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Combining Paracetamol (Acetaminophen) with Nonsteroidal Antiinflammatory Drugs: A Qualitative Systematic Review of Analgesic Efficacy for Acute Postoperative Pain

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BACKGROUND: There has been a trend over recent years for combining a nonsteroidal antiinflammatory drug (NSAID) with paracetamol (acetaminophen) for pain management. However, therapeutic superiority of the combination of paracetamol and an NSAID over either drug alone remains controversial. We evaluated the efficacy of the combination of paracetamol and an NSAID versus either drug alone in various acute pain models.

METHODS: A systematic literature search of Medline, Embase, Cumulative Index to Nursing and Allied Health Literature, and PubMed covering the period from January 1988 to June 2009 was performed to identify randomized controlled trials in humans that specifically compared combinations of paracetamol with various NSAIDs versus at least 1 of these constituent drugs. Identified studies were stratified into 2 groups: paracetamol/NSAID combinations versus paracetamol or NSAIDs. We analyzed pain intensity scores and supplemental analgesic requirements as primary outcome measures. In addition, each study was graded for quality using a validated scale.

RESULTS: Twenty-one human studies enrolling 1909 patients were analyzed. The NSAIDs used were ibuprofen ($n = 6$), diclofenac ($n = 8$), ketoprofen ($n = 3$), ketorolac ($n = 1$), aspirin ($n = 1$), tenoxicam ($n = 1$), and rofecoxib ($n = 1$). The combination of paracetamol and NSAID was more effective than paracetamol or NSAID alone in 85% and 64% of relevant studies, respectively. The pain intensity and analgesic supplementation was 35.0% ± 10.9% and 38.8% ± 13.1% lesser, respectively, in the positive studies for the combination versus paracetamol group, and 37.7% ± 26.6% and 31.3% ± 13.4% lesser, respectively, in the positive studies for the combination versus the NSAID group. No statistical difference in median quality scores was found between experimental groups.

CONCLUSION: Current evidence suggests that a combination of paracetamol and an NSAID may offer superior analgesia compared with either drug alone. (Anesth Analg 2010;110:1170–9)

Different classes of analgesics exert their effects through different mechanisms. Their side effects (e.g., respiratory depression with opioids or enteropathy with nonsteroidal antiinflammatory drugs [NSAIDs]) tend to be different and may be dose related. A combination of analgesics from different classes may provide additive analgesic effects with fewer side effects than when a single therapeutic drug is used. There has been a trend over recent years for combining NSAIDs with paracetamol (acetaminophen) for the management of acute postoperative pain,[1,2] but the therapeutic superiority of the combination over either drug alone remains controversial.[3,4] In 2002, Hyllested et al.[5] noted that paracetamol/NSAID combinations showed superior pain relief over paracetamol alone in 5 of 7 studies, but over an NSAID alone in only 2 of 4 studies, whereas Rømsing et al.[2] noted an advantage for such combinations over paracetamol alone in 6 of 9 studies but over an NSAID alone in only 2 of 6 studies. These authors noted that relevant studies were sparse. We have updated these reviews to include randomized controlled trials (RCTs) published since then with the aim of evaluating whether paracetamol/NSAID combinations provide superior efficacy in the treatment of acute postoperative pain to either drug alone.

EVIDENCE IN HUMAN CLINICAL STUDIES FOR THE USE OF PARACETAMOL/NSAID COMBINATIONS

We aimed to determine whether paracetamol/NSAID combinations provide superior efficacy in the treatment of acute postoperative pain to either drug alone.

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METHODS

A broad free-text search restricted to RCTs in English was undertaken in Medline, Embase, Cumulative Index to Nursing and Allied Health Literature, and PubMed, from January 1988 to June 2009. The full reports were retrieved for double-blind RCTs comparing paracetamol/NSAID combinations with 1 or both of their constituent drugs for pain relief. Variants of the search terms including "paracetamol/NSAIDs combination," "acetaminophen," "combination analgesics," "acute postoperative pain," and "ibuprofen/paracetamol" or individual drug names were entered as major subject headings. Reference lists of retrieved publications were checked for additional trials.

Exclusion criteria were (1) comparison of a paracetamol/NSAID combination with analgesics other than paracetamol or NSAIDs, (2) other pain models, e.g., chronic pain, and (3) retrospective, nonrandomized, or nonblinded trials. The retrieved reports were stratified according to the NSAID in the combination, the mode of administration (oral, IM, IV, rectal), and the surgical procedures studied.

Where possible, data on the following outcome measures were extracted from the retrieved publications in the form of mean/median and assessed for reported differences between the combination and constituent drug groups:

1. Pain intensity in the form of pain scores, e.g., postoperative visual analog scale (VAS) scores.
2. Supplemental postoperative analgesic requirements, e.g., opioid consumption.

In cases in which results of trials were reported only in graphical form, the means and SDs were estimated from these graphs. The difference in analgesic response among the study groups, i.e., % difference in pain intensity and % difference in analgesic supplementation, was extracted from the studies or calculated from the studies whenever possible. The mean/SD of the difference in analgesic response of all the positive studies was calculated.

