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REVIEW ARTICLE

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

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Editor's key points

- Meta-analysis of paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and cyclo-oxygenase 2 inhibitors' morphine-sparing effect.
- All resulted in lower 24 h morphine requirement (6–10 mg).
- No clinically significant advantages shown for one group over the others.
- Paracetamol perhaps is less effective at reducing morphine use but NSAIDs are associated with more bleeding.

Summary. Non-opioid analgesics, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), or cyclo-oxygenase 2 (COX-2) inhibitors are often given along with morphine as part of multimodal analgesia after major surgery. We have undertaken a systematic review and a mixed treatment comparison (MTC) analysis in order to determine explicitly which class of non-opioid analgesic, paracetamol, NSAIDs, or COX-2 inhibitors is the most effective in reducing morphine consumption and morphine-related adverse effects. Sixty relevant studies were identified. The MTC found that when paracetamol, NSAIDs, or COX-2 inhibitors were added to patient-controlled analgesia (PCA) morphine, there was a statistically significant reduction in morphine consumption: paracetamol [mean difference (MD) −6.34 mg; 95% credibility interval (CrI) −9.02, −3.65], NSAIDs (MD −10.18; 95% CrI −11.65, −8.72), and COX-2 inhibitors (MD −10.92; 95% CrI −12.77, −9.08). There was a significant reduction in nausea and postoperative nausea and vomiting with NSAIDs compared with placebo (odds ratio 0.70; 95% CrI 0.53, 0.88) but not for paracetamol or COX-2 inhibitors, nor for NSAIDs compared with paracetamol or COX-2 inhibitors. There was no statistically significant difference in sedation between any intervention and comparator. On the basis of six trials (n=695), 2.4% of participants receiving an NSAID experienced surgical-related bleeding compared with 0.4% with placebo. The MTC found that there is a decrease in 24 h morphine consumption when paracetamol, NSAID, or COX-2 inhibitors are given in addition to PCA morphine after surgery, with no clear difference between them. Similarly, the benefits in terms of reduction in morphine-related adverse effects do not strongly favour one of the three non-opioid analgesics.

Keywords: adverse effects; analgesia; analgesia, patient-controlled; analgesics, non-narcotic; morphine

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Multimodal analgesia, where morphine is given with a non-opioid such as paracetamol, is often used to reduce morphine-related adverse effects.[1–3] The underlying principle is that the different modes of action of morphine and the non-opioid drug allow optimum analgesia to be maintained with a lower dose of morphine and consequently a lower incidence of morphine-related adverse effects.

We were asked to undertake a systematic review comparing the relative effectiveness of paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and cyclo-oxygenase 2 (COX-2) inhibitors in reducing morphine consumption after major surgery.[4] The ideal evidence would be a systematic review of randomized controlled trials (RCTs) directly comparing the three drugs, preferably with a fourth arm for placebo. Importantly, thus far, there has been no explicit, statistically robust, comparison of the three non-opioids with one another, reflecting the paucity of direct head-to-head comparisons of the treatments. Previous systematic reviews using a standard meta-analysis compared each non-opioid with placebo. These concluded that all three reduced morphine consumption in the first 24 h after surgery, but only NSAIDs appear to reduce morphine-related adverse effects.[5–7]

There is an increasing interest in the development of statistical methods to address situations where there is a lack of head-to-head comparisons between treatments, specifically mixed treatment comparison (MTC), also called network meta-analysis.[8–10] MTC is an extension of traditional meta-analysis that uses indirect evidence (e.g. treatment

effect of drug A *vs* drug B calculated from the treatment effect of drug A *vs* drug C and drug B *vs* drug C), and direct evidence, if available, and uses a network of all available comparisons from all the available trials. It simultaneously compares all treatments and ranks them according to their effectiveness for a given outcome.[11] A key feature of MTC is that the randomized treatment comparison from each trial is used thereby maintaining randomization. This approach has been applied to a range of interventions including new generation antidepressants,[12] drug-eluting and bare-metal stents,[13] and stroke prevention treatments.[14]

The aim of our study was to apply the technique of MTC analysis to determine explicitly which class, if any, of non-opioid analgesic (paracetamol, NSAIDs, or COX-2 inhibitor) is most effective at reducing morphine consumption and morphine-related adverse effects when used as part of multimodal analgesia after major surgery. In addition, our review provides a substantial update of the recent work on this topic,[5] with the inclusion of 20 new trials, while excluding drugs that are no longer licensed (valdecoxib and rofecoxib) and the studies published by S.S. Reuben which have been retracted due to data falsification.[15]

