Preventive Acetaminophen Reduces Postoperative Opioid Consumption, Vomiting, and Pain Scores After Surgery

Systematic Review and Meta-Analysis

Brett Doleman, MBBS, David Read, BMBS, Jonathan N. Lund, DM, and John P. Williams, PhD

Background and Objectives: Preventive analgesia has been proposed as a potential strategy to reduce postoperative pain. However, there is currently no review that focuses on acetaminophen for preventive analgesia.

Methods: We conducted a search of MEDLINE, EMBASE, Cinahl, AMED, and CENTRAL databases identifying randomized controlled trials that compared preventive acetaminophen with postincision acetaminophen.

Results: Seven studies with 544 participants were included. Overall, the studies showed a reduction in 24-hour opioid consumption (standardized mean difference [SMD] of −0.52; 95% confidence interval [95% CI], −0.98 to −0.06), lower pain scores at 1 hour (MD, −0.50; 95% CI, −0.98 to −0.02) and 2 hours (MD, −0.34; 95% CI, −0.67 to −0.01), and a lower incidence of postoperative vomiting (risk ratio, 0.50; 95% CI, 0.31–0.83) in the preventive acetaminophen group. Current studies are limited by a potential risk of bias.

Conclusions: To our knowledge, this is the first review to describe a potential preventive effect of acetaminophen. However, well-conducted randomized controlled trials are necessary to substantiate the conclusions of this review.

(*Reg Anesth Pain Med* 2015;40: 706–712)

Postoperative pain is a common consequence of major surgery, with an incidence of approximately 80%, with 39% of these patients experiencing severe or extreme pain.[1] More than half of patients are treated with intravenous opioids after major surgery,[2] despite patient concerns over potential addiction and opioid-related adverse effects.[1] Therefore, alternative strategies to reduce opioid consumption have been proposed, such as the use of non–opioid-based multimodal analgesia.[3]

Acetaminophen is a commonly used analgesic. Although its mechanism of action is unclear, it has been suggested that it may mediate its effects through cyclooxygenase inhibition, serotonergic activation, and/or cannabinoid pathways.[4] Acetaminophen has proven efficacy as a postoperative analgesic,[5,6] with a number needed to treat (NNT) for a 50% pain reduction of 3.8 (95% confidence interval [95% CI], 3.4–4.4).[7] It also has a possible role in the prevention of postoperative nausea and vomiting.[8] Acetaminophen has a low incidence of side effects,[9] making it a common alternative to nonsteroidal anti-inflammatory drugs (NSAIDs) for high-risk patients.

It has been suggested that preventive analgesia might improve postoperative pain[10] and reduce the need for opioid analgesics after surgery. By providing early and adequate analgesia before surgical incision, preventive analgesia may reduce central sensitization resulting from surgical incision[11] and provide more effective pain control in the postoperative period compared with the same analgesic given after incision.[12] After initially promising results in animal models, 2 large conflicting reviews have been published examining the effects of preventive analgesia. The first showed no significant benefit of preventive analgesia on postoperative outcomes when using NSAIDs, epidural analgesia, ketamine, or intravenous opioids.[13] A more recent review,[14] however, found an opioid-sparing effect of preventive epidural analgesia, local anesthetic wound infiltration, and NSAIDs. Neither review evaluated other useful clinical end points such as reductions in opioid-related side effects or adverse events.[13,14]

However, the role of acetaminophen as a preventive analgesic is yet to be elucidated. Randomized controlled trials have been published during the last decade suggesting a possible beneficial effect, although this is the first meta-analysis to evaluate a potential role for preventive acetaminophen in postoperative pain management. Therefore, the aim of this review was to summarize the role of preventive acetaminophen compared with postincision acetaminophen in reducing postoperative pain, opioid consumption, and opioid-related side effects.

METHODS

This systematic review was produced in accordance with the PRISMA checklist.[15] The review was registered on the PROSPERO database with the registration number CRD42014013489. The original protocol was updated to compare preventive acetaminophen with a further active group composed of patients who had received postincision acetaminophen.

