Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review

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Background. Quantitative reviews of postoperative pain management have demonstrated that the number of patients needed to treat for one patient to achieve at least 50% pain relief (NNT) is 2.7 for ibuprofen (400 mg) and 4.6 for paracetamol (1000 mg), both compared with placebo. However, direct comparisons between paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) have not been extensively reviewed. The aims of this review are (i) to compare the analgesic and adverse effects of paracetamol with those of other NSAIDs in postoperative pain, (ii) to compare the effects of combined paracetamol and NSAID with those of either drug alone, and (iii) to discuss whether the adverse effects of NSAIDs in short-term use are justified by their analgesic effects, compared with paracetamol.

Methods. Medline (1966 to January 2001) and the Cochrane Library (January 2001) were used to perform a systematic, qualitative review of postoperative pain studies comparing paracetamol (minimum 1000 mg) with NSAID in a double-blind, randomized manner. A quantitative review was not performed as too many studies of high scientific standard (27 out of 41 valid studies, including all major surgery studies) would have been excluded.

Results. NSAIDs were clearly more effective in dental surgery, whereas the efficacy of NSAIDs and paracetamol seemed without substantial differences in major and orthopaedic surgery, although firm conclusions could not be made because the number of studies was limited. The addition of an NSAID to paracetamol may confer additional analgesic efficacy compared with paracetamol alone, and the limited data available also suggest that paracetamol may enhance analgesia when added to an NSAID, compared with NSAIDs alone.

Conclusion. Paracetamol is a viable alternative to the NSAIDs, especially because of the low incidence of adverse effects, and should be the preferred choice in high-risk patients. It may be appropriate to combine paracetamol with NSAIDs, but future studies are required, especially after major surgery, with specific focus on a potential increase in side-effects from their combined use.

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The aims of this review are (i) to compare the analgesic and adverse effects of paracetamol with those of other non-steroidal anti-inflammatory drugs (NSAIDs) in postoperative pain, (ii) to compare the effects of paracetamol–NSAID combination with those of either drug alone, and (iii) to discuss whether the adverse effects of NSAIDs in short-term use are justified by their analgesic effects compared with paracetamol. In recent systematic quantitative reviews of postoperative pain management based on placebo-controlled trials, ibuprofen 400 mg was shown to have a number needed to treat (NNT) of 2.7 compared with placebo,[1] whereas paracetamol had an NNT of 4.6.[2] NNT is the number of patients needed to treat for one patient to achieve at least 50% pain relief. However, the

analgesic effect of NSAIDs *vs* paracetamol assessed in direct comparisons has not been reviewed extensively before.[3–5]

Methods

A systematic review of the literature using Medline (1966 to January 2001) and the Cochrane Library (January 2001) was performed. The search profile included a comprehensive list of pain terms combined with 'paracetamol', 'acetaminophen', 'propacetamol', 'non-steroidal anti-inflammatory drugs (NSAID)' or individual drug names. Additional papers not indexed in the databases mentioned were retrieved by reviewing the reference lists from the published material.

Inclusion criteria were postoperative pain, double-blind design, randomized allocation, studies on man, English language and full journal publication. The statistical method had to be described in the study. Each report meeting the inclusion criteria was read by two of the authors and scored for inclusion and methodological quality using a three-item scale of 1–5.[6] Two of the authors agreed on the scores. Reports described as randomized were given 1 point and an additional point if the method of randomization was described and it was appropriate (table of random numbers, computer-generated coin-tossing). Conversely, 1 point was deducted if the method of randomization was inappropriate (alternative allocation, allocation according to date of birth). One point was given when the study was described as double-blind and an additional point if the method of double-blinding was described and was appropriate (identical placebo, dummy). Again, 1 point was deducted if the blinding was inappropriate. Finally, 1 point was given to studies with a description of withdrawals and dropouts. Studies without randomization and blinding were excluded from the review, so the minimum score of an included trial was 2 and the maximum score 5. The studies did not have to be placebo-controlled as the analgesic effect of paracetamol and NSAIDs compared with placebo has been established.[1 2] Clinical trials comparing paracetamol with NSAIDs [including acetylsalicylic acid (ASA)] were sought, as were studies evaluating paracetamol added to an NSAID against paracetamol or NSAID alone.

The dose of paracetamol had to be a minimum of 1000 mg when given as a single agent, because doses below 1000 mg may be insufficient.[7] However, studies employing lower doses of paracetamol were included when given in combination with another NSAID or when administered to children. A wide range of NSAID doses was included. The medication could be administered at different times, including pre- and postoperatively, and by different routes such as i.v., oral and rectal.

Analgesic efficacy was evaluated by significant differences in standard pain measures and/or consumption of opioids/rescue analgesia.

Results

A detailed description of all the studies is presented in Tables 1–3. The patient numbers in the tables excluded those receiving placebo, as it was the numbers receiving paracetamol and/or NSAIDs that we sought to evaluate. The studies were divided into the following comparisons: paracetamol *vs* NSAIDs (Table 1), paracetamol with NSAIDs *vs* paracetamol (Table 2) and paracetamol with NSAIDs *vs* NSAIDs (Table 3). The tables were subdivided into major and minor surgery. Some of the studies belonged to several categories and are therefore mentioned more than once.

We found a total of 47 double-blind and randomized studies, of which six had to be excluded because of inadequate randomization (consecutive allocation) or inadequate statistical methods.[8–13] Three further studies were excluded from evaluation because they failed to demonstrate statistically significant differences in pain scores or opioid consumption between groups receiving drugs of known analgesic efficacy and placebo controls, thus suggesting that the studies lacked sensitivity.[14–16] However, these studies are presented in the tables as they exhibit no apparent methodological problems and separation from placebo does not indicate ability to demonstrate a difference between active drugs. Several studies without placebo controls were included in the review, but these studies are considered to provide weaker evidence when no significant differences between active drugs were demonstrated.

Methodological quality scores ranged from 2 to 5 for all studies. The median value of quality scores for the positive studies (the studies which showed a difference in analgesic effect) and the negative studies were both 4. No statistical difference was found between the two groups using Mann–Whitney test (P=1.0).

Paracetamol vs NSAIDs

There were a total of 36 studies including 3362 patients undergoing a wide variety of surgical procedures (Table 1).