Each study was graded for quality, using the validated scale of Jadad et al.,[6] on the extent to which its design, data collection, and statistical analysis minimized or avoided bias as follows:

1. Randomization: If the reports were described as randomized, 1 point was given. An additional point was given if the method of randomization was described and adequate (e.g., using computer-generated or table of random numbers). One point was deducted if the method of randomization was inappropriate (e.g., randomization according to age or birthdays).
2. Blinding: If the reports were described as double blind, 1 point was given. An additional point was given if the method of blinding was described and appropriate (e.g., use of double dummy). One point was deducted if the method of blinding was inappropriate.
3. Patients' withdrawals: If the reports described the numbers and reasons for withdrawals, 1 point was given.

The possible range for these scores in the included studies was 2 to 5. A Mann-Whitney *U* test was used to assess the relationships between the positive and negative trials and the quality scores. Subgroup analyses were performed for the combination versus paracetamol and combination versus NSAID by surgical model and by NSAID.

Statistical heterogeneity across the studies was evaluated both qualitatively and quantitatively using the funnel plot and Cochran *Q* test, respectively. The computer software package, SPSS for Windows (SPSS, Chicago, IL), and Comprehensive Meta-Analysis™ (Biostat, Englewood, NJ) were used.

RESULTS

Thirty-two studies that evaluated paracetamol/NSAID combinations were found.[7–38] Eleven were excluded because of inadequate randomization, nonblinding, or comparison of the combinations with different classes of analgesics or studies in chronic pain.[7–17] Twenty-one RCTs in acute postoperative pain models with a total of 1909 patients were included for further analysis.[18–38]

Studies comparing paracetamol/NSAID combinations with paracetamol alone are summarized in Table 1, and those comparing paracetamol/NSAID combinations with NSAIDs alone are summarized in Table 2.

The evaluated NSAIDs were ibuprofen (n = 6),[21,23,27,30,33,38] diclofenac (n = 8),[19,20,26,29,31,32,34,36] ketoprofen (n = 3),[18,22,25] ketorolac (n = 1),[28] aspirin (n = 1),[35] tenoxicam (n = 1),[37] and rofecoxib (n = 1).[24] The models studied were dental surgery (n = 6)[20,23,24,27,29,30]; orthopedic surgery (n = 5)[18,21,22,25,37]; gynecological/inguinal surgery (n = 6)[19,31,32,34–36]; and ear, nose, and throat (ENT) surgery (n = 4).[26,28,33,38] Of these, 13 compared the effect of the combination with both an NSAID and paracetamol[20–22,24–26,29,31,32,34,36–38]; 20 compared the combination with paracetamol alone[18–29,31–38] (Table 1); and 14 compared the combination with an NSAID alone (Table 2).[20–22,24–26,29–32,34,36–38]

Results for Studies of a Combination Versus Paracetamol Alone

Twenty studies involving 1852 patients compared the efficacy of an analgesic combination with paracetamol alone (Table 1). Overall, 17 of these 20 studies (85%) showed that the combination was more effective than paracetamol alone in terms of lower pain scores, lower supplemental analgesic requirements, or better globally assessed pain relief (positive studies). For surgical model subgroup analysis, the ENT model had positive results for all 4 studies (100%)[26,28,33,38]; the dental model had 4 of 5 positive studies (80%)[20,23,24,27,29]; the orthopedic model had 4 of 5 positive studies (80%)[18,21,22,25,37]; and the gynecological/inguinal model had 5 of 6 positive studies (83%).[19,31,32,34–36] For NSAID subgroup analysis, all 5 ibuprofen studies showed consistently positive results (100%)[21,23,27,30,33,38]; the diclofenac studies had 6 of 8 positive results (75%)[19,20,26,29,31,32,34,36]; the 3 ketoprofen studies all showed positive results (100%)[18,22,25]; and the single rofecoxib, ketorolac, and aspirin studies each showed positive results.[24,28,35] However, the single tenoxicam combination study showed no difference in analgesic efficacy compared with paracetamol alone.[37]

Overall, mean (SD) reduction in pain intensity was 35.0% (10.9%); the reduction in analgesic supplementation was 38.8% (13.1%). The quality scores of the studies ranged from 2 to 5. The median quality score was 4 for the positive

Table 1. Studies of Paracetamol/Nonsteroidal Antiinflammatory Drugs (NSAID) Combinations Versus Paracetamol Alone