The study search was conducted in August 2014 by one of the study authors (B.D.). Electronic databases searched included MEDLINE (1946–2014), EMBASE (1974–2014), Cinahl (1981–2014), CENTRAL (1985–2014), and AMED (1985–2014). Search terms included the free text words within the title or abstract: "paracetamol," "acetaminophen," "ofirmev," "pefalgan" AND "surgery." The medical subject heading (MeSH) "SURGICAL PROCEDURES, OPERATIVE" was exploded and combined with the key words above (Appendix 1). Appropriate modifications were made for alternative databases. In addition, we searched references and citations for additional studies. The clinical trial databases Clinicaltrials.gov and the meta-register of Current Controlled Trials were searched to identify unpublished studies. Authors were contacted for further information if necessary.

We included studies that were randomized controlled trials of acetaminophen given preventively (defined as within 1 hour before induction of anesthesia) versus after incision (any time between postincision and within 30 minutes from the end of surgery). We included patients older than 16 years. All types of surgery were considered. We had no language restrictions in the search. Articles were translated if necessary using Google Translate. We excluded articles that focused on pediatric populations and articles that studied preventive acetaminophen versus placebo. Inclusion and exclusion criteria were independently assessed by

From the Division of Medical Sciences and Graduate Entry Medicine, University of Nottingham, Derby, United Kingdom.
Accepted for publication July 9, 2015.
Address correspondence to: Brett Doleman, MBBS, University of Nottingham, Royal Derby Hospital, Uttoxeter Rd, Derby DE22 3DT, United Kingdom (e-mail: dr.doleman@gmail.com).
The authors declare no conflict of interest.
This work was presented in part at the GAT conference of The Association of Anaesthetists of Great Britain and Ireland (June 17–19, 2015).

ISSN: 1098-7339
DOI: 10.1097/AAP.0000000000000311

2 study authors (B.D. and J.P.W.), and agreement was reached by consensus. The primary outcome was 24-hour opioid consumption. Other outcomes assessed included postoperative pain scores at rest, time to first analgesic request, nausea, vomiting, and pruritus.

Study information was extracted onto an electronic database by 2 study authors (B.D. and D.R.). Information included study name, sample size, percentage of female participants, mean age, duration of surgery, type of intervention and comparator, type of anesthesia, type of surgery, pain scale used, and outcomes measured. Risk of bias was assessed using the Cochrane Risk of Bias tool[16] by 2 study authors (B.D. and D.R.), and agreement was reached by consensus. Where outcome data were not available, authors were contacted to provide additional information. If no reply was received, data were extracted from graphs. If not reported, standard deviations were estimated from other studies within the meta-analysis.[17]

Pain scores and time to first analgesic are presented as mean differences (MDs). Pain scores were converted to a 10-point scale. Because of the different opioids used, 24-hour opioid consumption is presented as standardized MDs (SMDs). We regarded clinically significant SMD values as small, more than 0.3; moderate, more than 0.5; or large, more than 0.7. Dichotomous data are presented as risk ratios (RRs) and NNT where appropriate. All results are presented with 95% confidence intervals (95% CIs). Random-effects modeling was used because of significant clinical heterogeneity in the included studies.

Publication bias was assessed using a 1-tailed Egger linear regression test. Statistical heterogeneity was assessed using the I^2 statistic with P values derived from the χ^2 statistic. Investigation of heterogeneity was undertaken using the method of moments, random-effects meta-regression using the covariate of control group morphine equivalent consumption. Results are reported as the total proportion of the between-study heterogeneity explained (R^2) with a corresponding P value for the model. Sensitivity analysis was conducted by excluding studies at high risk of bias and removing studies that used spinal anesthesia and those that gave additional postoperative doses and using 1 study–removed analysis. All analyses were undertaken using Comprehensive Meta-analysis 3[18] and Review Manager 5.3 from the Cochrane Collaboration.[19]