Methods

MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched for the period January 2003 to February 2009 without language restrictions. Trials before 2003 were identified from the references of a previous good-quality systematic review (search end date July 2004),[5] selected because it had used explicit inclusion criteria, searched several relevant databases without language restrictions, and used appropriate search terms, reducing the likelihood of missing relevant studies. The reference lists of other relevant systematic reviews were checked. A detailed account of the study methods and results are available in our HTA report.[4]

We included RCTs, with at least 10 participants per trial arm, of adult patients requiring pain relief immediately after major surgery, which compared patient-controlled analgesia (PCA) morphine plus paracetamol (including propacetamol), NSAIDs, or COX-2 inhibitors (licensed for use in the UK) with PCA morphine plus placebo or PCA morphine plus a different non-opioid class.

The primary morphine-related outcomes of interest were cumulative morphine consumption in the first 24 h post-surgery, nausea and vomiting, and sedation. Secondary morphine-related outcomes included respiratory depression, urinary retention, pruritus, bowel dysfunction, and dizziness. Non-opioid-related adverse effects were also assessed.

Studies of PCA morphine with a background infusion, PCA opioids other than morphine, intrathecal opioids, peripheral nerve blocks, and studies with a 'no treatment' comparison group were excluded. Studies of rofecoxib and valdecoxib and those conducted by Reuben were also excluded from the current review.

We extracted data into a standardized data extraction form in Excel. A modified Jadad scale was used to assess study quality.[16] Two reviewers independently assessed whether studies met the inclusion criteria. One reviewer extracted data and assessed the quality, which was checked by a second reviewer. Any disagreements were resolved by discussion.

Statistical analysis

Where trials investigated variations of dose or mode of delivery of the same drug, the different regimens of the intervention were combined into one group. To maximize data available for analysis, we pooled trials reporting nausea alone with trials reporting postoperative nausea and vomiting (PONV).

For those outcomes with a complete network, that is, a direct or indirect comparison between every intervention, we performed a random-effects MTC using a Bayesian Markov chain Monte Carlo simulation and WinBUGS software to obtain relative effects, and probabilities of which of the four treatment classes paracetamol, NSAIDs, COX-2 inhibitors, and placebo were the most effective. Treatment effects were associated with 95% credibility intervals (CrIs), which mean that there is a 95% probability that the true treatment effect lies in that interval. Probabilities $<$95% indicated that the treatment is not statistically significantly better at a 5% level of significance compared with the other treatments.

In the analysis, we used non-informative priors. We used residual deviance to determine goodness of fit, with a residual deviance close to the total number of arms included in the analysis considered to be a good fit.[17] The robustness of the MTC was explored by performing the standard random-effects meta-analyses of trials making head-to-head comparisons between paracetamol, NSAIDs, or COX–2 inhibitors.

For the outcome of 24 h morphine consumption, we performed sensitivity analyses based on trial quality (in terms of whether or not there was adequate blinding), an individual drug rather than class of drug, and a *post hoc* sensitivity analysis to explore the effects of baseline morphine consumption.

Codes and further details of the analyses are available in the HTA report.[4]

Results

Retrieved trials

Sixty trials were included (Fig. 1). Twelve studies were of paracetamol or propacetamol, 16 were of COX-2 inhibitors (three types), and 38 were of NSAIDs (11 types) (Supplementary Table S1). Fifty-four trials were placebo-controlled. There were no trials that directly compared all three classes of drug. One directly compared COX-2 inhibitor with NSAID and five compared NSAID and paracetamol.

All participants received PCA morphine for at least 24 h after major surgery. A range of different major surgical operations were undertaken and included: thoracic (two studies), orthopaedic (23 studies), gynaecological (17 studies),

