

PAIN

Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials<sup>†</sup>

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**Background.** Acetaminophen is commonly used for the management of perioperative pain. However, there is a marked discrepancy between the extent to which acetaminophen is used and the available evidence for an analgesic effect after major surgery. The aim of this systematic review is to determine the morphine-sparing effect of acetaminophen combined with patient-controlled analgesia (PCA) with morphine and to evaluate its effects on opioid-related adverse effects.

**Methods.** MEDLINE and the Cochrane Library were searched to select randomized controlled trials which compared PCA morphine alone with PCA morphine plus acetaminophen administered orally or intravenously. Studies were evaluated for their quality based on the Oxford Quality Scale. Outcome measures were morphine consumption over the first 24 h after surgery, patient satisfaction and the incidence of morphine side-effects, including nausea and vomiting, sedation, urinary retention, pruritus and/or respiratory depression.

**Results.** Seven prospective randomized controlled trials, including 265 patients in the group with PCA morphine plus acetaminophen and 226 patients in the group with PCA morphine alone, were selected. Acetaminophen administration was not associated with a decrease in the incidence of morphine-related adverse effects or an increase in patient satisfaction. Adding acetaminophen to PCA was associated with a morphine-sparing effect of 20% (mean, –9 mg; CI –15 to –3 mg;  $P=0.003$ ) over the first postoperative 24 h.

**Conclusion.** Acetaminophen combined with PCA morphine induced a significant morphine-sparing effect but did not change the incidence of morphine-related adverse effects in the post-operative period.

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Systemic opioids are regarded as the gold standard in the relief of severe postoperative pain.<sup>1</sup> However, morphine administration after surgery carries a high risk of side-effects such as nausea, vomiting, pruritus, urinary retention and apnoea.<sup>1</sup> Numerous strategies have been proposed to reduce the incidence of side-effects and also to improve postoperative pain management. Kehlet and Dahl<sup>2</sup> have developed a multimodal approach to achieve this goal. This approach suggests that combining analgesics may not only improve postoperative pain control but also lower analgesics doses and consequently reduce the incidence of adverse events.<sup>2</sup> Several studies have demonstrated the opioid-sparing effect of non-opioid

analgesics.<sup>3–6</sup> A recent meta-analysis has documented that co-administration of non-steroidal anti-inflammatory drugs (NSAIDs) and morphine reduces opioid side-effects such as nausea, vomiting and sedation.<sup>7</sup> Nevertheless, NSAIDs have numerous contraindications and consequently cannot be used in >25% of postoperative patients.<sup>8</sup> Moreover, NSAIDs interact with primary haemostasis, thus precluding their use in some surgical procedures.<sup>9</sup>

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In contrast with NSAIDs, acetaminophen has very few contraindications and is relatively free from side-effects at clinical doses.<sup>10</sup> It can also be used in patients irrespective of age.<sup>10</sup> Most studies have demonstrated a significant morphine-sparing effect of acetaminophen.<sup>3–5</sup> However, the benefits of a combination of acetaminophen and morphine, in terms of side-effects, have not been documented. Therefore we performed a meta-analysis to evaluate the effect of adding acetaminophen to i.v. morphine administered by patient-controlled analgesia (PCA) on morphine consumption and the side-effects in patients undergoing major surgery.

## Materials and methods

This work was conducted according to Quality of Reporting of Meta-analyses (QUOROM) recommendations for improving the quality of meta-analysis.<sup>11</sup>

### Identification of the studies

Two electronic databases, PubMed® (MEDLINE/*Index Medicus*) and the Cochrane Controlled Trials Register published by the Cochrane Library, were searched via the Internet for studies published between January 1966 and April 2003. The medical subject heading terms used for the search were 'acetaminophen' or 'paracetamol', 'patient-controlled analgesia' and 'morphine'. Additional articles were retrieved by clicking on hyperlinks and by manually searching reference lists in original published articles, review articles and correspondence. The Bristol-Myers-Squibb company (Rueil-Malmaison, France) was also contacted to obtain complementary data. The authors of published studies were contacted for additional information on the methodology or results of their investigations when required.