RESULTS

Electronic database searching of MEDLINE, EMBASE, Cinahl, and AMED identified 3083 records. Searching of the CENTRAL database identified an additional 262 studies. Seventeen studies were identified from searching of study references and citations, and the authors of 1 study replied with information after searching unpublished studies on clinical trial databases (Fig. 1). After review of the abstracts, 68 studies were identified as potentially relevant to the research question. Studies were excluded for the following reasons: solely comparing acetaminophen with placebo (n = 60) and the active arm used proparacetamol (n = 1).

Seven studies were included in the final meta-analysis.[20–26] All studies were randomized controlled trials (Table 1). Accurate risk of bias assessment was difficult because of poor reporting in most of the trials. Blinding of outcome assessment was unclear in 6 of the studies, and only 2 studies described adequate allocation concealment (Fig. 2). Surgical procedures were diverse, with each study focusing on different types of surgery[27] with varying degrees of postoperative opioid consumption (0.4–35 mg). The percentage of female participants ranged from 15% to 100%. All studies used intravenous acetaminophen, with 2 studies giving additional postoperative doses.[21,24] Mean duration of surgery ranged from 60 to 135 minutes. The initial dose of acetaminophen was given 15 to 30 minutes before induction of anesthesia in 5 studies,[20–22,24,26] 30 minutes preoperatively in 1 study,[23] and 10 minutes before incision in 1 study.[25]

Postoperative Analgesia

Six studies[20–25] were included in the meta-analysis (Fig. 3). Overall, these studies showed lower 24-hour opioid consumption in the preventive acetaminophen group, with an SMD of −0.52 (95% CI, −0.98 to −0.06). Statistical heterogeneity was considerable (I^2 = 82%; P < 0.001). One study[26] that failed to show a reduction in pethidine consumption was not included in this analysis because there was no specified time frame over which opioid consumption was measured (47 vs 51 mg; P = 0.24).

There was no evidence of publication bias (P = 0.32). On meta-regression, morphine equivalent consumption in the control group predicted the majority of the heterogeneity between the studies (R^2 = 58%; P = 0.005). Sensitivity analysis showed that reductions in morphine were heavily influenced by 1 study,[20] and analysis of studies at a lower risk of bias resulted in lower opioid consumption (SMD, −0.98; 95% CI, −1.71 to −0.24). Removing

