhaoglu S, Bakkal K, Basar H. Intravenous paracetamol improves the quality of postoperative analgesia but does not decrease narcotic requirements. *J Neurosurg Anesth* 2008; **20**: 169–73

46 Dejonckheere M, Desjeux L, Deneu S, Ewalenko P. Intravenous tramadol compared to propacetamol for postoperative analgesia following thyroidectomy. *Acta Anesthesiol Belg* 2001; **52**: 29–33

47 Eremenko AA, Kuslieva EV. Analgesic and opioid-sparing effects of intravenous paracetamol in the early period after aortocoronary bypass surgery. *Anesteziol Reanimatol* 2008; **5**: 11–4

48 Juhl GI, Norholt SE, Tonnesen E, Hiesse-Provost O, Jensen TS. Analgesic efficacy and safety of intravenous paracetamol (acetaminophen) administered as a 2 g starting dose following third molar surgery. *Eur J Pain* 2006; **10**: 371–7

49 Kemppainen T, Kokki H, Tuomilehto H, Seppä J, Nuutinen JL. Acetaminophen is highly effective in pain treatment after endoscopic sinus surgery. *Laryngoscope* 2006; **116**: 2125–8

50 Landwehr S, Kiencke P, Giesecke T, Eggert D, Thumann G, Kampe S. A comparison between IV paracetamol and IV metamizol for postoperative analgesia after retinal surgery. *Curr Med Res Opin* 2005; **21**: 1569–75

51 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. *Curr Ther Res* 2005; **66**: 294–306

52 Ohnesorge H, Bein B, Hanss R, *et al.* Paracetamol versus metamizol in the treatment of postoperative pain after breast surgery: a randomized, controlled trial. *Eur J Anaesthesiol* 2009; **26**: 648–53

53 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

54 Tiippana E, Bachmann M, Kalso E, Pere P. Effect of paracetamol and coxib with or without dexamethasone after laparoscopic cholecystectomy. *Acta Anaesthesiol Scand* 2008; **52**: 673–80

55 Beaussier M, Weickmans H, Paugam C, *et al.* A randomized, double-blind comparison between parecoxib sodium and propacetamol for parenteral postoperative analgesia after inguinal hernia repair in adult patients. *Anesth Analg* 2005; **100**: 1309–15

56 Delbos A, Boccard E. The morphine-sparing effect of propacetamol in orthopedic postoperative pain. *J Pain Symptom Manage* 1995; **10**: 279–86

57 Farkas JC, Larroututou P, Morin JP, *et al.* Analgesic efficacy of an injectable acetaminophen versus a dipyrone plus pitofenone plus fenpiverinium association after abdominal aortic repair. *Curr Ther Res* 1992; **51**: 19–27

58 Fletcher D, Negre I, Barbin C, *et al.* Postoperative analgesia with I.V. propacetamol and ketoprofen combination after disc surgery. *Can J Anaesth* 1997; **44**: 479–85

59 Hahn TW, Mogensen T, Lund C, *et al.* Analgesic effect of I.V paracetamol: possible ceiling effect of paracetamol in postoperative pain. *Acta Anaesthesiol Scand* 2003; **47**: 138–45

60 Hans P, Brichant JF, Bonhomme V, Triffaux M. Analgesic efficiency of propacetamol hydrochloride after lumbar disc surgery. *Acta Anesthesiol Belg* 1993; **44**: 129–33

61 Hiller A, Silvanto M, Savolainen S, Tarkkila P. Propacetamol and diclofenac alone and in combination for analgesia after elective tonsillectomy. *Acta Anaesthesiol Scand* 2004; **48**: 1185–9

62 Hynes D, McCarroll M, Hiesse-Provost O. Analgesic efficacy of parenteral paracetamol (propacetamol) and diclofenac in post-operative orthopaedic pain. *Acta Anaesthesiol Scand* 2006; **50**: 374–81

63 Jarde O, Boccard E. Parenteral versus oral route increases paracetamol efficacy. *Clin Drug Invest* 1997; **14**: 474–81