### Quality assessment of the studies

Each study was subjected to a quality assessment by two investigators (C.R. and E.M.) who were not blinded to the authors or results. Disagreements were resolved by discussion. In cases of persistent disagreement, a third reviewer (F.B.) could help to reach a consensus after separately reviewing the report. Each article was scored using a five-point scale that evaluates randomization, blinding and completeness of patient follow-up (Oxford validity scale).<sup>12</sup> One point was given if the study was described as randomized. An additional point was given if the randomization method was described and was appropriate (e.g. computer-generated table of random numbers), whereas one point was subtracted if the randomization method was described and was inappropriate (e.g. alternate allocation or allocation by the date of birth). Similarly, one point was assigned to studies described as double-blind, two points were assigned to studies for which the double-blinding method was described and was appropriate

(identical placebo, active placebo, double-dummy), and no points were assigned to studies for which the double-blinding method was described and was inappropriate. One point was given if the article specified the numbers and reasons for withdrawals and dropouts. Thus, the highest possible score was 5. We included studies with scores  $\geq 3$ .

### Selection criteria

Criteria for study selection were as follows: randomized controlled design, quality assessment score  $\geq 3$  (14), adults (age  $>18$  yr) who underwent surgery which required morphine administered by PCA, acetaminophen compared with a placebo, oral or i.v. administration, report of data on morphine side-effects such as nausea, vomiting, sedation, urinary retention, respiratory depression and patient satisfaction.

Criteria for study exclusion were score  $\leq 2$  on the three-item Oxford validity five-point scale (14), children ( $<18$  yr), use of a continuous morphine infusion in addition to PCA, use of continuous regional analgesia in addition to PCA, PCA with an opioid other than morphine, control group with an NSAID, administration of another non-opioid analgesic in both groups or rectal route for administration of acetaminophen.

### Outcome measures

The primary evaluation criterion was the presence of post-operative nausea and/or vomiting (PONV). The regimen of prophylactic anti-emetic were also extracted when available. Other endpoints, such as postoperative urinary retention, sedation defined by the report of sedation or drowsiness, pruritus, apnoea or respiratory depression and patient satisfaction (including patient's pain relief assessment), were analysed. Patient satisfaction was collected as a dichotomous variable (excellent or good vs fair or poor). Morphine requirement at 24 h was recorded.

### Statistics

Unless stated otherwise, an intention-to-treat analysis was performed based on the original data. All analyses were performed with Review Manager software (version 4.2, Cochrane Collaboration, Nordic Cochrane Center, Copenhagen). The odds ratio (OR) and 95% confidence intervals (CI) were calculated for dichotomous data and the results were expressed graphically. All criteria were analysed separately. When the test for heterogeneity was significant ( $P < 0.1$ ), a random effects analysis was carried out. For continuous data (morphine consumption during the first 24 h), we calculated weighted mean differences (WMDs), taking into account study size and standard deviation of morphine consumption as reported in the individual trials. All tests were two-sided, and  $P$ -values  $< 0.05$  were considered statistically significant.

## Results

### Identification of trials

Twenty-one articles were identified by the MEDLINE search. Fifteen of these were excluded for the following reasons. Two were randomized studies without a control group,<sup>13 14</sup> in two studies morphine was not administered by PCA,<sup>15 16</sup> in three studies a drug different from morphine (alfentanil,<sup>17</sup> oxycodone,<sup>18</sup> promedol<sup>19</sup>) was used for PCA, in two studies acetaminophen was given by the rectal route,<sup>5 20</sup> and one study was performed in children.<sup>21</sup> Three articles were letters, editorials or literature reviews<sup>10 22 23</sup>. In one study the duration of the comparison between acetaminophen and placebo was limited to 6 h.<sup>24</sup> In another study, patients received a continuous infusion of morphine in addition to PCA.<sup>3</sup> Finally, six trials from the MEDLINE search met the selection criteria (Fig. 1). A manual search of cross-references identified an additional study, which was excluded because patients did not receive PCA morphine.<sup>25</sup> The Cochrane Controlled Trials Register search retrieved 11 studies. Only four of these reported the use of i.v. or oral acetaminophen after surgery combined

with PCA morphine, and all of them had already been identified by the MEDLINE search. Bristol-Myers-Squibb communicated the results of a non-indexed study published as an abstract and presented at the Annual Meeting of the Société Française d'Anesthésie-Réanimation in 2001.<sup>26</sup> Finally, seven randomized studies evaluating the effects of acetaminophen co-administered with PCA morphine were included in the meta-analysis (Fig. 1 and Table 1).