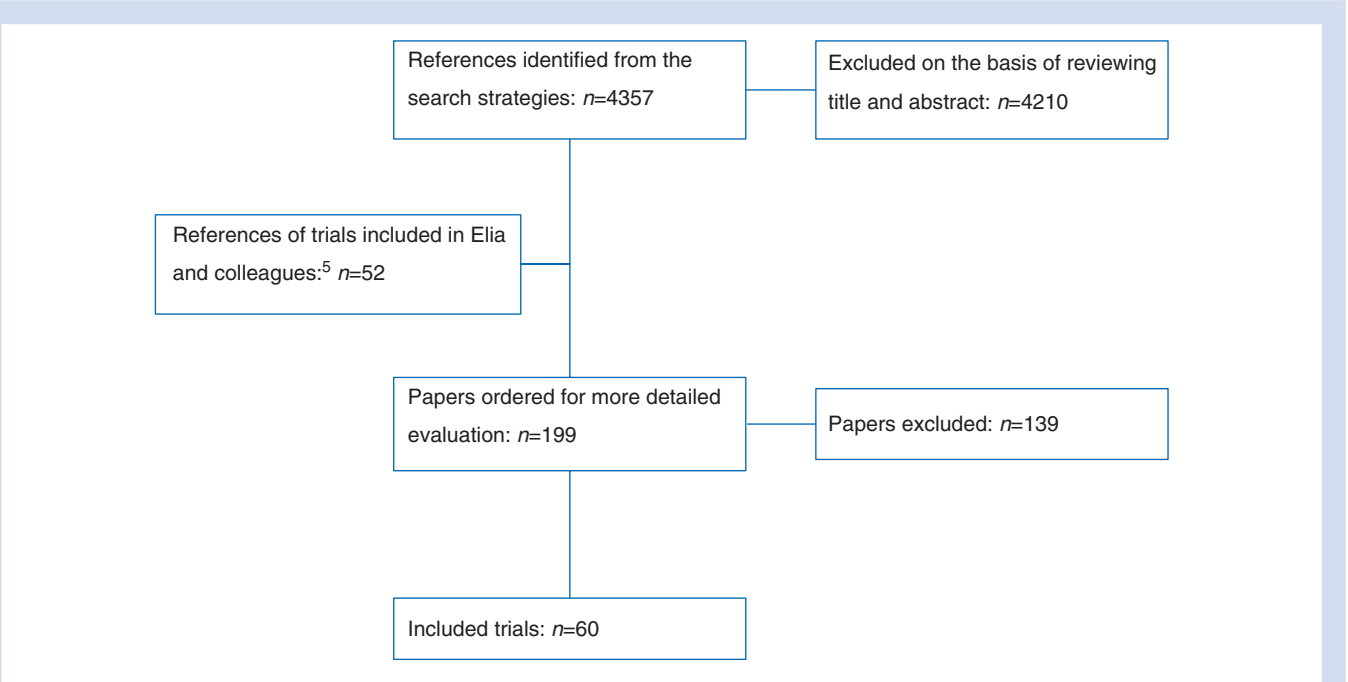

Fig 1 Flow diagram of trial selection.

obstetric (five studies), and general surgery (13 studies). The number of participants ranged from 20 to 514 and over 40% of trials had **20** or fewer participants in each trial arm.

The assessed quality was variable: the method of randomization was adequate in 57% of trials and mentioned in the remaining trials (this was a minimum criterion for inclusion); 60% did not describe allocation concealment; 48% mentioned double blinding and 42% described an adequate method of blinding; participant flow was described but incomplete in 32% and described and adequate in 48%.

Morphine consumption

There was considerable variability in baseline morphine consumption. The mean in the placebo group was 45.3 mg (SD 22.2) and ranged from 8.6 to 141.5 mg. This varied within surgical groups and across all studies [e.g. in studies involving hysterectomy, the mean (SD) ranged from 19.5 (8.3) to 93 (6) mg].

A connected network of the four treatment classes (56 trials) was formed for cumulative 24 h morphine consumption (Fig. 2) which consisted of 10 comparisons of paracetamol with placebo, 33 comparisons of NSAIDs with placebo, 15 comparisons of COX-2 inhibitors with placebo, five comparisons of NSAIDs with paracetamol, and one comparison of NSAIDs with COX-2 inhibitors. Four studies were excluded from the network because of missing data.[18–21]

Compared with placebo, there was a statistically significant (at a level of 5%) reduction in mean cumulative 24 h morphine consumption with paracetamol, NSAIDs, and COX-2 inhibitors, that is, the CrI did not cross the line of no effect (zero) (Table 1). The difference ranged from a mean reduction of 6.34 mg (95% CrI: −9.02, −3.65) for paracetamol to 10.92 mg (95% CrI: −12.77, −9.08) for COX-2 inhibitors compared with placebo (unadjusted analysis). A comparison of the active treatments showed that both NSAIDs and COX-2 inhibitors were better than paracetamol, but there was no statistically significant difference between NSAIDs and COX-2 inhibitors.