64 Kampe S, Warm M, Landwehr S, *et al.* Clinical equivalence of IV paracetamol compared to IV dipyrone for postoperative analgesia after surgery for breast cancer. *Curr Med Res Opin* 2006; **22**: 1949–54

65 Lahtinen P, Kokki H, Hendolin H, Hakala T, Hynynen M. Propacetamol as adjunctive treatment for postoperative pain after cardiac surgery. *Anesth Analg* 2002; **95**: 813–9

66 Leykin Y, Casati A, Rapotec A, *et al.* Comparison of parecoxib and proparacetamol in endoscopic nasal surgery patients. *Yonsei Med J* 2008; **49**: 383–8

67 Ma EL, Wang XR, Jiang ZM, Cui Y, Wang R, Liu J. A randomized, double blind, and controlled clinical trial of the non-addictive propacetamol in postoperative analgesia. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao [Acta Acad Med Sin]* 2003; **25**: 329–32

68 Mimoz O, Incagnoli P, Gillon MC, *et al.* Analgesic efficacy and safety of nefopam vs. propacetamol following hepatic resection. *Anaesthesia* 2001; **51**: 520–5

69 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. *Br J Anaesth* 2005; **94**: 642–8

70 Peduto VA, Ballabio M, Stefanini S. Efficacy of propacetamol in the treatment of postoperative pain. Morphine-sparing effect in orthopedic surgery. Italian Collaborative Group on Propacetamol. *Acta Anaesthesiol Scand* 1998; **42**: 293–8

71 Siddik SM, Aouad MT, Jalbout MI, Rizk LB, Kamar GH, Baraka AS. Diclofenac and/or propacetamol for postoperative pain management after cesarean delivery in patients receiving patient controlled analgesia morphine. *Reg Anesth Pain Med* 2001; **26**: 310–5

72 Van Aken H, Thys L, Veekman L, Buerkle H. Assessing analgesia in single and repeated administrations of propacetamol for postoperative pain: comparison with morphine after dental surgery. *Anesth Analg* 2004; **98**: 159–65

73 Varrassi G, Marinangeli F, Agro F, *et al.* A double-blinded evaluation of propacetamol versus ketorolac in combination with patient-controlled analgesia morphine: analgesic efficacy and tolerability after gynecologic surgery. *Anesth Analg* 1999; **88**: 611–6

74 Vuilleumier PA, Buclin T, Biollaz J. Comparison of propacetamol and morphine in postoperative analgesia. *Schweiz Med Wochen* 1998; **14**: 259–63

75 Zhou TJ, Tang J, White PF. Propacetamol versus ketorolac for treatment of acute postoperative pain after total hip or knee replacement. *Anesth Analg* 2001; **92**: 1569–75

76 Campbell WI, Patterson CC. Quantifying meaningful changes in pain. *Anaesthesia* 1998; **53**: 121–5

77 Cepeda MS, Africanoa JM, Poloa R, Alcalaa R, Carr DB. What decline in pain intensity is meaningful to patients with acute pain? *Pain* 2003; **105**: 151–7

78 Gray A, Kehlet H, Bonnet F, Rawal N. Predicting postoperative analgesia outcomes: NNT league tables or procedure-specific evidence? *Br J Anaesth* 2005; **94**: 710–4

79 Bandolier. Oxford league table of analgesics in acute pain. Available from http://www.medicine.ox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesics/lftab.html (accessed June 7, 2010)

80 Elia N, Lysakowski C, Tramer MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. *Anesthesiology* 2005; **103**: 1296–1304

81 Marret E, Kurdi O, Zufferey P, Bonnet F. Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials. *Anesthesiology* 2005; **102**: 1249–60

82 Maund E, McDaid C, Rice S, Wright K, Jenkins B, Woolacott N. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review. *Br J Anaesth* 2011; **106**: 292–7

83 The electronic Medicines Compendium (eMC). Perfalgan 10 mg/ml solution for infusion. Available from http://www.medicines.org.uk/EMC/medicine/14288/SPC/Perfalgan+10mg+ml++Solution+for+Infusion/ (accessed June 7, 2010)