### Study designs, patients, type of anaesthesia and surgery

All seven randomized studies were published in or after 1997. Most of them reported i.v. acetaminophen administration with a placebo-controlled i.v. saline.<sup>4 26–29</sup> In one study, acetaminophen or placebo was administered orally (identical tablets).<sup>30</sup> In another study, the control group received PCA i.v. morphine without a placebo, excluding double-blinding.<sup>31</sup> In a third trial, i.v. acetaminophen or propacetamol were compared with a placebo on day 1.<sup>26</sup> All the studies used a multiple dose design. Finally, 265 patients received acetaminophen plus morphine and 226 patients received morphine alone.

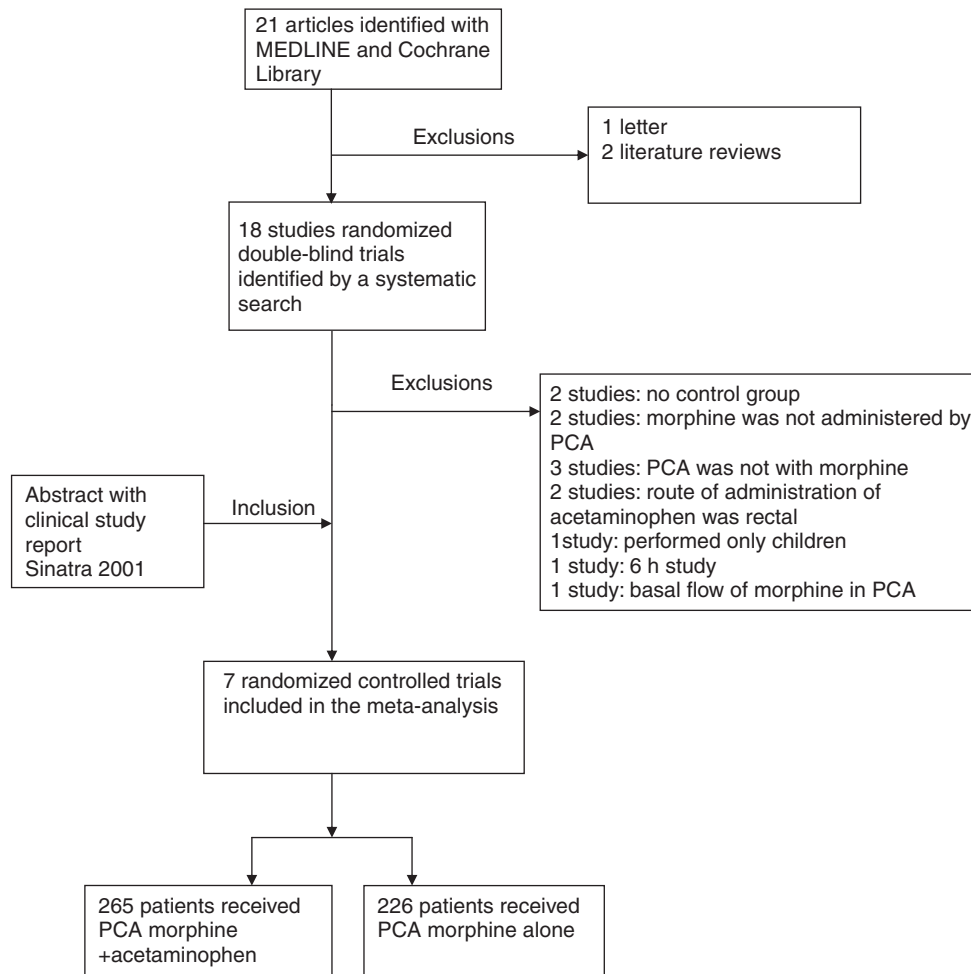


Fig 1 Flowchart of systematic research.

**Table 1** Summary of data from the seven studies included in the meta-analysis. PONV, postoperative nausea and vomiting; UR, urinary retention; †↓ VAS decreased with acetaminophen; → no significant difference for VAS; ‡→ identical; † decreased