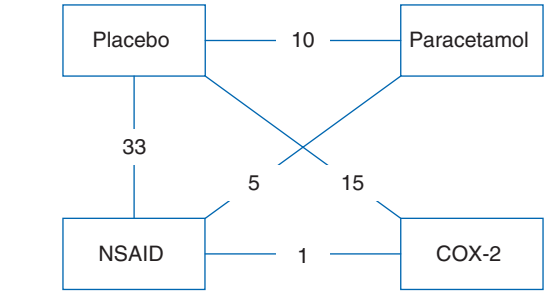

Fig 2 Network of studies for 24 h morphine consumption. The numbers represent the number of studies in which the two treatments are compared. If a study compares three treatments, it will be counted three times.

COX-2 inhibitors had the highest probability (74%) of being the best at reducing 24 h cumulative morphine consumption, although a probability of <95% indicates some uncertainty. The residual deviance (186) was larger than the number of arms included in the analysis (116), indicating that the model was not a perfect fit (Table 1).

When the model was adjusted for baseline morphine consumption, the results were broadly similar to those of the

Table 1 Pairwise comparisons for primary morphine-related outcomes. The first treatment is the intervention and the second is the control. A negative mean difference indicates that the intervention was more effective than the control treatment. An OR <1 indicates that the intervention has performed better than the control. *Adjusted for baseline morphine consumption

Comparison	Morphine consumption, unadjusted, mean difference, mg (95% CrI)	Morphine consumption, adjusted,* mean difference, mg (95% CrI)	Nausea and PONV, pairwise OR (95% CrI)	Sedation, pairwise OR (95% CrI)
Paracetamol *vs* placebo	−6.34 (−9.02, −3.65)	−8.68 (−11.43, −5.94)	1.00 (0.60, 1.53)	1.62 (0.32, 5.02)
NSAID *vs* placebo	−10.18 (−11.65, −8.72)	−9.45 (−10.90, −8.01)	0.70 (0.53, 0.88)	0.53 (0.20, 1.01)
COX-2 *vs* placebo	−10.92 (−12.77, −9.08)	−10.67 (−12.42, −8.94)	0.88 (0.61, 1.25)	0.63 (0.18, 1.49)
NSAID *vs* paracetamol	−3.85 (−6.80, −0.89)	−0.77 (−3.75, 2.21)	0.74 (0.44, 1.17)	0.51 (0.08, 1.63)
COX-2 *vs* paracetamol	−4.58 (−7.83, −1.35)	−1.99 (−5.24, 1.24)	0.93 (0.51, 1.63)	0.63 (0.07, 2.33)
COX-2 *vs* NSAID	−0.74 (−3.03, 1.56)	−1.22 (−3.43, 1.00)	1.28 (0.81, 1.97)	1.40 (0.30, 4.31)
Number of arms; residual deviance	116; 186	116; 114	86; 97	31; 41

unadjusted model, indicating that the results were robust (Table 1). However, any benefits that NSAIDs and COX-2 inhibitors had over paracetamol were marginal and no longer statistically significant. There was consistency between the MTC and the standard meta-analysis results.[4]

The analysis of studies grouped by an individual drug rather than drug class indicated that the decision to group together paracetamol and propacetamol and to group together different COX-2 inhibitors was reasonable as the mean difference in morphine consumption was similar for the individual drugs within the two classes and the CrI overlapped. In contrast, the reduction in the morphine consumption of individual NSAIDs compared with placebo ranged from 4.8 to 16.7 mg and the CrI for some NSAIDs barely overlapped, suggesting that there may be variability in the effectiveness of individual NSAIDs. The impact of study quality was minimal.[4]

Morphine-related adverse effects

On the basis of a network of 43 trials, only NSAIDs had a statistically significant benefit in reducing nausea or PONV compared with placebo [odds ratio (OR) 0.70; 95% CrI: 0.53, 0.88]. COX-2 inhibitors were slightly less effective than NSAIDs and there was almost no difference between paracetamol and placebo (Table 1). NSAIDs had the highest probability of being most effective for this outcome (78%). There was consistency between the MTC and the standard meta-analysis results.[4]

On the basis of a network of 19 trials, there was no statistically significant difference between any intervention and placebo in reducing morphine-related sedation (Table 1). There was a trend towards paracetamol being less effective than placebo and COX-2 inhibitors being less effective than NSAIDs, with wide CrI indicating considerable uncertainty. Although NSAIDs were the most effective at reducing sedation, the probability that this was the most effective treatment for reducing sedation was only 53%. There was consistency between the MTC and the standard meta-analysis results

On the basis of pairwise comparisons, there was no statistically significant difference between intervention and placebo for secondary morphine-related outcomes, with the exception of pruritus, where paracetamol and NSAIDs were statistically significantly more effective at reducing pruritus compared with placebo.