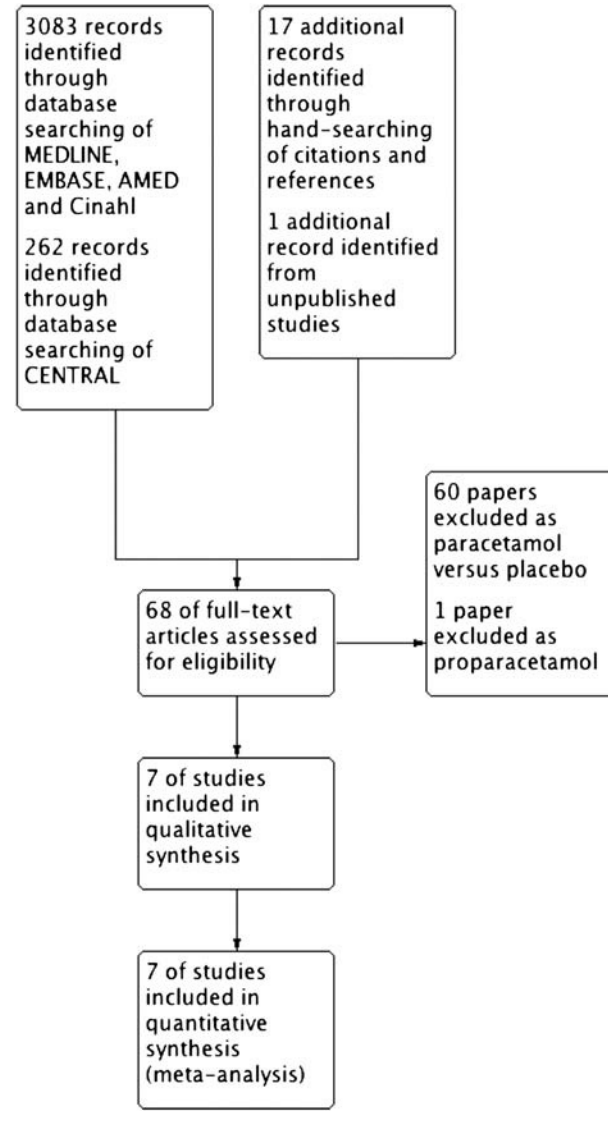

FIGURE 1. PRISMA flowchart for included studies.

TABLE 1. Characteristics of Included Studies

Study	Sex	Sample Size	Mean age	Surgery Duration (min)	Intervention	Placebo	Surgery	Type of Anesthesia	Pain Score	Outcomes
Arici 2009	100%	55	50.1	118	1000 mg intravenous acetaminophen 30 min before induction and 1000 mg before skin closure	Saline	Elective abdominal hysterectomy	General anesthesia	Visual analog scale (10)	Pain scores, sedation, morphine consumption, nausea, vomiting, respiratory depression, pruritus, constipation, length of stay
Arslan 2013	66%	200	42.9	94	1000 mg intravenous acetaminophen 10 min before incision and 1000 mg 10 min after surgery	Saline	Laparoscopic cholecystectomy	General anesthesia	Visual analog scale (10)	Pain scores, tramadol consumption, nausea, vomiting, respiratory depression, pruritus, rash, allergy, stomach irritation, diarrhea, constipation, headache, sedation, dry mouth, sweating, hypotension, patient satisfaction
Ayogen 2008	15%	80	44.6	135	1000 mg intravenous acetaminophen 15 min before induction and 1000 mg 15 min before the end of surgery	NR	Total hip replacement and spinal surgery	General anesthesia	Visual analog scale (10)	Pain scores, meperidine consumption, sedation
Hassan 2014	100%	60	26.5	63.9	1000 mg intravenous acetaminophen 30 min before induction and 1000 mg 30 min before the end of surgery	NR	Cesarean section	General anesthesia	Visual analog scale (10)	Pain scores, first analgesic drug dose after paracetamol, time of second analgesic drug, pethidine consumption, nausea and vomiting, respiratory depression, urinary retention, drowsiness
Khalili 2013	32%	50	41.8	75	15 mg/kg intravenous acetaminophen 30 min before surgery and 15 mg/kg before skin closure	Saline	Orthopedic lower limb	Spinal anesthesia	Verbal rating scale (10)	Pain scores, meperidine consumption, sedation, dizziness, nausea, vomiting, patient satisfaction
Koteswara 2014	41%	39	42.2	111	1000 mg intravenous acetaminophen 15 min before induction and 1000 mg at the end of surgery	NR	Functional endoscopic sinus surgery	General anesthesia	Visual analog scale (10)	Pain scores, time to first analgesic, tramadol consumption, nausea, vomiting, respiratory depression, pruritus, rash, allergy, hypotension
Toygar 2008	50%	60	45.3	88	1000 mg intravenous acetaminophen 15 min before induction and 1000 mg 15 min before end of surgery	NR	Single level discectomy surgery	General anesthesia	Visual analog scale (10)	Pain scores, morphine consumption, time to morphine request, nausea, vomiting, urinary retention

Sex reported as percentage of female participants.
NR indicates not reported.