Reference, quality score, study outcome	Sample size	Treatment groups	Type of surgery	Outcome measures and analgesic results for combination/% difference in the improvement of outcome measures	Adverse events (significant difference between groups)
Aubrun et al.,[18] Score 3, +ve study	50	1. Propacetamol 2000 mg 2. Ketoprofen 100 mg + propacetamol 2000 mg Propacetamol 6 hourly, ketoprofen 8 hourly given for 24 h after surgery	Orthopedic surgery—spinal fusion surgery	1. Pain intensity (VAS): +ve 2. Pain relief (VAS): −ve 3. Morphine usage (PCA): +ve Pain intensity was 22% lesser Morphine usage was 33% lesser	No difference Nausea and vomiting: 28%–32% Drowsiness: 48%–52%
Beck et al.,[19] Score 3, −ve study	65	1. Paracetamol 20 mg/kg 2. Paracetamol 40 mg/kg 3. Diclofenac 100 mg + paracetamol 20 mg/kg Single rectal dose with 24 h observation period after surgery	Gynecological surgery—vaginal or abdominal hysterectomy	1. Pain scores (VAS): −ve 2. Morphine usage (PCA): −ve No difference in the outcome measures	Nausea and vomiting: 13%–22% Only morphine related adverse effects: more in group 1 which required more morphine
Breivik et al.,[20] Score 5, +ve study	68	1. Diclofenac 100 mg 2. Paracetamol 1000 mg 3. Diclofenac 100 mg + paracetamol 1000 mg Single rectal dose with 8 h observation period after surgery	Dental surgery—impacted third molar surgery	1. Pain intensity (VAS): +ve 2. Pain relief score: +ve 3. Global assessment: +ve Pain intensity was 41% lesser	No difference Nausea and drowsiness: 25%–33%
Dahl et al.,[21] Score 5, +ve study	61	1. Ibuprofen 800 mg 2. Paracetamol 1000 mg 3. Ibuprofen 800 mg + paracetamol 1000 mg All drugs were given orally 1 h before surgery and again at 6 and 12 h after initial dose	Orthopedic surgery—anterior cruciate ligament reconstruction	1. Pain scores (VAS): +ve 2. Supplemental analgesic requirements: +ve Pain intensity was 35% lesser Analgesic requirements was 68% lesser	No difference Nausea and vomiting: 11%
Fletcher et al.,[22] Score 5, +ve study	45	1. Propacetamol 2000 mg 2. Ketoprofen 50 mg 3. Ketoprofen 50 mg + propacetamol 2000 mg 4. Placebo All drugs were given IV 6 hourly for 2 days after the surgery	Orthopedic surgery—disk surgery	1. Pain intensity (VAS): +ve 2. Morphine usage (PCA): +ve Pain intensity was 55% lesser Morphine usage was 56% lesser	No difference Nausea and vomiting: 14%–27% Drowsiness: 7%–27% Urinary retention: 14%–27%
Gazal et al.,[23] Score 5, +ve study	201	1. Ibuprofen (5 mg/kg) + paracetamol (15 mg/kg) 2. Paracetamol (20 mg/kg) 3. Paracetamol (15 mg/kg) Single oral dose given 1 h before the surgery	Dental surgery—extractions in children	1. Pain intensity (children's hospital of eastern Ontario pain scale): +ve 2. 5 point face scale for distress: +ve Pain intensity was 20% lesser	No adverse effects were reported
Haglund et al.,[24] Score 5, +ve study	120	1. Rofecoxib 50 mg + paracetamol 1000 mg 2. Rofecoxib 50 mg 3. Paracetamol 1000 mg 4. Placebo Single oral dose with 8 h observation period after surgery	Dental surgery—impacted third molar surgery	1. Pain intensity (VAS): +ve 2. Global assessment for pain relief: +ve 3. % patients using rescue medication: +ve Pain intensity was 20% lesser % of patients using rescue medication was 31% lesser	No difference Headache: 3%–12% Drowsiness: 3%–10% Fatigue: 11%–12%
Hiller et al.,[25] Score 5, +ve study	120	1. Paracetamol 60 mg/kg rectally and 40 mg/kg orally 2. Ketoprofen 2 mg IV twice 3. Paracetamol + ketoprofen as above One dose given after G.A. induction and second dose 8 h later	Orthopedic surgery—elective pediatric orthopedic procedures	1. Objective Pain Scale (OPS): +ve 2. Morphine usage: +ve 3. Time to first morphine request: +ve Pain intensity was 34% lesser Morphine usage was 36% lesser Time to first morphine was 54% longer	No difference Nausea: 42%–56% Vomiting: 47–63% Urinary retention: 8%
Hiller et al.,[26] Score 3, +ve study	71	1. Propacetamol 2 g 2. Diclofenac 75 mg 3. Propacetamol 2 g + diclofenac 75 mg Single IV dose started after general anesthetic induction	ENT—tonsillectomy in adults	1. Pain intensity (VAS): −ve 2. PCA oxycodone: +ve No difference in pain intensity PCA oxycodone was 29% lesser	No difference Nausea: 33%–52% Vomiting: 16%–32% Headache: 24%–32%

(*Continued*)

Table 1. (*Continued*)