Major surgery

There were four valid studies in major abdominal and gynaecological surgery[17–20] and one involving laparoscopic cholecystectomy,[21] including a total of 398 patients. In the most robust study,[20] rectal diclofenac 50 mg was superior to rectal paracetamol regarding pain scores, but resulted in an equivalent morphine-sparing effect (36 and 40% respectively). There were no significant differences between paracetamol and NSAIDs in pain scores or postoperative morphine requirement in the other four studies. However, there were problems in these studies. Montgomery and colleagues[17] studied a single rectal dose of diclofenac or paracetamol administered preoperatively and assessed its efficacy over 24 h. However, there were significant differences in age and body mass index between the groups,

Table 1 Paracetamol *vs* NSAIDs in postoperative pain. *n* refers to the number of patients involved in the specific comparisons, not total number of patients in the study. Analgesic outcome results for paracetamol *vs* NSAID: '↑ = greater effect' means that paracetamol was more effective than NSAID; '→ = same effect' means that paracetamol and NSAID had the same effect; '↓ = less effect' means that paracetamol was less effective than NSAID. Analgesic outcome results were quantified when possible (e.g. VAS scores, rescue medication, PCA). Ordinal scale measures cannot be used for quantitative comparisons. OPS = objective and behavioural pain score; P = paracetamol; S = suppository

Author (quality score)	*n*	Type of surgery	Treatment groups	Administration	Treatment duration and timing	Outcome measures	Analgesic outcome: paracetamol *vs* NSAID ↑ = greater effect → = same effect ↓ = less effect	Opioid requirement or analgesic remedication: paracetamol *vs* NSAID	Adverse effects (significant differences)
Major surgery									
Montgomery *et al.*, 1996[17] (4)	40	Elective gynaecological surgery (abdominal)	1. P 1500 mg 2. Diclofenac 100 mg 3. P 1500 mg + diclofenac 100 mg	Supp	Single dose, pre-emptive	1. Pain on deep breathing (VAS) 2. Morphine usage (PCA)	→	→	Not described
Witjes *et al.*, 1992[19] (3)	65	Cholecystectomy	1. Naproxen 500 mg × 2 2. P 1000 mg × 4 3. Placebo	Supp	3 days, pre-emptive	1. Pain score (0–3) 2. Usage of buprenorphine	→ P not different from placebo	→	No statistical evaluation
Varrassi *et al.*, 1999[18] (5)	174	Elective hysterectomy (abdominal)	1. Propacetamol 2000 mg 2. Ketorolac 30 mg	i.v.	Two doses, first dose at extubation	1. Morphine usage (PCA) 2. Pain intensity (VAS) 3. Pain intensity (1–5) 4. Overall analgesic efficacy (1–5)	→	→	No difference
Cobby *et al.*, 1999[20] (4)	44	Elective hysterectomy (abdominal)	1. Diclofenac 50 mg 2. P 1300 mg 3. Placebo	Supp	Three doses, first dose at wound closure	1. Morphine usage (PCA) 2. Pain intensity (VAS) 3. Pain relief (0–10)	↓ VAS 24 h (average): P 39 Diclofenac 18	→	No statistical evaluation
Dahl *et al.*, 1997[15] (4)	66	Elective hysterectomy (abdominal)	1. Ibuprofen 800 mg 2. P 1000 mg 3. Placebo	Oral	Single dose, pre-emptive	1. Pain intensity (VAS) 2. Pain intensity (1–5) 3. Quality of sleep	→ Active drug equal to placebo	→ Active drug equal to placebo	No difference between all groups (nausea or perioperative bleeding)
Owen *et al.*, 1997[21] (4)	75	Laparoscopic cholecystectomy	1. Ibuprofen SR (sustained release) 1600 mg × 1 2. P 1000 mg × 4	Oral	7 days, first dose pre-emptive	1. Pain intensity (0–4) 2. Overall efficacy 3. Quality of sleep	→	→	No difference
Minor surgery									
McQuay *et al.*, 1986[22] (4)	120	Elective orthopaedic	1. Ketorolac 5 mg 2. Ketorolac 10 mg 3. Ketorolac 20 mg 4. P 500 mg 5. P 1000 mg	Oral	Single dose, postoperative	1. Pain intensity (0–3) 2. Pain intensity (0–7) 3. Pain intensity (VAS) 4. Pain relief (0–4) 5. Pain relief (VAS)	→ (*vs* ketorolac 10 and 20 mg)	→	More sedation with ketorolac 10 and 20 mg compared with P 500 mg
McQuay *et al.*, 1990[23] (5)	120	Elective orthopaedic	1. Bromfenac 5 mg 2. Bromfenac 10 mg 3. Bromfenac 25 mg 4. P 1000 mg 5. Placebo	Oral	Single dose, postoperative	1. Pain intensity (0–3) 2. Pain intensity (0–7) 3. Pain relief (0–4) 4. Pain relief (VAS)	→ Active drug better than placebo	↓ (*vs* bromfenac 25 mg) Remedication not required: P 37% bromfenac (25 mg) 63% → (*vs* bromfenac 10 mg)	No difference

Table 1 *Continued*

Author (quality score)	*n*	Type of surgery	Treatment groups	Administration	Treatment duration and timing	Outcome measures	Analgesic outcome: paracetamol *vs* NSAID ↑ = greater effect → = same effect ↓ = less effect	Opioid requirement or analgesic remedication: paracetamol *vs* NSAID	Adverse effects (significant differences)
Fletcher *et al.*, 1997[24] (5)	30	Disc surgery	1. Propacetamol 2000 mg × 4 2. Ketoprofen 50 mg × 4 3. Ketoprofen 50 mg × 4 + propacetamol 2000 mg × 4 4. Placebo	i.v.	48 h, first dose at skin closure	1. Pain intensity at rest and mobilization (VAS) 2. Morphine usage (PCA)	→ (pain at rest) ↓ (pain on movement) Active drug better than placebo	→	No difference
Van Lancker *et al.*, 1999[14] (3)	49	Arthroscopy	1. Propacetamol 30 mg kg^{-1} 2. Tenoxicam 0.5 mg kg^{-1} 3. Propacetamol + tenoxicam 4. Placebo	i.v.	Single dose, pre-emptive	1. Pain intensity (VAS)	→ Active drug equal to placebo	→ Active drug equal to placebo	No difference
Huang *et al.*, 1986[27] (3)	75	Tubal occlusion in local anaesthesia	1. P 1300 mg 2. Meclofenamate 100 mg 3. Meclofenamate 200 mg 4. Placebo	Oral	Pre-emptive, single dose	1. Pain intensity (1–5)	↓	→	No data
Schachtel *et al.*, 1989[25] (4)	73	Episiotomy	1. Ibuprofen 400 mg 2. P 1000 mg 3. Placebo	Oral	Single dose, postoperative	1. Pain intensity (0–3) 2. Pain relief (0–4) 3. Overall evaluation of analgesic efficacy (1–5)	↓ Active drug better than placebo	→	None
Skovlund *et al.*, 1991[26] (4)	30	Episiotomy	1. Naproxen 500 mg 2. P 1000 mg	Oral	Single dose, postoperative	1. Pain intensity (VAS)	→	No data	No statistical evaluation
Derkay *et al.*, 1998[16] (3)	94 children	Myringotomy	1. P 10 mg kg^{-1} 2. Ibuprofen 10 mg kg^{-1} 3. Placebo	Oral	Single dose, pre-emptive	1. OPS	→ Active drug equal to placebo	→ Active drug equal to placebo	No difference
Bean-Lijewski and Stinson, 1997[28] (4)	125 children	Myringotomy	1. P 15 mg kg^{-1} 2. Ketorolac 1 mg kg^{-1}	Oral	Single dose, postoperative	1. OPS	→ (3 of 5 assessments and authors' conclusion) ↓ (2 of 5 assessments)	No data	No difference
Baer *et al.*, 1992[29] (3)	44 children	Adenoidectomy with or without myringotomy	1. Diclofenac 12.5 mg 2. P 125 mg	Supp	Single dose, pre-emptive	1. Pethidine usage 2. Pain behaviour: crying, anxiety, alertness, breathing	→	↓ No. requiring pethidine: P 20 diclofenac 9	No difference (bleeding)
Rømsing *et al.*, 2000[30] (5)	48 children	Tonsillectomy	1. Diclofenac 2–3 mg kg^{-1} per 24 h in two doses 2. P 90 mg kg^{-1} per 24 h in four doses	Oral	Multiple doses, first dose day 1 after surgery	1. Pain intensity at rest and at drinking (Poker Chip Tool)	→	No data	Higher incidence in P group: nausea and vomiting
Schmidt *et al.*, 2001[33] (4)	80	Tonsillectomy	1. Diclofenac 50 mg 2. P 1000 mg	Supp	Single dose, pre-emptive	1. Pain intensity (VAS)	→	→	Intraoperative blood loss significantly greater in diclofenac group