Study reference (quality assessment)	No. of patients		Surgery	Treatment	Route of administration	Time of first administration and duration of treatment	Outcome measures	VAS scores 24 h after surgery†	Opioid consumption†
	Acetaminophen group	Control group							
28 (5)	15	15	Surgery of herniated disc	Dextrose 5% 125 ml Placebo Propacetamol 2 g×4/24 h Ketoprofen 50 mg×4/24 h Propacetamol+ketoprofene	IV, two separate injections	Skin closure 48 h	Pain intensity at rest and on movement Morphine consumption Side-effects	→	→
29 (5)	21	21	Spinal stabilization surgery	Saline 100 ml Placebo Propacetamol 2 g×4/24 h	IV, 15 min	30 min before end of surgery 72 h	Morphine consumption Pain scores Side-effects: PONV, UR, pruritus, sedation, respiratory depression	↓	↓ ( $P<0.001$ )
31 (3)	38	38	Elective hepatic resection Alone	Morphine PCA + Nefopam 20 mg×4/24 h + Propacetamol 2 g×4/24 h	IV	When hepatic resection was complete 24 h	Morphine consumption Pain intensity at rest and on coughing Global efficacy Side-effects: PONV, sedation	→	→
4 (5)	46	51	Hip arthroplasty	Dextrose 5% 100 ml Propacetamol 2 g×4/24 h Placebo	IV, 15 min	After extubation 24 h	Morphine consumption Pain scores Global efficacy Side-effects: PONV, UR	→	↓ ( $P<0.001$ )
30 (5)	26	29	Open reduction and internal fixation of acute limb fractures	Acetaminophen (two 500 mg tablets/4 h) Placebo (identical tablets)	Oral	After surgery 72 h	Morphine consumption Pain scores Global efficacy Side-effects: UR	↓ At day 1 ( $P=0.03$ ) → At day 2 ( $P=0.05$ )	→
27 (5)	20	20	Elective Caesarean delivery	Normal saline 100 ml for i.v. solution Placebo rectal and i.v. Diclofenac rectal 100 mg×4/24 h and placebo i.v. Propacetamol 2 g×4/24 h i.v. and placebo rectal Diclofenac rectal and propacetamol i.v.	Rectal and i.v. (all patients: one i.v. injection and one suppository)	At skin closure 24 h	Pain scores at rest and on coughing Morphine consumption Global efficacy Side-effects	→	→
26 (5)	99	52	Hip or knee arthroplasty	IV infusion Acetaminophen 1 g×4/24 h Propacetamol 2 g×4/24 h Placebo	IV, 15 min	After surgery 24 h	Analgesic efficacy Morphine consumption Global efficacy Side-effects	↓ ( $P=0.005$ )	↓

The PCA system was programmed to deliver morphine with a bolus dose of 1 mg in six trials<sup>26–31</sup> and 0.015 mg kg<sup>-1</sup> in one study.<sup>4</sup> In three studies, the maximal dose per 4 h could be increased, additional boluses could be given or lockout time decreased if analgesia was inadequate.<sup>26 27 29</sup> The lockout intervals were fixed at 5 min,<sup>30</sup> 6 min,<sup>26 27</sup> 7 min,<sup>31</sup> 10 min<sup>28 29</sup> and 15 min.<sup>4</sup> Three studies did not restrict the dose of morphine administered, and four studies reported a maximum cumulative dose (20 mg over 4 h,<sup>31</sup> 25 mg over 4 h<sup>26 27</sup> and 0.25 mg kg<sup>-1</sup> over 4 h<sup>29</sup>).

General anaesthesia was maintained with halogenates and nitrous oxide in five trials.<sup>4 28–31</sup> No regional anaesthesia technique or local wound infiltration was used intraoperatively to reduce post-surgical pain.

Most of the surgical procedures were orthopaedic, and were performed under general anaesthesia in five studies<sup>4 26 28–31</sup> and/or spinal or epidural anaesthesia in one study.<sup>26</sup> One trial investigated liver surgery,<sup>31</sup> and another investigated gynaecological surgery (Caesarean delivery) under spinal anaesthesia with bupivacaine 12 mg and fentanyl 12.5 µg.<sup>27</sup>

In most of the studies, patients received i.v. titrated morphine at the end of surgery until pain was relieved, before the PCA i.v. morphine was started.<sup>4 28 29 31</sup> When analgesia was not effective, some authors increased the maximum PCA morphine dose per 4 h from 0.15 to 0.20 mg kg<sup>-1</sup> after 1 h, and up to 0.25 mg kg<sup>-1</sup> per 4 h if analgesia remained inadequate.<sup>29</sup> Others allowed additional

rescue boluses of morphine 2 mg with PCA,<sup>2 6</sup> and others considered additional boluses of PCA solution until the pain VAS score was <3, then decreased lockout time to 5 min and then increased the maximum dose per 4 h.<sup>27</sup>

### Morphine side-effects and acetaminophen

Postoperative nausea and vomiting were the most frequent morphine side-effects and were reported in all seven trials.<sup>4 26–31</sup> The incidence of PONV was 23(range 6–52)% in the control group and 24(7–43)% in the acetaminophen group. Information about the treatment of PONV (ondansetron 4 mg i.v.) was provided in only one study.<sup>27</sup> Acetaminophen administration resulted in a non-significant reduction in PONV (OR=0.99; 95% CI, 0.64–1.55; *P*=0.98) (Fig. 2).