Reference, quality score, study outcome	Sample size	Treatment groups	Type of surgery	Outcome measures and analgesic results for combination/% difference in the improvement of outcome measures	Adverse events (significant difference between groups)
Ianiro et al.,[27] Score 4, +ve study	40	1. Paracetamol 1000 mg 2. Paracetamol 1000 mg + ibuprofen 600 mg 3. Placebo Single oral dose 30 min before procedure	Dental surgery—dental root canal treatment	1. Pain sensitivity from cold test or surgical drilling of tooth: +ve No pain intensity or analgesic consumption outcomes used Data cannot be used for statistical calculation	No adverse effects were reported
Mather et al.,[28] Score 2, +ve study	80	1. Paracetamol 20 mg/kg 2. Placebo + morphine 0.1 mg/kg 3. Paracetamol 20 mg/kg + ketorolac 0.5 mg/kg Single dose as premedication and 24 h after surgery. Paracetamol was given orally and ketorolac was given intramuscularly	ENT—tonsillectomy	Supplemental morphine usage: +ve Supplemental morphine usage was 21% lesser	No difference between the paracetamol and combination group Greater incidence of vomiting in morphine group, i.e., group 2 Vomiting: 15%–52%
Matthews et al.,[29] Score 4, −ve study	28	1. Diclofenac 50 mg 2. Diclofenac 50 mg + paracetamol 500 mg 3. Paracetamol 500 mg Single oral dose before surgery with 12 h observation period after surgery	Dental surgery—impacted third molar surgery	Pain intensity (VAS): −ve No difference in the outcome measure	No adverse effects were reported
Montgomery et al.,[31] Score 4, +ve study	59	1. Paracetamol 1500 mg 2. Diclofenac 100 mg 3. Paracetamol 1500 mg + diclofenac 100 mg Single rectal dose given before surgery with 24 h observation after the surgery	Elective gynecological surgery	1. Pain intensity (VAS): +ve 2. PCA morphine usage: +ve Pain intensity was 40% lesser Morphine usage was 38% lesser	Higher nausea and vomiting scores for group 1 because of more morphine usage Nausea: 5%–13% Vomiting: 26%–40%
Munishankar et al.,[32] Score 4, +ve study	78	1. Paracetamol 1000 mg 2. Diclofenac 100 mg 3. Paracetamol 1000 mg + diclofenac 100 mg First dose was given immediately after surgery. Paracetamol was given 6 hourly and diclofenac 8 hourly for 24 h after first dose	Gynecological surgery—cesarean section	1. Pain intensity (VAS): −ve 2. PCA morphine: +ve No difference in the pain intensity Morphine usage was 38% lesser	No difference Nausea and vomiting: 27%–42%
Pickering et al.,[33] Score 3, +ve study	98	1. Paracetamol 20 mg/kg + rofecoxib 0.625 mg/kg 2. Paracetamol 20 mg/kg + ibuprofen 5 mg/kg 3. Paracetamol 20 mg/kg + placebo All drugs were given orally 1 h before surgery. Then only paracetamol was given 4 hourly for 8 h after surgery	ENT—pediatric tonsillectomy	1. Pain intensity (VAS) 2. Need for supplemental analgesic +ve for paracetamol + ibuprofen group in VAS and analgesic requirements −ve for paracetamol + rofecoxib group in VAS and analgesic requirements Pain intensity was 33% lesser at time of administration of supplemental analgesia % of patients using rescue medication was 34% lesser	No difference in vomiting or antiemetic use Vomiting: 22%–33%
Riad et al.,[34] Score 5, +ve study	108	1. Diclofenac 1 mg/kg 2. Paracetamol 40 mg/kg 3. Diclofenac 1 mg/kg + paracetamol 40 mg/kg All drugs were given rectally 1 h before surgery	Inguinal hernia surgery in children	1. Wong and Baker scale (FACES) Pain Rating Scale: +ve 2. Supplemental morphine requirements: +ve Pain intensity was 33% lesser Morphine usage was 47% lesser	Time to discharge from recovery room significantly longer for paracetamol group

(*Continued*)

Table 1. (*Continued*)

Reference, quality score, study outcome	Sample size	Treatment groups	Type of surgery	Outcome measures and analgesic results for combination/% difference in the improvement of outcome measures	Adverse events (significant difference between groups)
Rubin et al.,[35] Score 4, +ve study	246	1. Paracetamol 648 mg and acetylsalicylic acid 648 mg 2. Acetylsalicylic acid 800 mg and caffeine 65 mg 3. Paracetamol 1000 mg 4. Placebo single oral dose	Gynecological surgery—episiotomy	1. Pain intensity (0–4 scale)-+ve 2. Remedication: −ve Pain intensity was 50% lesser No difference in the requirement for remedication	No difference Nausea and drowsiness reported as 4%–9%
Siddik et al.,[36] Score 3, +ve study	80	1. Placebo 2. Diclofenac 100 mg rectally 3. Propacetamol 2 g IV 4. Propacetamol 2 g + diclofenac 100 mg as above Paracetamol was given IV 6 hourly and diclofenac rectally 8 hourly for 24 h after surgery	Gynecological surgery—caesarean section	1. Pain intensity (VAS): +ve 2. PCA morphine: +ve Pain intensity was 37% lesser Morphine usage was 49% lesser	No difference Nausea and vomiting: 10%–16% Drowsiness: 5% Purities: 20%–30%
Van Lancker et al.,[37] Score 3, −ve study	74	1. Propacetamol 30 mg/kg 2. Tenoxicam 0.5 mg/kg 3. Propacetamol 30 mg/kg + tenoxicam 0.5 mg/kg 4. Placebo All drugs were given IV 1 h before the surgery, then only proparacetamol was repeated after 6 h with observation period of 24 h after surgery	Orthopedic surgery—arthroscopy	1. Pain intensity (VAS): −ve No difference in pain intensity	No difference Nausea and vomiting: 4%–8% Headache: 4%–12% Drowsiness: 4%
Viitanen et al.,[38] Score 4, +ve study	160	1. Paracetamol 40 mg/kg 2. Ibuprofen 15 mg/kg 3. Paracetamol 40 mg/kg + ibuprofen 15 mg/kg 4. Placebo Single rectal dose	ENT—pediatric tonsillectomy	Supplemental analgesic requirements during first 24 h and after discharge: +ve Supplemental analgesic requirements was 25% lesser after discharge	Vomiting: 24%–32% Drowsiness: 5% Abdominal pain: 3%–10% Paracetamol group was drowsier than other groups
Total	1852				