Table 1 *Continued*

Author (quality score)	*n*	Type of surgery	Treatment groups	Administration	Treatment duration and timing	Outcome measures	Analgesic outcome: paracetamol *vs* NSAID ↑ = greater effect → = same effect ↓ = less effect	Opioid requirement or analgesic remedication: paracetamol *vs* NSAID	Adverse effects (significant differences)
Rusy *et al.*, 1994[31] (2)	50 children	Tonsillectomy with or without adenoidectomy	1. Ketorolac 1 mg kg^{-1} + simulated rectal examination 2. P 35 mg kg^{-1}	Ketorolac i.v. P supp	Single dose, pre-emptive	1. OPS	→ (serum concentrations of P were below anti-pyretic level)	→	Significantly more blood loss and need for additional haemostasis measures in ketorolac group
Watcha *et al.*, 1992[32] (2)	61 children	Bilateral myringotomy	1. P 10 mg kg^{-1} 2. Ketorolac 1 mg kg^{-1} 3. Placebo (postoperative pain treated with P 15–20 mg kg^{-1} given as supp)	Oral	Single dose, pre-emptive	1. OPS	↓ OPS score: P 4 Ketorolac 1 P equal to placebo	No comparison made between P and ketorolac	No difference
Cooper *et al.*, 1989[34] (5)	120	Dental	1. Ibuprofen 400 mg 2. P 1000 mg 3. Placebo	Oral	Single dose, pre-emptive	1. Pain intensity (0–3) 2. Pain relief (0–4) 3. Pain half gone 4. Overall evaluation of analgesic efficacy (0–4)	↓ % very good or excellent overall impression: P 27% Ibuprofen 52% Active drug better than placebo	→	More drowsiness in P group
Cooper *et al.*, 1998[42] (4)	151	Dental	1. Ketoprofen 100 mg 2. Ketoprofen 25 mg 3. P 1000 mg 4. Placebo	Oral	Single dose, postoperative	1. Pain intensity (0–3) 2. Pain intensity (VAS) 3. Pain relief (0–4)	→ (*vs* ketoprofen 100 mg) ↑ (*vs* ketoprofen 25 mg) Active drug better than placebo	→	No difference
Dionne, 1986[35] (2)	20	Dental	1. Flurbiprofen 50 mg 2. P 1000 mg	Oral	2 doses, pre-emptive and 4 h postoperative	1. Pain intensity (0–3) 2. Pain intensity (VAS) 3. Global evaluation	↓ (0–4 h) VAS summed: P 88.25 flurbiprofen 46.95 → (4–8 h)	No data	No difference
Irvine *et al.*, 1982[43] (3)	33	Dental	1. Diflunisal 500 mg 2. P 1000 mg	Oral	1.5 days, first dose postoperative	1. Pain intensity (0–4) 2. Assessment of analgesic efficacy (0–4)	→	No data	None
Kiersch *et al.*, 1994[36] (5)	181	Dental	1. Naproxen sodium 440 mg 2. P 1000 mg 3. Placebo	Oral	Single dose, postoperative	1. Pain intensity (0–3) 2. Pain intensity (VAS) 3. Pain relief (0–4) 4. Pain half gone 5. Overall efficacy (0–4)	↓ VAS summed pain intensity difference 6 h: P 41.5 Naproxen sodium: 127.5 Active drug better than placebo	↓ (time to remedication)	No difference
McGaw *et al.*, 1987[37] (4)	84 children	Dental	1. aluminium ibuprofen 200 mg 2. P 240–360 mg related to weight 3. Placebo	Oral	Single dose, postoperative	1. Pain intensity (1–4) 2. Pain relief (1–5) 3. Global rating (1–5)	↓ P equal to placebo	No data	Too few for statistical analysis

Table 1 *Continued*

Author (quality score)	*n*	Type of surgery	Treatment groups	Administration	Treatment duration and timing	Outcome measures	Analgesic outcome: paracetamol *vs* NSAID ↑ = greater effect → = same effect ↓ = less effect	Opioid requirement or analgesic remedication: paracetamol *vs* NSAID	Adverse effects (significant differences)
Mehlisch *et al.*, 1984[47] (4)	107	Dental	1. Aspirin 650 mg 2. P 1000 mg 3. Placebo	Oral	Single dose, postoperative	1. Pain intensity (0–3) 2. Pain relief (0–4) 3. Pain half gone 4. Overall efficacy (1–5)	↑ Active drug better than placebo	→	No data
Mehlisch *et al.*, 1990[38] (5)	612	Dental	1. Ibuprofen 400 mg 2. P 1000 mg 3. Placebo	Oral	Single dose, postoperative	1. Pain intensity (1–4) 2. Pain relief (1–4)	↓ Active drug better than placebo	↓ Remedication: P 57% ibuprofen 41%	No difference
Mehlisch *et al.*, 1995[39] (5)	200	Dental	1. Ibuprofen 400 mg 2. P 1000 mg 3. Placebo	Oral	Single dose, postoperative	1. Pain intensity (0–3) 2. Pain relief (0–4) 3. Global assessment (0–4)	↓ Active drug better than placebo	↓ Remedication: P 60% ibuprofen 26%	No difference
Moore *et al.*, 1985[49] (3)	25 children	Dental	1. Aluminium ibuprofen 200 mg 2. P 240–360 mg related to weight 3. Placebo	Oral	Single dose, postoperative	1. Pain intensity (1–4) 2. Pain relief (1–5) 3. Overall efficacy (1–5)	No comparison made between P and ibuprofen	No comparison made between P and ibuprofen	None
Nystrom *et al.*, 1988[40] (4)	88	Dental	1. Diflunisal 500 mg × 1 2. P 1000 mg × 2	Oral	Single and 2 doses, first dose postoperative	1. Pain intensity (VAS)	↓ Pain reduction: P 36% diflunisal 63%	→	No difference
Olstad *et al.*, 1986[41] (3)	24	Dental	1. Indoprofen 400 mg × 2 2. P 1000 mg × 4	Oral	3 days, first dose postoperative	1. Pain intensity (VAS)	↓	No data	Significant increase in bleeding on postoperative days 3, 4 and 5 in indoprofen group (minimal)
Rodrigo *et al.*, 1989[44] (3)	32	Dental	1. Diflunisal 500 mg × 1 2. P 1000 mg × 2	Oral	Single and 2 doses, first dose preoperative	1. Pain intensity (VAS)	→	No remedication	None
Seymour *et al.*, 1996[45] (4)	124	Dental	1. Ketoprofen 12.5 mg 2. Ketoprofen 25 mg 3. P 1000 mg 4. Placebo	Oral	Single dose, postoperative	1. Pain intensity (VAS) 2. Global assessment (1–5)	→ Active drug better than placebo	→	None
Breivik *et al.*, 1999[48] (5)	68	Dental	1. Diclofenac 100 mg 2. P 1000 mg 3. Diclofenac 100 mg + P 1000 mg	Oral	Single dose, postoperative	1. Pain intensity (VAS) 2. Pain relief (0–4) 3. Overall effect (1–4)	↑ (0.5–3 h) → (0.5–8 h)	→	No difference
Cheung *et al.*, 1992[46] (3)	30	Dental	1. Tenoxicam 40 mg 2. P 1000 mg	Oral	Single dose, pre-emptive	1. Pain intensity (VAS)	→	→	Too few for statistical analysis