Postoperative sedation was evaluated in six trials,<sup>4 27–31</sup> five of which used a sedation score.<sup>4 27–30</sup> Sedation was measured using a five-point-scale in three trials,<sup>4 27 29</sup> and with a four-point scale in two trials.<sup>28 30</sup> Among the 174 patients who did not receive acetaminophen, 52 (30[5–51]%) experienced sedation. In the acetaminophen group, sedation was reported in 34(0–65)% (OR=1.30; 95% CI 0.79–2.16; *P*=0.30) (Fig. 3).

Urinary retention was reported in five studies.<sup>4 26 28–30</sup> In one study, patients had a systematic bladder catheterization.<sup>31</sup> The incidence was not significantly different between the two groups (4.8[0–27]% for acetaminophen and 5.8[0–24]% for placebo [OR=0.90; 95% CI, 0.36–2.23; *P*=0.82]) (Fig. 4).

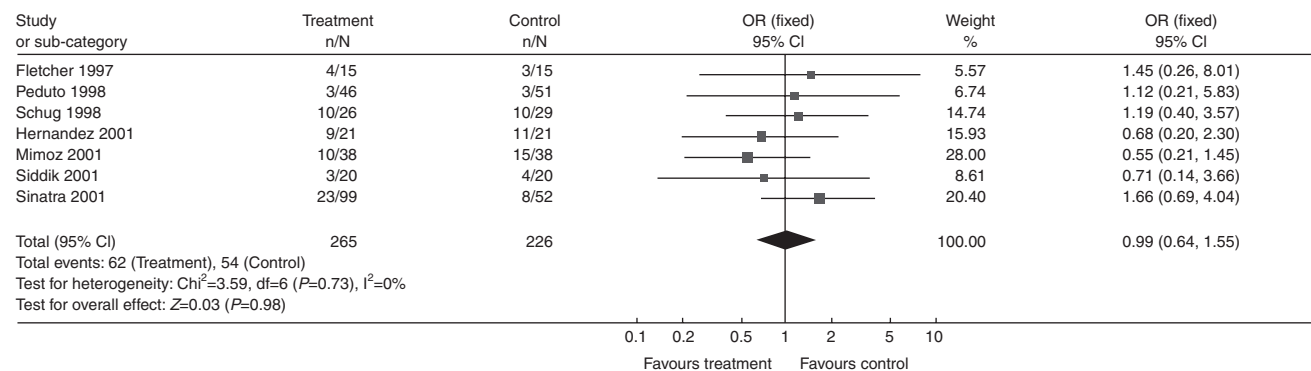


Fig 2 Effect of acetaminophen vs placebo on postoperative nausea and vomiting.<sup>4 26–31</sup>