Study outcome: "+ve" means that the combination was superior to paracetamol alone. "−ve" means that the combination was not superior to paracetamol alone.
VAS = visual analog scale; PCA = patient-controlled analgesia; ENT = ear-nose-throat.

studies and 3 for the negative studies (Mann-Whitney *U* test: $P = 0.18$).

Figure 1 is a funnel plot of the included studies for the treatment effect against a measure of study size. The asymmetric funnel suggests the possibility of a systematic difference between smaller and larger studies or systematic heterogeneity. In addition, a test of statistical heterogeneity yielded a highly significant result (Q value = 38.4, $df(Q) = 18$, $P = 0.003$), giving substantial evidence of statistical heterogeneity. The results of these heterogeneity tests further add legitimacy for the appropriateness of a qualitative over quantitative systematic review for these studies.

Results for Studies of a Combination Versus NSAIDs Alone

Fourteen studies involving 1129 patients compared the efficacy of an analgesic combination with an NSAID alone (Table 2). Overall, 9 of these 14 studies (64%) showed that the combination was more effective than an NSAID alone in terms of lower pain scores, lower supplemental analgesic requirements, or better globally assessed pain relief for the combination group. For surgical model subgroup analysis, the ENT model showed positive results for both studies (100%)[26,38]; the dental model had 3 of 4 positive studies (75%)[20,24,29,30]; the orthopedic model had 2 of 4 positive studies (50%)[21,22,25,37]; and the gynecological model had 2 of 4 positive studies (50%).[31,32,34,36] For the NSAID subgroup analysis, the ibuprofen studies had 2 of 3 positive results (67%)[21,30,38]; the diclofenac studies had 4 of 7 positive results (57%)[20,26,29,31,32,34,36]; both the ketoprofen studies had positive results (100%)[22,25]; and the single rofecoxib combination study showed positive results.[24] However, the single tenoxicam combination study showed no difference in analgesic efficacy compared with an NSAID alone.[37]

Overall, the mean (SD) reduction in pain intensity was 37.7% (26.6%); the reduction in analgesic supplementation was 31.3% (13.4%). The quality scores for the studies ranged from 3 to 5. The median value for the positive studies was 5 and 4 for the negative studies (Mann-Whitney *U* test: $P = 0.39$).

Figure 2 is a funnel plot of the included studies for the treatment effect against a measure of study size. Once again, the asymmetric funnel suggests the presence of systematic heterogeneity. In addition, a test of statistical heterogeneity yielded a highly significant result (Q value = 35.4, $df(Q) = 13$, $P = 0.002$), giving substantial evidence of statistical heterogeneity.

Table 2. Studies of Paracetamol/Nonsteroidal Antiinflammatory drugs (NSAID) Combinations Versus NSAIDs Alone