which could have affected the opioid requirements. Witjes and colleagues[19] used a relatively insensitive four-point pain scale and consumption of buprenorphine tablets as efficacy measures and found no differences in pain scores between active medication and placebo, but a reduction (P=0.048) in opioid consumption on the day of surgery (consumption of buprenorphine tablets: placebo group 2.3, paracetamol group 1.5, naproxen group 1.8). There were no differences between NSAIDs, paracetamol and placebo on the subsequent 2 days, suggesting low study sensitivity. Out of the three best studies,[18 20 21] only one had a placebo control[20] and therefore proven sensitivity. In this study,[20] diclofenac was superior to paracetamol regarding pain scores. The two other studies[18 21] showed no significant difference in pain scores and none of the three studies showed differences in opioid requirement. In three studies,[17 19 20] paracetamol was administered rectally, which may give lower bioavailability.[3] High bioavailability of paracetamol was present in two out of the three best studies, as paracetamol was administered orally in the study of Owen and colleagues[21] and i.v. in the study of Varrassi and colleagues.[18] In these studies, there were no significant differences in pain scores or opioid consumption between paracetamol and NSAIDs. In summary, the limited number of studies with an optimal design precludes firm conclusions about a potential difference in analgesic effect between paracetamol and NSAIDs in major abdominal surgery. So far, the studies failed to show a substantial difference in analgesic efficacy between paracetamol and NSAIDs.

Orthopaedic surgery

Three trials including 270 orthopaedic patients were analysed.[22–24] None showed any differences in pain scores at rest. However, in one study evaluating pain on movement after disc surgery, ketoprofen was superior.[24] In two robust studies with proven sensitivity, both employing 1000 mg oral doses of paracetamol, McQuay and colleagues found lower opioid requirements after bromfenac 25 mg but not 10 mg compared with paracetamol,[23] but no difference when paracetamol was compared with ketorolac 10–20 mg.[22] In summary, three studies have shown that the efficacy of paracetamol was not substantially different from that of NSAIDs, but again the limited number of studies precludes firm conclusions about the potential difference between paracetamol and NSAIDs. Paracetamol was administered orally or i.v. in all studies avoiding the more unpredictable bioavailability associated with the rectal route.

Gynaecological surgery

There were three trials involving a total of 178 patients after episiotomy[25 26] (103 patients) or tubal occlusion[27] (75 patients). In two placebo-controlled studies, ibuprofen (400 mg)[25] and meclofenamate (100 and 200 mg)[27] improved pain scores compared with paracetamol, but no differences in rescue medication were demonstrated. In the third study, which included only 30 patients, paracetamol was equivalent to naproxen 500 mg but the study sensitivity was not proven.[26] In summary, NSAID was superior to paracetamol in two assay-sensitive trials involving two different surgical procedures.

Ear, nose and throat surgery

There were six valid studies that involved a total of 408 children undergoing ear, nose and throat surgery (myringotomy, adenoidectomy, tonsillectomy).[28–33] One study showed ketorolac (1 mg kg^{-1}) to be superior to paracetamol (10 mg kg^{-1})[32] and paracetamol equal to placebo, possibly reflecting the low dose. Four other studies showed that diclofenac[29 30 33] and ketorolac[31] were equivalent to paracetamol concerning objective pain scores and visual analogue scale (VAS) scores. In the study of Bean-Lijewski and Stinson,[28] there was no clear conclusion. In three out of the six studies, no comparison of opioid requirements could be made.[28 30 32] Opioid requirements were lowered by diclofenac in one study[29] but equivalent to paracetamol in two other studies involving diclofenac and ketorolac.[31 33] In a study of tonsillectomy, rectal paracetamol (35 mg kg^{-1}) was equivalent to ketorolac (1 mg kg^{-1}) i.v. despite all serum concentrations of paracetamol being below the antipyretic level.[31] However, even when high doses of oral paracetamol (90 mg kg^{-1} per 24 h) were given to children after tonsillectomy, this did not improve analgesia compared with diclofenac (2–3 mg kg^{-1} per 24 h).[30] Only one of these six studies included a placebo control.[32] There are problems in interpreting these studies because pain rating in children is difficult. Five out of six studies included no placebo control[28–31 33] and could not differentiate between paracetamol and NSAID. In the study with a placebo control, ketorolac was superior to a relatively low dose of paracetamol (10 mg kg^{-1}).[32]

Dental surgery

Of 16 dental studies, eight showed that NSAIDs were superior to paracetamol with respect to pain scores (1329 patients),[34–41] five showed that they were equivalent (370 patients)[42–46] and two that paracetamol 1000 mg was superior to aspirin 650 mg[47] and diclofenac 100 mg.[48] One study was not evaluated as the statistical comparison of paracetamol with NSAIDs was not performed.[49] Of the eight studies in which NSAIDs were superior regarding pain scores, three also showed NSAIDs to be superior regarding remedication (993 patients).[36 38 39] Of the six studies showing no differences in pain scores, study sensitivity was unproven in three[43 44 46] but the other three studies were robust.[42 45 48] In one study, assay sensitivity was inferred because paracetamol plus codeine was superior to paracetamol.[48] In this study, which involved 68 patients, paracetamol 1000 mg and diclofenac 100 mg were equivalent regarding total pain relief and summed pain intensity difference over 8 h but paracetamol was superior to diclofenac in the first 3 h postoperatively (P=0.001). This could be due to slow onset of action of the enteric-coated diclofenac preparation.[48] Cooper and colleagues[42] showed