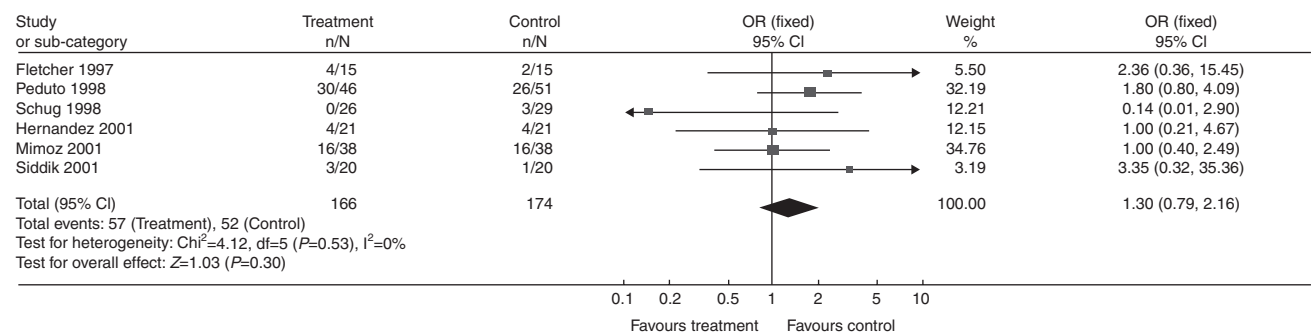
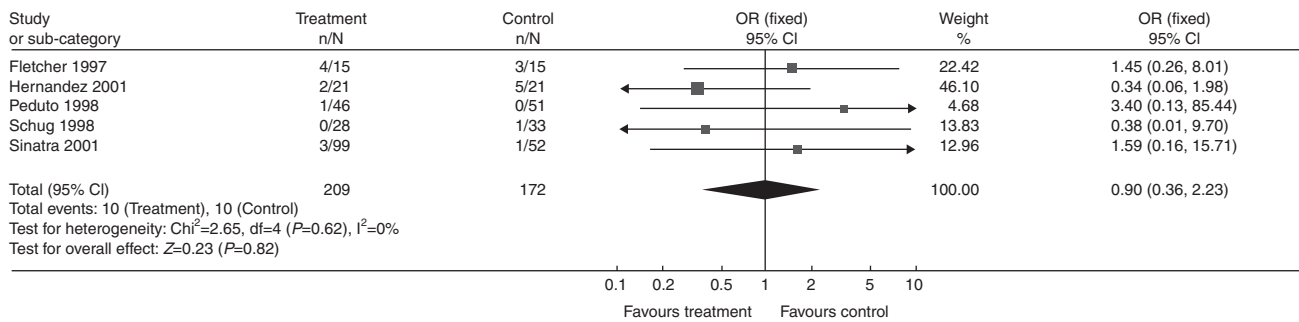
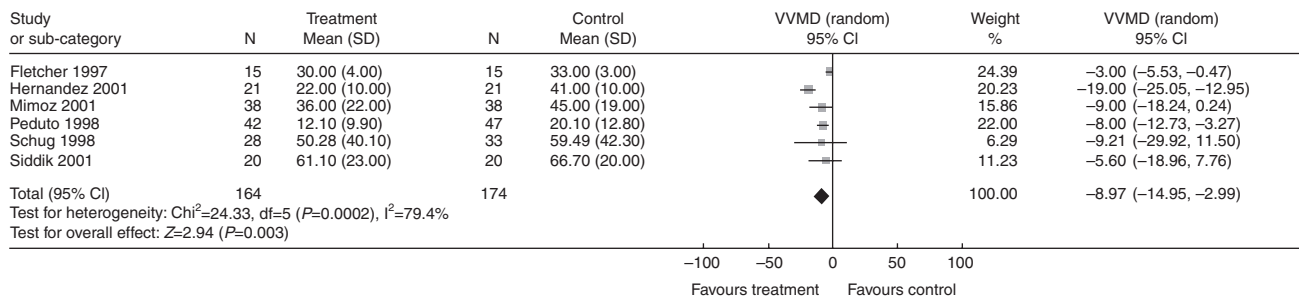


Fig 3 Effect of acetaminophen vs placebo on sedation.<sup>4 27–31</sup>



**Fig 4** Effect of acetaminophen vs placebo on postoperative urinary retention.<sup>4 26 28–30</sup>



**Fig 5** Effect of acetaminophen vs placebo on postoperative morphine consumption during the first 24 h.<sup>4 27–31</sup>

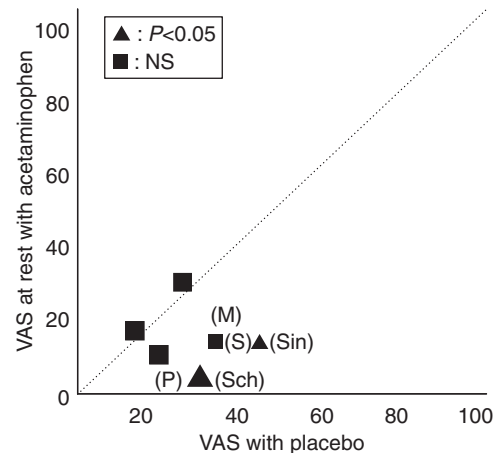
Pruritus was noted in only three studies. It was the second most frequent reported side-effect of PCA i.v. morphine.<sup>26 27 29</sup> One study described an i.v. injection of naloxone 0.2 mg to alleviate pruritus.<sup>27</sup> The overall incidences were 19(10–40)% in the control group and 11(8–20)% in the acetaminophen group. No significant difference was noted between the two groups (OR=0.62; 95% CI, 0.29–1.32;  $P=0.21$ ).