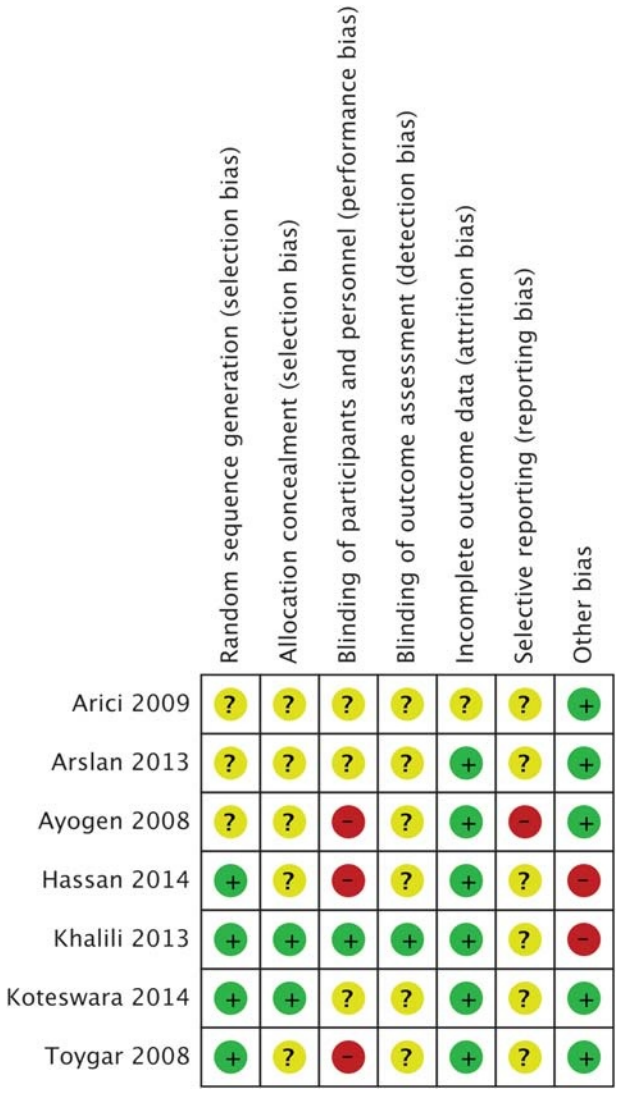

FIGURE 2. Risk of bias for the included studies. Green indicates low risk, yellow indicates unclear risk, and red indicates high risk.

the study that used spinal anesthesia[23] did not affect the results. Excluding studies that gave additional postoperative doses led to a lower opioid consumption in the preventive group (SMD, −0.81; 95% CI, −1.36 to −0.25).

Time to first analgesic request was reported in 4 studies.[22–25] These studies showed a beneficial effect in the preventive acetaminophen group, with patients requesting their first analgesic 12.48 minutes later (95% CI, 1.39–23.58 minutes) than the postincision group. Statistical heterogeneity was considerable (I^2 = 89%; P < 0.001). There was also evidence of possible publication bias (P = 0.04).

Pain Scores

Pain scores were lower in the preventive acetaminophen group at 1 hour (Fig. 4), with an MD of −0.50 (95% CI, −0.98 to −0.02). There was evidence of considerable statistical heterogeneity (I^2 = 76%; P = 0.001) and some evidence of publication bias (P = 0.1). At 2 hours (Fig. 5), there was also a reduction in pain scores (MD, −0.34; 95% CI, −0.67 to −0.01), with evidence of heterogeneity between studies (I^2 = 52%; P = 0.08). There was also evidence of possible publication bias (P = 0.06). There were no significant reductions at 4 hours (MD, −0.82; 95% CI, −1.73 to 0.10), 6 hours (MD, −0.02; 95% CI, −0.59 to 0.56), 12 hours (MD, −0.16; 95% CI, −0.48 to 0.16), or 24 hours (MD, −0.14; 95% CI, −0.44 to 0.15).