Reference, quality score, study outcome	Sample size	Treatment groups	Type of surgery	Outcome measures and analgesic results for combination/% difference in the improvement of outcome measures	Adverse events (significant difference)
Breivik et al.,[20] Score 5, +ve study	68	1. Diclofenac 100 mg 2. Paracetamol 1000 mg 3. Diclofenac 100 mg + paracetamol 1000 mg Single oral dose with 8 h observation period after surgery	Dental surgery—impacted third molar surgery	1. Pain intensity (VAS): +ve 2. Pain relief score: +ve 3. Global assessment: +ve Pain intensity was 50% lesser	No difference Nausea and drowsiness: 25%–33%
Dahl et al.,[21] Score 5, −ve study	61	1. Ibuprofen 800 mg 2. Paracetamol 1000 mg 3. Ibuprofen 800 mg + paracetamol 1000 mg All drugs were given orally 1 h before surgery and again at 6 and 12 h after initial dose	Orthopedic surgery—anterior cruciate ligament reconstruction	1. Pain scores (VAS): −ve 2. Supplemental analgesic requirements: −ve No difference in the outcome measures	No difference Nausea and vomiting: 11%
Fletcher et al.,[22] Score 5, +ve study	45	1. Propacetamol 2000 mg 2. Ketoprofen 50 mg 3. Ketoprofen 50 mg + propacetamol 2000 mg 4. Placebo All drugs were given IV 6 hourly for 2 days after the surgery	Orthopedic surgery—disk surgery	1. Pain intensity (VAS): +ve 2. Morphine usage (PCA): +ve Pain intensity was 40% lesser Morphine usage was 56% lesser	No difference Nausea and vomiting: 14%–27% Drowsiness: 7%–27% Urinary retention: 14%–27%
Haglund et al.,[24] Score 5, +ve study	120	1. Rofecoxib 50 mg + paracetamol 1000 mg 2. Rofecoxib 50 mg 3. Paracetamol 1000 mg 4. Placebo Single oral dose with 8 h observation period after surgery	Dental surgery—impacted third molar surgery	1. Pain intensity (VAS): +ve 2. Global assessment for pain relief: +ve 3. % patients using rescue medication: +ve Pain intensity was 13% lesser % of patients using rescue medication was 23% lesser	No difference Headache: 3%–12% Drowsiness: 3%–10% Fatigue: 11%–12%
Hiller et al.,[25] Score 5, +ve study	120	1. Paracetamol 60 mg/kg rectally and 40 mg/kg orally 2. Ketoprofen 2 mg IV twice 3. Paracetamol + ketoprofen as above One dose given after GA induction and second dose 8 h later	Orthopedic surgery—elective pediatric orthopedic procedures	1. Objective Pain Scale (OPS): +ve 2. Morphine usage: +ve 3. Time to first morphine request: +ve Pain intensity was 31% lesser Morphine usage was 26% lesser Time to first morphine was 33% longer	No difference Nausea: 42%–56% Vomiting: 47%–63% Urinary retention: 8%
Hiller et al.,[26] Score 3, +ve study	71	1. Propacetamol 2 g 2. Diclofenac 75 mg 3. Propacetamol 2 g + diclofenac 75 mg All drugs were IV single dose	ENT—tonsillectomy in adults	1. Pain intensity (VAS): −ve 2. PCA oxycodone: +ve No difference in pain intensity PCA oxycodone was 14% lesser	No difference Nausea: 33%–52% Vomiting: 16%–32% Headache: 24%–32%
Matthews et al.,[29] Score 4, −ve study	28	1. Diclofenac 50 mg 2. Diclofenac 50 mg + paracetamol 500 mg 3. Paracetamol 500 mg Single oral dose before surgery	Dental surgery—impacted third molar surgery	Pain intensity (VAS): −ve No difference in pain intensity	No adverse effects were reported
Menhinick et al.,[30] Score 4, +ve study	57	1. Placebo 2. Ibuprofen 600 mg 3. Ibuprofen 600 mg + paracetamol 1000 mg All drugs were administered after dental surgery Single oral dose with 8 h observation period after surgery	Dental surgery—impacted third molar surgery	1. Pain intensity (VAS) and categorical pain scale: +ve 2. Pain relief for 8 h postoperatively: +ve Pain intensity was 82% lesser	No difference Nausea: 5%–21% Headache: 28%–53%
Montgomery et al.,[31] Score 4, −ve study	59	1. Paracetamol 1500 mg 2. Diclofenac 100 mg 3. Paracetamol 1500 mg + diclofenac 100 mg Single rectal dose given before surgery with 24 h observation after the surgery	Elective gynecological surgery	1. Pain intensity (VAS): −ve 2. PCA morphine usage: −ve No difference in the outcome measures	Nausea: 5%–13% Vomiting: 26%–40% Significantly higher nausea and vomiting scores for group 1

(*Continued*)

Table 2. (*Continued*)

Reference, quality score, study outcome	Sample size	Treatment groups	Type of surgery	Outcome measures and analgesic results for combination/% difference in the improvement of outcome measures	Adverse events (significant difference)
Munishankar et al.,[32] Score 4, −ve study	78	1. Paracetamol 1000 mg 2. Diclofenac 100 mg 3. Paracetamol 1000 mg + diclofenac 100 mg Paracetamol was given 6 h and diclofenac 8 hourly for 24 h after first dose	Gynecological surgery—caesarean section	1. Pain intensity (VAS): −ve 2. PCA morphine: −ve No difference in the outcome measures	No difference Nausea and vomiting: 27%–42%
Riad et al.,[34] Score 5, +ve study	108	1. Diclofenac 1 mg/kg 2. Paracetamol 40 mg/kg 3. Diclofenac 1 mg/kg + paracetamol 40 mg/kg All drugs were given rectally 1 h before surgery	Inguinal hernia surgery in children	1. Wong and Baker scale (FACES) Pain Rating Scale: +ve 2. Supplemental morphine requirements: +ve Morphine usage was 35% lesser	No adverse effects were reported Time to discharge from recovery room significantly longer for paracetamol group
Siddik et al.,[36] Score 3, +ve study	80	1. Placebo 2. Diclofenac 100 mg rectally 3. Propacetamol 2 g IV 4. Propacetamol 2 g + diclofenac 100 mg as above Paracetamol given IV 6 h and diclofenac rectally 8 hourly for 24 h after surgery	Gynecological surgery—caesarean section	1. Pain intensity (VAS): −ve 2. PCA morphine: +ve No difference in the pain intensity Morphine usage was 38% lesser	No difference Nausea and vomiting: 10%–16% Drowsiness: 5% Purities: 20%–30%
Van Lancker et al.,[37] Score 3, −ve study	74	1. Propacetamol 30 mg/ kg 2. Tenoxicam 0.5 mg/kg 3. Propacetamol 30 mg kg + tenoxicam 0.5 mg/kg 4. Placebo All drugs were given IV 1 h before the surgery, then only proparacetamol was repeated after 6 h with observation period of 24 h after surgery	Orthopedic surgery—arthroscopy	1. Pain intensity (VAS): −ve No difference in pain intensity	No difference Nausea and vomiting: 4%–8% Headache: 4%–12% Drowsiness: 4%
Viitanen et al.,[38] Score 4, +ve study	160	1. Paracetamol 40 mg/kg 2. Ibuprofen 15 mg/kg 3. Paracetamol 40 mg/kg + ibuprofen 15 mg/kg 4. Placebo Single rectal dose	Pediatric tonsillectomy	Supplemental analgesic requirements during first 24 h & after discharge: +ve Supplemental analgesic requirements were 27% lesser after discharge	Vomiting: 24%–32% Drowsiness: 5% Abdominal pain: 3%–10% Paracetamol group was drowsier than other groups
Total	1129				