Table 2 Paracetamol combined with NSAIDs *vs* paracetamol in postoperative pain. *n* refers to the number of patients involved in the specific comparisons, not the total number of patients in the study. Analgesic outcome results for paracetamol and NSAID *vs* paracetamol: '↑ = greater effect' means that the combination was better than paracetamol alone; '→ = same effect' means that the combination had the same effect as paracetamol alone; '↓ = less effect' means that the combination was less effective than paracetamol alone. Analgesic outcome results were quantified when possible (e.g. VAS scores, rescue medication, PCA). Ordinal scale measures cannot be used for quantitative comparisons. P = paracetamol; Supp = suppository

Author (quality score)	*n*	Type of surgery	Treatment groups	Administration	Treatment duration and timing	Outcome measures	Analgesic outcome: paracetamol + NSAID *vs* paracetamol ↑ = greater effect → = same effect ↓ = less effect	Opioid requirement or analgesic remedication. Paracetamol + NSAID *vs* paracetamol	Adverse effects (significant differences)
Major surgery									
Montgomery *et al.*, 1996 [17] (4)	59	Elective gynaecological surgery (abdominal)	1. P 1500 mg 2. Diclofenac 100 mg 3. P 1500 mg + diclofenac 100 mg	Supp	Single dose, pre-emptive	1. Pain at deep breathing (VAS) 2. Morphine usage (PCA)	→	↑ Morphine use: P 44.9 mg P + diclofenac 27.1 mg	Only morphine-related adverse effects
Beck *et al.*, 2000[53] (3)	65	Vaginal or abdominal hysterectomy	1. P 20 mg kg^{-1} 2. P 40 mg kg^{-1} 3. Diclofenac 100 mg + P 20 mg kg^{-1}	Supp	Single dose, pre-emptive	1. Morphine usage (PCA) 2. Pain scores (VAS)	→ (compared with both P doses)	→ (compared with both P doses)	Only morphine-related adverse effects
Minor surgery									
Rubin *et al.*, 1984[50] (4)	246	Episiotomy	1. P 648 mg and acetylsalicylic acid 648 mg 2. Acetylsalicylic acid 800 mg and caffeine 65 mg 3. P 1000 mg 4. Placebo	Oral	Single dose, postoperative	1. Pain intensity (0–4) 2. Remedication	↑ Active drug better than placebo	→	No difference
Van Lancker *et al.*, 1999[14] (3)	74	Arthroscopy	1. Propacetamol 30 mg kg^{-1} 2. Tenoxicam 0.5 mg kg^{-1} 3. Propacetamol 30 mg kg^{-1} + tenoxicam 0.5 mg kg^{-1} 4. Placebo	i.v.	Single dose, pre-emptive	1. Pain intensity (VAS)	→ Active drug equal to placebo	→ Active drug equal to placebo	No difference
Mather *et al.*, 1995[51] (2)	80 children	Tonsillectomy	1. P 20 mg kg^{-1} 2. Placebo + morphine 0.1 mg kg^{-1} 3. P 20 mg kg^{-1} + ketorolac 0.5 mg kg^{-1}	Oral	Single dose, pre-emptive	1. Morphine usage only; no pain scores		↑ No. of patients requiring extra morphine: P9 P + ketorolac 1	Greater incidence of vomiting in morphine group
Fletcher *et al.*, 1997[24] (5)	45	Disc surgery	1. Propacetamol 2000 mg × 4 2. Ketoprofen 50 mg × 4 3. Ketoprofen 50 mg × 4 + propacetamol 2000 mg × 4 4. Placebo	i.v.	48 h, first dose at skin closure	1. Pain intensity at rest and mobilization (VAS) 2. Morphine usage (PCA)	↑ (at rest) ↑ (on movement) Active drug better than placebo	↑ Morphine requirement: propacetamol 43.4 mg propacetamol + ketoprofen 23.4 mg	No difference

Table 2 *Continued*

Author (quality score)	*n*	Type of surgery	Treatment groups	Administration	Treatment duration and timing	Outcome measures	Analgesic outcome: paracetamol + NSAID *vs* paracetamol ↑ = greater effect → = same effect ↓ = less effect	Opioid requirement or analgesic remedication. Paracetamol + NSAID *vs* paracetamol	Adverse effects (significant differences)
Aubrun *et al.*, 2000[52] (3)	50	Spinal fusion surgery	1. Propacetamol 2000 mg × 4 2. Ketoprofen 100 mg × 3 and propacetamol 2000 mg × 4	i.v.	24 h, first dose at skin closure	1. Pain intensity (VAS) 2. Pain relief (VAS) 3. Morphine usage (PCA)	↑ (for pain intensity) → (for pain relief)	↑ (during PCA) Total morphine consumption: propacetamol 49 mg propacetamol + ketoprofen 33 mg	No difference
Breivik *et al.*, 1999[48] (5)	68	Dental	1. Diclofenac 100 mg 2. P 1000 mg 3. Diclofenac 100 mg and P 1000 mg	Oral	Single dose, postoperative	1. Pain intensity (VAS) 2. Pain relief (0–4) 3. Overall effect (1–4)	↑ Mean VAS (8 h): P 37 P + diclofenac 19	↑	No difference

paracetamol 1000 mg to be equivalent to ketoprofen 100 mg and superior to ketoprofen 25 mg. Seymour and colleagues[45] showed equivalence between paracetamol 1000 mg and ketoprofen 25 mg but did not examine a higher dose. In these three studies,[42 45 48] there were also no differences in opioid requirements. In all dental studies the medication was given orally, thus making bioavailability comparable. In summary, NSAIDs seem to be superior to paracetamol in dental surgery, regarding both pain scores and remedication. Most of the studies in dental surgery were robust, with relatively sensitive pain measurement scales, adult patients and medication administered orally.