Opioid Side Effects

Four studies[20,22,24,25] reported the incidence of postoperative nausea, and 5 studies reported the incidence of postoperative vomiting.[20,22,24–26] One study[26] included both nausea and vomiting requiring antiemetic treatment and was included in the vomiting outcome. There was no significant difference in the risk of postoperative nausea, with an RR of 0.78 (95% CI, 0.43–1.41). There was evidence of publication bias (P = 0.03). However, there was a lower risk of postoperative vomiting (Fig. 6) in the preventive group, with an RR of 0.50 (95% CI, 0.31–0.83) and an NNT of 11 (95% CI, 6.1–32.5) to prevent an episode of vomiting. There was no statistical evidence of publication bias (P = 0.24). The statistical heterogeneity for nausea and vomiting was I^2 = 33% (P = 0.21) and I^2 = 0% (P = 0.96), respectively. Two studies[20,22] reported postoperative pruritus, although one was not included in the meta-analysis because no events occurred in either group.[22] The RR was 0.32 (95% CI, 0.01–7.57).

DISCUSSION

This is the first meta-analysis to evaluate the role of preventive acetaminophen in postoperative pain management. The results of this review demonstrate that preventive acetaminophen results in lower postoperative pain scores up to 2 hours postoperatively. However, the clinical effect was small. In addition, a moderate clinically significant reduction in 24-hour opioid consumption was observed, with a delayed time to first analgesic request and a reduction in the incidence of postoperative vomiting. However, reductions in 24-hour opioid consumption were dependent on baseline group usage, with a larger consumption in the control group, predicting larger reductions in the preventive group. Despite this early analgesic effect, preventive acetaminophen did not reduce pain scores beyond the immediate postoperative period

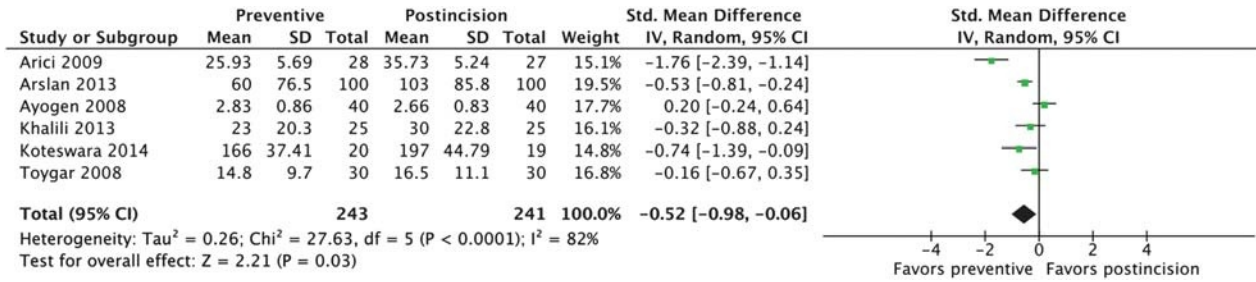

FIGURE 3. Forest plot for 24-hour opioid consumption.

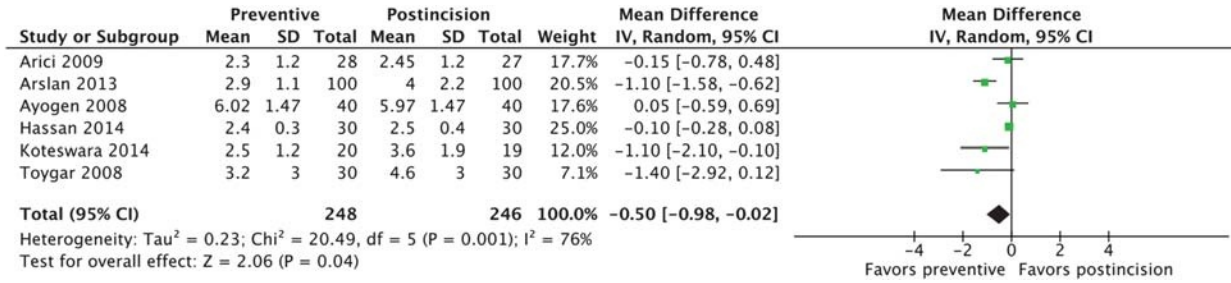

FIGURE 4. Forest plot for pain scores at 1 hour.

or reduce any other opioid-related side effects, although studies may currently be underpowered for these outcomes.