Study outcome: "+ve" means that the combination was superior to NSAID alone. "−ve" means that the combination was not superior to NSAID alone.
VAS = visual analog scale; PCA = patient-controlled analgesia.

There was no evidence of an increased incidence of side effects with combinations compared with individual drugs alone. Most studies reported no difference between the side effect profiles with combination therapy versus single-drug therapy. The incidence of nausea and vomiting was significantly higher in some studies for the single-therapy groups that required more morphine as rescue medication.[19,31] In general, adverse effects were mild and infrequent in all the studies, and mostly related to known side effects of the investigated drugs. The most common side effects reported were nausea, vomiting, drowsiness, and headache (Tables 1 and 2). There were no serious adverse effects reported for any of the combination analgesics tested in combination or alone.

DISCUSSION

This review suggests that combining paracetamol and an NSAID confers additional analgesic efficacy over either drug alone. The combination of paracetamol and an NSAID was more effective than paracetamol or an NSAID alone in 85% and 64% of the studies, respectively. The subgroup analysis by surgical model and NSAID type confirms our overall results and further strengthens our conclusion. This conclusion is consistent with many previous expert reviews that recommend the use of combination analgesics.[3,4,39–45] The recommendations from most of the previous expert reviews were based on logic rather than evidence, and in this review, we have attempted to provide the evidence.

Overall, ibuprofen was one of the NSAIDs most widely evaluated in the studies reviewed. The value of combining it with paracetamol was confirmed in all of the 5 studies against paracetamol alone,[21,23,27,30,33,38] and 2 of the 3 studies against an NSAID alone.[21,30,38] Ibuprofen has a well-established reputation for safety and efficacy compared with other NSAIDs.[46–54] However, even with ibuprofen, the risks are a function of the dose and duration of use.[55] Hence, the case for combining ibuprofen with paracetamol to obtain increased analgesia without increasing the dose of the NSAID is strong.

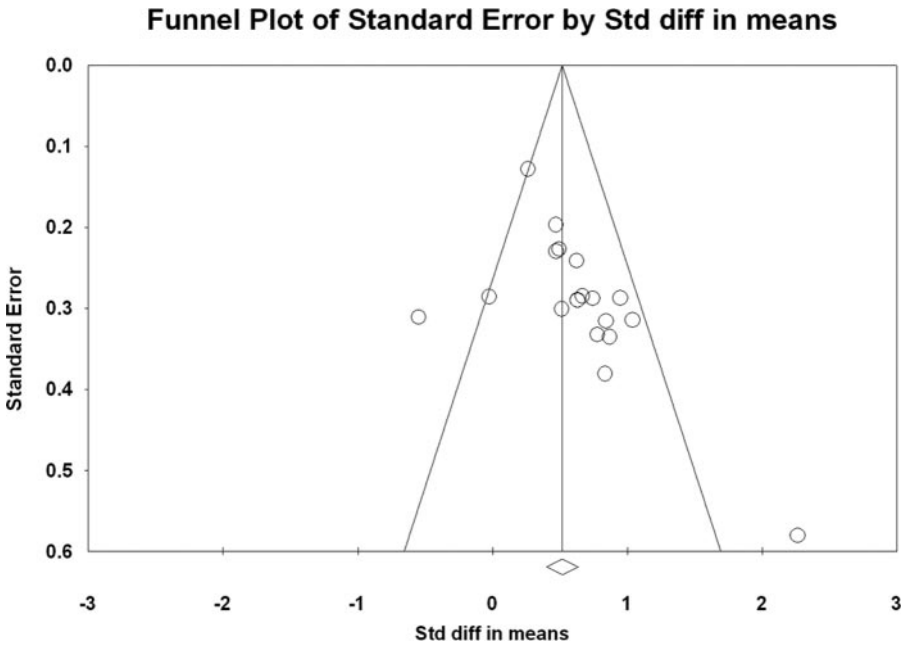

Figure 1. Funnel plot of the treatment effect against a measure of study size for studies of paracetamol/nonsteroidal antiinflammatory drug combinations versus paracetamol alone.