Summary

Out of 33 valid studies, three (all dental studies) showed that the NSAID was superior to paracetamol with respect to both pain scores and opioid requirement or remedication,[36 38 39] two studies showed that NSAIDs reduced opioid requirement or remedication only compared with paracetamol,[23 29] and 10 studies showed that analgesia was improved by NSAIDs compared with paracetamol regarding pain scores, but either did not report opioid requirement or remedication[32 35 37 41] or found no differences.[20 24 25 27 34 40] Sixteen studies showed no differences between paracetamol and NSAIDs in pain scores,[17–19 21–23 26 29–31 33 42–46] and 10 of these studies also showed no differences in opioid requirement or remedication.[17–19 21 22 31 33 42 45 46] Five of these 16 studies[19 22 23 42 45] showed significant differences between active drugs and placebo, strengthening their conclusion of no difference between NSAID and paracetamol. Two studies found paracetamol to be superior to NSAID regarding pain scores, but not remedication requirement.[47 48] One study had an unclear conclusion[28] and one study made no statistical comparison between paracetamol and NSAIDs.[49]

The efficacies of paracetamol and NSAIDs may depend on the type of surgery. Of the three best studies in major abdominal/gynaecological surgery (including laparoscopic cholecystectomy), two found no significant differences between paracetamol and NSAIDs[18 21] and one demonstrated that NSAIDs were superior[20] as regards pain scores. In all three studies, no significant difference was found in opioid requirement. However, there are several methodological problems in these studies and thus no clear conclusion can be made regarding the efficacy of NSAIDs and paracetamol in major surgery. In orthopaedic surgery, three robust studies showed that the efficacy of paracetamol was comparable to that of NSAIDs,[22–24] but more data are needed to allow final conclusions. In gynaecological minor surgery (episiotomy and laparoscopic tubal ligation), no clear conclusion could be made, but NSAIDs seemed to be more efficacious in two assay-sensitive studies. In ear, nose and throat surgery, no clear conclusion could be made but paracetamol and NSAIDs seemed equivalent. In dental

Table 3 Paracetamol combined with NSAIDs *vs* NSAIDs in postoperative pain. *n* refers to the number of patients involved in the specific comparisons, not total number of patients in the study. Analgesic outcome results for paracetamol and NSAID *vs* NSAID: '↑ = greater effect' means that the combination was better than NSAID alone; '→ = same effect' means that the combination had the same effect as NSAID alone; '↓ = less effect' means that the combination was less effective than NSAID alone. Analgesic outcome results were quantified when possible (e.g. VAS scores, rescue medication, PCA). Ordinal scale measures cannot be used for quantitative comparisons. P = paracetamol; Supp = suppository

Author (quality score)	*n*	Type of surgery	Treatment groups	Administration	Treatment duration and timing	Outcome measures	Analgesic outcome: P + NSAID *vs* NSAID ↑ = greater effect → = same effect ↓ = less effect	Opioid requirement or analgesic remedication. P + NSAID *vs* NSAID	Adverse effects (significant differences)
Major surgery									
Montgomery *et al.*, 1996[17] (4)	59	Elective gynaecological surgery (abdominal)	1. P 1500 mg 2. Diclofenac 100 mg 3. P 1500 mg + diclofenac 100 mg	Supp	Single dose, pre-emptive	1. Pain at deep breathing (VAS) 2. Morphine usage (PCA)	→	→	Only morphine-related side-effects
Minor surgery									
Van Lancker *et al.*, 1999[14] (3)	74	Arthroscopy	1. Propacetamol 30 mg kg^{-1} 2. Tenoxicam 0.5 mg kg^{-1} 3. Propacetamol 30 mg kg^{-1} + tenoxicam 0.5 mg kg^{-1} 4. Placebo	i.v.	Single dose, pre-emptive	1. Pain intensity (VAS)	→ Active drug equal to placebo	→ Active drug equal to placebo	No difference
Fletcher *et al.*, 1997[24] (5)	45	Disc surgery	1. Propacetamol 2000 mg × 4 2. Ketoprofen 50 mg × 4 3. Ketoprofen 50 mg + propacetamol 2000 mg × 4 4. Placebo	i.v.	48 h, first dose at skin closure	1. Pain intensity at rest and mobilization (VAS) 2. Morphine usage (PCA)	↑ (at rest) ↑ (on movement) Active drug better than placebo	→	No difference
Breivik *et al.*, 1999[48] (5)	68	Dental	1. Diclofenac 100 mg 2. P 1000 mg 3. Diclofenac 100 mg + P 1000 mg	Oral	Single dose, postoperative	1. Pain intensity (VAS) 2. Pain relief (0–4) 3. Overall effect (1–4)	↑ Mean VAS (8 h): diclofenac 38 P + diclofenac 19	↑	No difference
Matthews *et al.*, 1984[54] (4)	18	Dental	1. Diclofenac sodium 50 mg × 2 2. Diclofenac sodium 50 mg × 2 + P 500 mg × 2 3. P 500 mg × 2 4. Placebo	Oral	Two doses, first dose immediately postoperative	1. Pain intensity (VAS)	→ P equal to placebo	→	None

surgery, NSAIDs seemed to be superior to paracetamol regarding pain scores and remedication requirements.

Thus, overall, NSAIDs seem to be superior to paracetamol in postoperative pain management, but the magnitude of the difference may depend on the type of surgery performed. In major surgery, the efficacies of NSAIDs and paracetamol seem to be comparable, whereas in minor surgery NSAIDs seem to be superior.

The combination of paracetamol and NSAID vs paracetamol alone

There was a total of eight studies, out of which seven could be included.[17 24 48 50–53] These involved 613 patients (Table 2). The last study failed to separate active drugs from placebo.[14] Each study involved a different surgical procedure, making comparisons difficult. In four of the studies,[24 48 50 52] the combinations of paracetamol with ASA, of paracetamol with ketoprofen 50 and 100 mg and of paracetamol with diclofenac were associated with lower pain scores than paracetamol alone. In the study of paracetamol and ketoprofen, the combination reduced pain scores both at rest and on movement after disc surgery compared with paracetamol alone.[24] In a study involving spinal fusion surgery,[52] the combination of propacetamol and ketoprofen 100 mg improved pain scores assessed by VAS pain intensity differences. Pain relief scores, on the other hand, were not significantly different between the two groups in this study. In two studies involving major gynaecological surgery,[17 53] there were no differences in pain scores and in one study[51] the pain scores were not measured.

In their assessment of opioid consumption, five out of the seven studies[17 24 48 51 52] reported significant reductions, ranging from 33–46%, when both drugs were used compared with paracetamol alone. However, in one of the studies these findings may have been exaggerated by the low dose of paracetamol and demographic differences between the study groups, as discussed above.[17] In the study involving spinal fusion surgery,[52] the combination of propacetamol and ketoprofen reduced consumption of morphine under patient-controlled analgesia (PCA). In only one of the seven studies was there no advantage in adding an NSAID to paracetamol.[53] This study compared high-dose rectal paracetamol (40 mg kg^{-1}) with diclofenac 100 mg added to paracetamol (20 mg kg^{-1}) and with paracetamol (20 mg kg^{-1}) alone. The lack of difference between a low dose of paracetamol (20 mg kg^{-1}) and its combination with a full dose of an NSAID may suggest low study sensitivity.

In summary, the addition of an NSAID to paracetamol seems to provide additional analgesic efficacy. However, whether this additional analgesic efficacy is a result of a true additive effect or a reflection of NSAIDs being more effective than paracetamol is not clear.