Non-opioid-related adverse effects

The most commonly reported adverse effects were those associated with NSAIDs: surgical bleeding, gastrointestinal bleeding, oliguria, and renal failure. Owing to a paucity of trials, an MTC was not possible. Six studies comparing NSAID with placebo reported the primary non-opioid outcome of interest, surgical bleeding.[20,22–26] Overall, 2.4% of participants receiving an NSAID experienced surgical-related bleeding compared with 0.4% receiving placebo.

Discussion

The results of the MTC found that all three classes of non-opioids resulted in a statistically significant reduction in 24 h morphine consumption compared with placebo. Although both NSAIDs and COX-2 inhibitors had a statistically significant greater reduction in 24 h morphine consumption compared with paracetamol, there was no statistically or clinically significant difference in morphine consumption between COX-2 inhibitors and NSAIDs.

The impact on morphine-related adverse effects was inconsistent with the findings for 24 h morphine consumption. Only NSAIDs resulted in a statistically significant reduction in nausea/PONV and there was no statistically significant difference between paracetamol, COX-2 inhibitors, and NSAIDs in the reduction in nausea or PONV, or sedation. Regarding non-opioid adverse effects, almost all were associated with NSAIDs, with approximately six times as many

patients receiving NSAIDs experiencing surgical bleeding compared with those receiving placebo.

The inconsistency between morphine consumption and morphine-related adverse effects may indicate that the reduction in morphine consumption achieved is insufficient to decrease morphine-related adverse effects. Or it may be due to the trials being underpowered to detect a reduction in adverse effects.

The MTC identified that although NSAIDs were marginally better at reducing nausea or PONV and sedation than COX-2 inhibitors or paracetamol, there was no statistically or clinically significant difference between all three classes of non-opioid. Paracetamol was ranked lower than the other two drugs for each of the primary outcomes; therefore, arguably NSAIDs or COX-2 inhibitors might be considered a preferential option. However, any clinical decision on which non-opioid to use in multimodal analgesia should be based on the benefits of reduction in morphine-related adverse effects balanced against the adverse effect profile of the class of non-opioid. There does not appear to be a strong case for routine use of any of the three non-opioids in addition to PCA morphine in the 24 h immediately after surgery for the purpose of reducing morphine consumption, given the small benefits over placebo. However, the improvement of analgesia post-surgery is also of clinical importance and likely to be of value to the patient beyond the immediate 24 h after surgery, but this is outside the scope of our review.

MTC does have limitations. The key assumption underpinning MTC is that the included trials are exchangeable. This is similar to the assumption underlying traditional meta-analysis that consideration should be given to whether studies are clinically similar enough for a pooled treatment effect to be meaningful. Although there was considerable variability in morphine consumption (based on the placebo group) between trials, possibly due to differences in the type of surgery or the trial populations, the analysis which adjusted for baseline morphine consumption did not alter which drug class was most effective at reducing 24 h morphine consumption. This finding, together with the narrow inclusion criteria used, means that the assumption of exchangeability was justified. An alternative approach would have been to group the data by the type of surgery. However, due to the variability in morphine consumption within surgery types, this would have been of limited value. The findings suggest that the higher the expected morphine use (influenced by a range of factors including surgery type), the greater the reduction in morphine will be with the addition of the non-opioids. However, this cannot be considered definitive as this was a *post hoc* exploratory analysis.

The feasibility of incorporating covariates in an MTC has been demonstrated,[27] although the methods are under continuing development. As with all meta-analyses incorporating covariates, the analysis is based on aggregate data and may be influenced by unknown confounding factors. This can only be resolved by analysis of individual patient data from studies. Additional limitations are that the analyses did not take into consideration any effect differences between the three non-opioids at different levels of morphine consumption. Furthermore, the assumption was made that because patients were receiving PCA morphine, optimum analgesia was maintained and pain control was the same in all arms. This does not take into account any synergistic action between morphine and the three non-opioids.

Given the evidence for the variability in the effects of individual NSAIDs on 24 h morphine consumption, further synthesis may be warranted to explore whether there is similar variability on the impact of morphine-related adverse effects. Future studies should use one or more morphine-related adverse effects as a primary outcome measure and power calculation should be based on these outcomes and not morphine consumption.

In conclusion, when paracetamol, NSAIDs, and COX-2 inhibitors are compared with each other, the differences in morphine consumption were small and unlikely to be of clinical significance. In addition, the benefits in terms of a reduction in morphine-related adverse effects do not strongly favour one of the three non-opioid classes.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Conflict of interest

None declared.

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