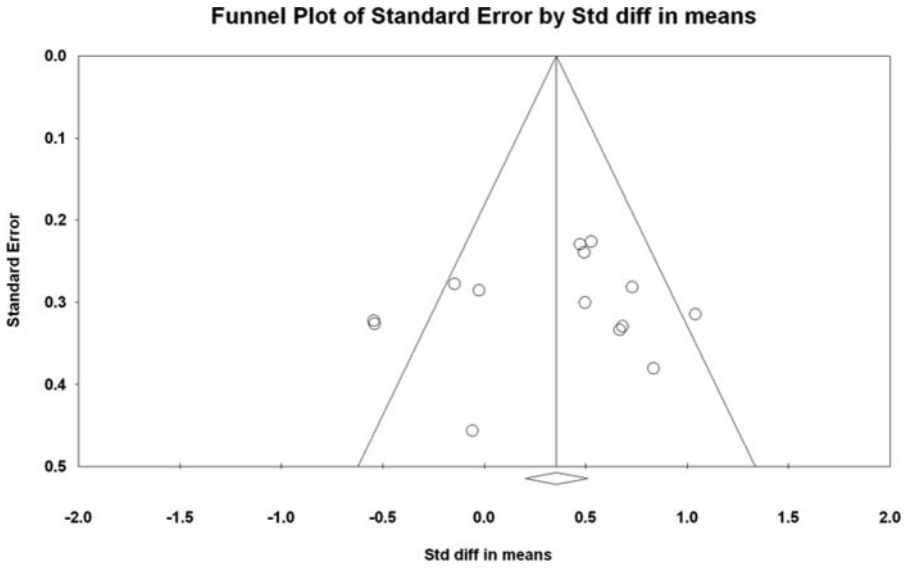

Figure 2. Funnel plot of the treatment effect against a measure of study size for studies of paracetamol/nonsteroidal antiinflammatory drug (NSAID) combinations versus NSAID alone.

Limitations of our study include its qualitative approach and the wide range of acute pain models included in the studies reviewed.[56] We note continuing debate over combining of different surgical models in acute pain studies.[56–59] A commentary criticized combining results from different surgical models in pain studies on the basis of comparisons of relative risk and seeking aid from the dubious ally of heterogeneity tests.[56] The authors argued that different models of acute pain may well produce different outcomes on the basis of the results for paracetamol 975/1000 mg in acute pain trials. On the contrary, there are at least 2 systematic reviews and 1 commentary that suggest that there is little difference between the different acute surgical models in the estimate of analgesic efficacy.[57–59] A quantitative meta-analysis would certainly not be possible for the included RCTs in this review because of heterogeneity of study design. Our subgroup analysis by surgical model provides considerable reassurance in relation to any influence of this heterogeneity on our overall qualitative findings.

Some of the negative studies included in this review may not have adequate sensitivity to detect a difference in pain scores between groups because the VAS pain scores were relatively low in the control groups. Moderately severe pain (e.g., VAS score >30 mm) is required in pain studies to achieve adequate sensitivity because it may not be possible to detect any difference if there is little or no pain.[60] The mean pain scores in the control groups were ≤30 mm in 4 of the 5 negative studies that compared the combination with NSAIDs.[21,29,31,32,37] In all 4 studies, the analgesics were given preemptively, either before surgery or immediately after surgery before pain developed.[21,29,31,37] In addition, it should be noted that some studies with small group sizes may not have adequate power to detect a difference even if present.[21,29,31,32,37]

Three recent animal studies also provide evidence in favor of combinations of paracetamol and NSAIDs for analgesia.[61–63] All 3 studies used the mouse acetic acid abdominal constriction test, a validated pain model in rodents, to measure analgesic effect of drug combinations.[64] Miranda et al.[61] compared antinociception induced by the intraperitoneal coadministration of combinations of paracetamol with the widely used NSAIDs diclofenac, ibuprofen, ketoprofen, meloxicam, metamizol, naproxen, nimesulide, parecoxib, and piroxicam. They concluded that all of the combinations were synergistic. Qiu et al.[62] and Miranda et al.[63] investigated the antinociceptive effect of oral paracetamol and ketoprofen alone or in combination and the antinociceptive effect of intraperitoneal administration of paracetamol, ketoprofen, and morphine alone or in combination, respectively. Similar dose-response curves were obtained in these 2 animal studies in favor of adding an NSAID to paracetamol.

There are some potential disadvantages in combining NSAIDs and paracetamol. A combination may be disadvantageous when individual drugs are specifically suited to a patient's symptoms (e.g., when only the antipyretic action of paracetamol is required for fever). Combining analgesics may increase the incidence of adverse effects. The use of fixed-dose combinations may reduce flexibility in dose titration, or conversely may expose patients to unnecessarily large doses of NSAIDs with consequent adverse effects, particularly in susceptible patients. Furthermore, combinations will not be suitable for patients with contraindications to either drug alone. For example, paracetamol should be used with caution (if at all) in patients with preexisting liver disease, whereas a history of gastrointestinal ulcers or renal impairment precludes use of traditional NSAIDs. The combination of paracetamol and long-acting NSAIDs such as tenoxicam has the theoretical disadvantage of pharmacokinetic incompatibility because tenoxicam has a much longer elimination half-life than paracetamol.

We conclude that a combination of acetaminophen and NSAIDs may provide superior analgesia than either drug alone.

DISCLOSURE

Dr. Merry's unit has received grants from AFT Pharmaceuticals Ltd for research into a combination of paracetamol and ibuprofen.

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