Paracetamol combined with NSAID vs NSAID alone

A total of five studies were found (Table 3), but only four of them, involving 190 patients, were included in our evaluation.[17 24 48 54] One study was excluded because of failure to separate active drugs from placebo.[14] In the most robust trial, the combination of propacetamol with ketoprofen 50 mg reduced pain scores at rest and on movement compared with ketoprofen alone after disc surgery, but there was no associated reduction in opioid requirement.[24] Oral diclofenac 100 mg combined with paracetamol 1000 mg reduced pain intensity scores, improved pain relief scores and reduced the need for rescue analgesia compared with diclofenac alone after dental surgery,[48] though this finding in part reflects the slow onset of an enteric-coated preparation. A dental surgery study[54] found no differences between the combination of diclofenac with paracetamol and diclofenac alone, but the doses of diclofenac and paracetamol were only 50 and 500 mg respectively. In the remaining study, which involved elective gynaecological surgery,[17] there were no significant differences between diclofenac alone and its combination with paracetamol in either pain scores or opioid requirement. However, this study[17] has weaknesses because of differences in age and body mass index, as discussed above.

In summary, the available data are sparse but two trials suggest that standard doses of paracetamol do enhance analgesic efficacy when added to NSAIDs compared with NSAIDs alone.

Adverse effects of paracetamol vs NSAID

Relatively few studies have compared the adverse effects of NSAIDs and paracetamol, especially in the postoperative period. An exhaustive review of adverse effects is beyond the scope of this article but some important data regarding major adverse effects are presented together with a number of less well-known facts.

Gastrointestinal

Ultrastructural damage to the gastric surface epithelium occurs within minutes after ingestion of NSAIDs and gross endoscopically detectable haemorrhages and erosions in the gastroduodenal epithelium occur within hours.[55] A review of short-term NSAID use concluded that there was no evidence of an increased risk of severe gastrointestinal complications during perioperative (<1 week) NSAID treatment.[56] However, patients with active or previous gastroduodenal ulcer were excluded from most of the studies reviewed, and the risk of severe complications from short-term use of NSAIDs cannot be excluded in these patients.[56] A study by Strom and colleagues,[57] including 10 272 patients, showed that ketorolac was associated with a small increased risk of gastrointestinal bleeding (odds ratio=1.17) when analgesic therapy lasted for 5 or fewer days. However, the risk was significantly greater and clinically important when ketorolac was used in higher

doses, in older patients and for more than 5 days.[57] A multicentre study of 875 cases of upper gastrointestinal bleeding, verified by endoscopy, suggested that any use of aspirin for more than a 7-day period increased the risk of bleeding by about seven times, and that diclofenac, indometacin, naproxen and piroxicam were associated with a risk similar to that of aspirin.[58] Paracetamol, propyphenazone and metamizole were not associated with this increased risk.

Allergic

NSAIDs may exacerbate asthma, especially in patients with aspirin-induced asthma.[59] Settipane and colleagues[60] determined the prevalence of cross-reactivity to high-dose paracetamol in 50 aspirin-sensitive asthmatic patients and in 20 non-aspirin-sensitive asthmatic control subjects. The study showed that non-aspirin sensitive asthmatic patients did not react to paracetamol, whereas in aspirin-sensitive patients 16 and 20% developed bronchospasm with paracetamol 1000 and 1500 mg respectively. The reactions were generally mild and easily reversed.

Hepatic

Overdose of paracetamol can occasionally lead to irreversible liver injury that can be lethal.[61] The single adult dose that must be ingested to produce severe liver damage is about 150–250 mg kg^{-1}, corresponding to a plasma concentration equal to or greater than 200 mg $litre^{-1}$.[62] Hepatotoxicity has been reported in chronic alcoholics after ingestion of therapeutic doses of paracetamol.[63] However, paracetamol did not induce adverse effects in the liver in 20 patients with chronic liver disease (six with alcoholic liver disease) who were studied over 2 weeks in a double-blind cross-over design in which the patients were given paracetamol 4000 mg day^{-1} or placebo.[64]

Very rare hepatic injury has been observed for nearly all NSAIDs currently on the market, but diclofenac, sulindac and aspirin may be more commonly associated with liver disease.[65]

Renal

Prostaglandins have little influence on renal blood flow (RBF) or glomerular filtration rate (GFR) in normal healthy individuals[66] but oppose the renal vasoconstriction induced by catecholamines, vasopressin and angiotensin in states such as hypovolaemia, congestive heart failure and cirrhosis with ascites.[67] These conditions also prevail in many postoperative patients, who may have major shifts in fluid compartments as well as activation of the neurohumoral stress response. A recent meta-analysis of the influence of NSAIDs on the postoperative renal function of 183 patients with normal preoperative renal function found significantly reduced sodium and potassium excretion and 21–28% reduction in creatinine clearance on day 1 compared with controls. No significant differences were present on day 2 other than a mean rise in serum creatinine of 15 μmol $litre^{-1}$.[68]

A retrospective cohort study[69] found no evidence of an increased incidence of renal failure among 10 000 patients receiving postoperative ketorolac even in the presence of established risk factors, unless therapy exceeded 5 days, when the risk doubled. These conflicting sources of information are difficult to reconcile, but suggest that the readily demonstrable biochemical and haemodynamic effects do not often progress to an adverse outcome. Paracetamol exerts weaker inhibition of peripheral prostaglandin synthesis than NSAIDs.[70,71] It does produce effects on sodium and water excretion comparable to those of NSAIDs,[71] but not on RBF and GFR,[71] even in the stressed kidney.[72]

Haematological

Most studies comparing the effects of NSAIDs and paracetamol on haemostasis have been performed in tonsillectomy patients. In two studies that involved a total of 1544 children treated with ASA 300–1000 mg or paracetamol 240–1000 mg, post-tonsillectomy haemorrhage was seen in 3.1–3.8% in the ASA group and 0.3–0.5% in the paracetamol group.[73,74] Two studies compared blood loss after preoperative administration of non-ASA NSAIDs (rectal diclofenac 0.65–1.0 mg kg^{-1} or i.v. ketorolac 1 mg kg^{-1}) and paracetamol. Both studies found significantly greater blood loss in patients receiving NSAIDs and significantly longer duration of surgery[33] or a greater number of patients requiring additional measures to obtain haemostasis compared with paracetamol.[31] Other prospective[75,76] and retrospective[77,78] studies have found increased postoperative bleeding in patients receiving perioperative ketorolac for tonsillectomy.

Miscellaneous

NSAIDs have significant inhibitory effects on heterotopic bone formation,[79] whereas the effects on fracture union are debatable.[80] However, similar studies on bone healing are not available for paracetamol.

Aspirin and ibuprofen have been shown to disrupt sleep compared with paracetamol and placebo. Thirty-seven male and female subjects had their sleep pattern recorded one night after ingestion of aspirin 650 mg, paracetamol 650 mg or ibuprofen 400 mg.[81] Aspirin and ibuprofen disrupted sleep by increasing the number of awakenings and the percentage of time spent in stage wake and by decreasing sleep efficiency. Paracetamol did not differ significantly from placebo on any measure of the recorded sleep pattern.