Most of the studies monitored the respiratory rate,<sup>4 26 28 29</sup> but only two studies reported the incidence of respiratory depression<sup>26 28</sup> (defined as  $SpO_2 < 95\%$  and sedation score  $> 3$  or ventilatory frequency  $< 10$ ). In one study, respiratory depression defined by hypopnoea occurred in one patient in the active group, and in one patient in the control group in the recovery room.<sup>28</sup>

### Morphine-sparing effects and acetaminophen

All studies except one reported morphine consumption during the first 24 h after surgery. Morphine consumption was reported the day after surgery in one study and data from this trial were not pooled for morphine consumption.<sup>26</sup> Mean morphine consumption during the first day was 42 (20–67) mg in the control groups. The 24-h morphine consumption was significantly reduced by adding acetaminophen, with a mean reduction of 9 mg (95% CI, -15 to -3 mg;  $P=0.003$ ) (Fig. 5). Thus parecatamol reduced morphine consumption by 20%.

Pain was assessed using different scales (five-point verbal rating scale [VRS]<sup>4 26 29</sup> or 10 cm visual analogue scale [VAS]).<sup>4 26–28 30 31</sup> Postoperative pain was evaluated



**Fig 6** L'Abbé plot of mean VAS scores 24 h after surgery for acetaminophen vs placebo in trials for which data were available: solid triangles, VAS scores were significantly ( $P < 0.05$ ) lower in the acetaminophen group than in the placebo group; solid squares, no significant difference in VAS scores in the acetaminophen group compared with the placebo group. M, Mimoz *et al.*<sup>31</sup>; S, Siddik *et al.*<sup>27</sup>; Sin, Sinatra *et al.*<sup>26</sup>; P, Peduto *et al.*<sup>4</sup>; Sch, Schug *et al.*<sup>30</sup>; F, Fletcher *et al.*<sup>28</sup>

at rest and on movement,<sup>27 28 31</sup> or globally.<sup>4 29 30</sup> In one study, the authors reported that pain scores were comparable in both groups but did not provide data.<sup>29</sup> We constructed a L'Abbé plot of mean VAS scores 24 h after surgery, using global, VAS or VAS at rest scores (Fig. 6). Only two studies showed a significant decrease in VAS scores 24 h after surgery,<sup>26 30</sup> and four studies show no significant differences.

### *Satisfaction and acetaminophen use*

In most of the studies patients were asked to rate their overall satisfaction concerning pain treatment, with different verbal rating scales (0–3,<sup>26,29,31</sup> 0–5<sup>4</sup> or 0–10<sup>30</sup>). We combined the results available and obtained an odds ratio of 1.41 (95% CI, 0.88–2.26;  $P=0.15$ ). Satisfaction scores were comparable in both groups.

## **Discussion**

This systematic review of seven randomized controlled trials documents that postoperative acetaminophen combined with PCA morphine provides a statistically significant morphine-sparing effect but does not decrease the incidence of morphine side-effects.

Analgesic protocols combining PCA i.v. morphine and acetaminophen are often used after surgical procedures prone to inducing moderate to severe postoperative pain. Most of the studies in this meta-analysis included patients scheduled for orthopaedic surgery. In these patients, a modest (although statistically significant) reduction in morphine dose resulted in a non-significant difference in the incidence of opioid side-effects. However, others have suggested that acetaminophen has a limited efficacy to control pain after major surgery.<sup>4,15,29</sup> Aubrun and colleagues<sup>15</sup> noted a significant (7 mg) decrease in morphine consumption over the first postoperative 24 h in a recent large single-blind randomized study. However, patients who used PCA morphine were excluded from this study. Thus morphine was administered subcutaneously. Moreover, subcutaneous doses were fixed and determined by physicians within a range of 5–10 mg. Morphine requirements decreased by 37% in patients with moderate pain, but only by 18% in patients with severe pain. However, >20% of patients had received NSAIDs in addition to acetaminophen; thus NSAIDs might have interfered with the morphine-sparing effect of acetaminophen. The efficacy of non-opioid analgesics is often reported as their morphine-sparing effect. The morphine-sparing effect of acetaminophen seems to be weaker than the one documented with NSAIDs.<sup>28</sup> In a systematic review evaluating the efficacy of acetaminophen, Romsing and colleagues<sup>23</sup> concluded that acetaminophen had a lower efficacy than NSAIDs. Concurrent use of acetaminophen and NSAIDs was superior to acetaminophen alone, but no evidence was found of a superior analgesic effect of the combination compared with NSAIDs alone.<sup>23</sup> In contrast, Hyllested and colleagues<sup>22</sup> found no substantial analgesic difference between NSAIDs and acetaminophen in major surgery. However, the number of studies was limited.<sup>22</sup>