Correspondingly, the normal decrease in nocturnal body temperature was attenuated and melatonin synthesis suppressed after NSAID compared with placebo administration in 75 subjects.[82]

Diclofenac has been shown to alter the pharmacokinetics of active morphine metabolites in patients with postoperative pain.[83] Even though morphine consumption decreased by 20% after diclofenac was administered, the concentration of the active metabolite, morphine-6-glucur-

onide, was unchanged and a significant reduction in respiratory rate occurred.[83]

Discussion

Paracetamol was found to have analgesic efficacy comparable to that of NSAIDs in many of the studies reviewed, but overall, NSAIDs seem to be superior for postoperative pain management, although there seem to be differences in the efficacies of paracetamol and NSAIDs depending on the type of surgery performed. In major and orthopaedic surgery, the efficacies of NSAIDs and paracetamol seem to be comparable and in dental surgery NSAIDs seem superior.

Paracetamol and NSAIDs (ibuprofen and diclofenac) have been assessed compared with placebo in recent Cochrane systematic reviews.[1 2] Paracetamol 1000 mg had an NNT of 4.6 compared with placebo, ibuprofen 400 mg had an NNT of 2.7 and diclofenac 50 mg an NNT of 2.3.[1 2] In these Cochrane reviews, the NNT differences between paracetamol and NSAIDs were calculated from placebo-controlled studies in which dental studies constituted the majority. However, we cannot be certain whether these findings reflect inherent differences in efficacy between the drugs or differences in the sensitivity of the surgical models to NSAIDs and paracetamol. The NNT values may be misleading in the setting of moderate to major surgery, but the limited number of comparative studies in major surgery precludes final conclusions.

The opioid-sparing effect of NSAIDs has often been used as an analgesic efficacy parameter. However, recent studies have suggested that NSAIDs may reduce morphine requirements by reducing the excretion of the active metabolite, morphine-6-glucuronide. Morphine sparing cannot, therefore, be assumed to result in parallel reductions in opioid-related adverse effects. Fentanyl sparing may be a more appropriate surrogate end-point for future NSAID studies as this drug has minimal renal excretion and inactive metabolites.

The addition of NSAIDs to paracetamol may confer additional analgesic efficacy compared with paracetamol alone. Given the conclusion of the direct comparative studies—that NSAIDs may be more effective than paracetamol—the key question is whether the addition of paracetamol to an NSAID will be worthwhile in patients able to take either medication. Even though few robust data are available, standard doses of paracetamol may enhance analgesic efficacy when added to NSAIDs, compared with NSAIDs alone (two trials). Further evidence of this is seen in non-surgical studies of patients with rheumatoid arthritis, in whom indometacin (150 mg day^{-1}) alone and the combination of indometacin (50 mg day^{-1}) with paracetamol (4 g day^{-1}) had the same analgesic effect, but the combination had fewer and milder side-effects.[84] In two other studies, treatment with a combination of naproxen with paracetamol had a greater analgesic effect than treatment with higher naproxen doses alone.[85 86] A review[87] concerning paracetamol in rheumatoid arthritis suggests that there is increasing evidence that combined paracetamol and NSAID treatment is more effective than treatment with NSAIDs alone. The findings that the combination appears to be more effective than either drug alone may support the suggestion that NSAIDs are not greatly superior to paracetamol.

A formal quantitative review (meta-analysis) was not performed as too many studies of high scientific standard would have had to be discarded if we had used the method introduced by McQuay and Moore to convert different pain scales to a common denominator and thereby make them comparable.[88] The key problem for many quantitative reviews is that a large number of papers must be discarded if they do not use standard scales of pain assessment, use analgesic drug consumption (e.g. PCA), employ pre-emptive techniques or involve local anaesthetic blocks. The next problem may be that the remaining trials are not representative.[89] Of the valid studies in this review, 27 out of 41 (including all major surgery studies) would have had to be discarded if a quantitative review were to have been performed. There are also problems concerning qualitative reviews, as the simple vote-counting method may mislead. It ignores the sample size of the constituent studies, the magnitude of the effect in the studies and the validity of their design even when randomized.[90] Inadequate or unclear randomization can overestimate the treatment effect by 30–41% and non-double-blind conditions can overestimate it by 17%.[6] However, quality scores of the studies in this review had a median value of 4 on a scale of 1–5 and there were no differences in quality scores between studies showing a difference in analgesic effect and those that did not show such a difference.

A further perennial challenge for analgesic studies is the multidimensional and mutually opposed nature of the assessments: as pain improves patients are less likely to request analgesia, yet we seek statistically significant differences in one of these dimensions without attempting to anchor the other. Thus, in the study of Owen and colleagues,[21] for example, the difference in pain scores between ibuprofen and paracetamol almost achieved statistical significance in favour of the NSAID (P=0.057) despite 50% lower opioid consumption in these patients, but as conventional levels of significance were not reached in either measure and as there was no placebo control this study was considered to represent weak evidence of equality. Had the opioid administration been fixed in both groups, one might surmise that there would have been a significant difference in pain scores, and thus strong evidence for the superiority of NSAIDs. Despite these problems, we consider that the comparison of paracetamol with NSAID in postoperative pain management is important, especially as the side-effects of these compounds are so different.

The very low apparent risk of paracetamol therapy suggests a highly favourable risk:benefit ratio, which might justify a role for paracetamol as a near-routine postoperative background analgesic. Where the additional analgesic effect of an NSAID is particularly sought, as after relatively minor or ambulatory surgery and when the perceived risks from NSAIDs are low, NSAIDs may be preferred as background analgesic.

There were bioavailability problems, especially in the major surgery and paediatric studies, as paracetamol was administered rectally, making the analgesic effect unpredictable compared with the oral or i.v. route. The pharmacokinetics of paracetamol has been reviewed recently, and the bioavailability of paracetamol given by the rectal route ranged from 24–98%.[3] Serum and saliva concentrations after high-dose rectal and oral paracetamol were studied in postoperative adult patients,[91] and it was concluded that administering paracetamol 2000 mg rectally resulted in serum and saliva concentrations during the first 4 h that never exceeded the minimum effective antipyretic serum concentration.

In conclusion, the existing direct comparative studies show that NSAIDs are more effective than paracetamol in some situations, e.g. dental surgery, but the differences are less obvious after other types of surgery. In many studies, paracetamol was given in insufficient doses or administered rectally, potentially underestimating the efficacy, whereas the reduction in morphine requirements may overestimate the inherent analgesic efficacy of the NSAIDs. Paracetamol is definitely a viable alternative to the NSAIDs, especially because of the lower incidence of adverse effects, and should be the preferred choice in high-risk patients. In the absence of firm data, paracetamol should also be considered instead of NSAIDs for pain management after major or orthopaedic surgery, as few differences in efficacies were found in existing data. After tonsillectomy, paracetamol is also recommended because of less bleeding. It may be appropriate to combine paracetamol with NSAIDs, but future studies are required, especially after major surgery. In such studies, there should also be a specific focus on a potential increase in side-effects from their combined use.

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