Acetaminophen failed to decrease morphine-related adverse effects. Most of the studies included in the current meta-analysis demonstrated a morphine-sparing effect but not a decrease in morphine side-effects. In the largest trial including 550 patients, morphine side-effects in patients

receiving acetaminophen were similar to those in patients not receiving it, despite a decrease in morphine requirements in the acetaminophen group.<sup>15</sup> However, the subcutaneous morphine doses administered were low. Indeed, the median subcutaneous dose of morphine was 10 mg in the control group. Also, adverse effects such as PONV are only partly attributable to opioids.<sup>32</sup> The analgesic effect of acetaminophen depends on the rate and amount of active drug reaching the central nervous system, and several authors have recently recommended the use of a loading dose and/or a larger dose of acetaminophen to achieve therapeutic concentrations more rapidly and more completely.<sup>30</sup> However, it has recently been demonstrated<sup>17</sup> that acetaminophen could have a ceiling effect at i.v. doses of 5 mg kg<sup>-1</sup>, which is lower than previously suggested. Therefore increasing the oral single dose of acetaminophen for the treatment of acute postoperative pain was not associated with a decrease in the number needed to treat.<sup>33</sup>

This systematic review may have some limitations. Publication bias with underpublication of studies that show no significant difference can limit the validity of meta-analyses.<sup>34</sup> However, consulting the company manufacturing acetaminophen may have reduced this bias. Another potential limitation of this meta-analysis could result from the fact that not all morphine side-effects were reported in every study. In fact, some trials did not study all the morphine side-effects. However, the most commonly reported side-effect (PONV) was reported in all trials. The quality of trials included in a systematic review may alter its results.<sup>35</sup> Therefore, the Jadad scale has been proposed to limit this bias.<sup>12</sup> Meta-analyses of trials with Jadad scores <3 significantly exaggerate the benefits of treatment.<sup>35,36</sup> All seven trials selected in this systematic review had a methodology of high quality.

This meta-analysis may lack power because it included too few patients. Nevertheless, the limited amount of morphine spared over 24 h makes it unlikely that a more extensive inclusion would demonstrate a clinically relevant decrease in the incidence of PONV related to acetaminophen use. However, there is a need for more well-designed large-scale studies to establish whether adding acetaminophen does or does not decrease morphine side-effects.<sup>37</sup> Surprisingly, considering the fact that acetaminophen is so commonly used, very few studies were available and many of these had to be excluded. Studies of acetaminophen administration by the rectal route were excluded because of the unpredictable analgesic effect of this route of administration.<sup>38</sup> Rectal acetaminophen bioavailability is very unpredictable and can be delayed. Therefore insufficient pain control could be explained by low plasma concentrations of acetaminophen. Absorption of acetaminophen is more predictable when the drug is given orally after surgery. The mean oral bioavailability of acetaminophen is 82.2%.<sup>39</sup> Gastric emptying can be delayed by some surgical procedures such as abdominal or gynaecological surgery. Two trials included in the systematic review were performed

in patients undergoing hepatectomy or Caesarean section. However, acetaminophen was administered intravenously in these patients. The only trial included in the current meta-analysis that administered acetaminophen orally was performed in patients scheduled for orthopaedic surgery. Moreover, the dose of acetaminophen was 6 g per day (1 g every 4 h), 25% more than doses used intravenously. For this reason, oral administration of acetaminophen after surgery was not considered to be an exclusion criterion. In addition, we did not consider studies where morphine was administered by continuous infusion associated with PCA because they were not designed to evaluate a reduction in morphine demand and were associated with a higher risk of morphine side-effects.<sup>40</sup>

In conclusion, the current meta-analysis demonstrates that acetaminophen significantly decreases morphine consumption by <10 mg in 24 h and does not decrease the incidence of side-effects after major surgery.

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