Although investigations in animal models were originally promising, the first review of the clinical evidence for preventive analgesia was disappointing.[13] A more recently published review from 2005 has however shown a potential benefit of preventive analgesia with NSAIDs, epidural anesthesia, and local anesthetic wound infiltration.[14] Despite this, evidence for a potential role for other perioperative agents such as acetaminophen and gabapentinoids remains unclear.[28] With the latest review, now nearly a decade old, updated evidence may emerge on the role of other agents capable of producing a preventive analgesic effect for postoperative pain management. A simple change in clinical practice such as a change in timing of perioperative acetaminophen administration could have important implications for postoperative pain management.

Preventive acetaminophen was found to reduce the risk of postoperative vomiting. The RR for reductions in vomiting compared well with traditional antiemetics such as cyclizine, dexamethasone, metoclopramide, and ondansetron.[29] The potential mechanism may include a reduction in morphine consumption in the preventive group. However, a meta-analysis of randomized controlled trials examining perioperative acetaminophen in postoperative nausea and vomiting found that reductions in nausea were associated with reductions in pain scores rather than reductions in morphine consumption.[8] Other direct mechanisms may be involved, such as reuptake of the cannabinoid agonist anandamide.[8]

Our results with regard to immediate postoperative pain relief gained with preventive acetaminophen contradict the expected pharmacokinetics of acetaminophen administration. As postincision doses of intravenous acetaminophen were generally given at the end of surgery, it would be expected that therapeutic concentrations of acetaminophen given at this time were more likely in the first 2 hours postoperatively and last longer into the postoperative period compared with the preventive acetaminophen group. With specific regard to the pharmacokinetic properties of acetaminophen, peak plasma concentration is rapidly reached at infusion, and with pain scores recorded 0 to 2 hours postoperatively and the duration of surgery between 60 to 135 minutes, effect site concentrations of acetaminophen are more likely to be in the therapeutic range in the postincision group. Furthermore, as the elimination half-life of acetaminophen is 2 to 4 hours in adults,[4] any dose of acetaminophen given before surgery would more likely be subtherapeutic in the preventive group. Therefore, a potential preventive analgesic effect is likely responsible for the lower pain scores observed immediately postoperatively in the preventive group.

There are several limitations in this review. The major limitation relates to the risk of bias in the included studies (Fig. 2). Only 2 studies described adequate allocation concealment, 4 described adequate randomization, and 1 described adequate blinding of outcome assessment. All have the potential to bias-effect estimates in the preventive group.[30] Second, although some outcomes were statistically significant, only reductions in the incidence of vomiting and, to a lesser extent, opioid consumption were clinically significant. However, meta-regression demonstrated that a higher control group opioid consumption predicted larger absolute reductions in opioid consumption, suggesting that preventive acetaminophen might be more effective in more painful procedures, a finding consistent with previous research.[31,32] Only 1 study in the review had a 24-hour morphine usage more than 20 mg, which may influence the clinical significance of results obtained. Third, surgical procedures were diverse, as were other study characteristics, which may have contributed to statistical and clinical heterogeneity.[33] Heterogeneity, indirectness of evidence, possible publication bias, and risk of bias downgrade the GRADE strength of recommendation to very low quality.[34] Furthermore, the small number of included studies may currently be underpowered for some dichotomous outcomes in relation to opioid-related side effects and acetaminophen adverse events, which were poorly reported.

The results of this review should be interpreted as preliminary and emphasize the need for further rigorously conducted and reported randomized controlled trials examining preventive versus postincision acetaminophen for postoperative pain. Future trials should aim to address concerns over publication bias by using prospective registration and attempt to address concerns over internal validity by conducting rigorously designed and reported studies. Furthermore, future studies should aim to use

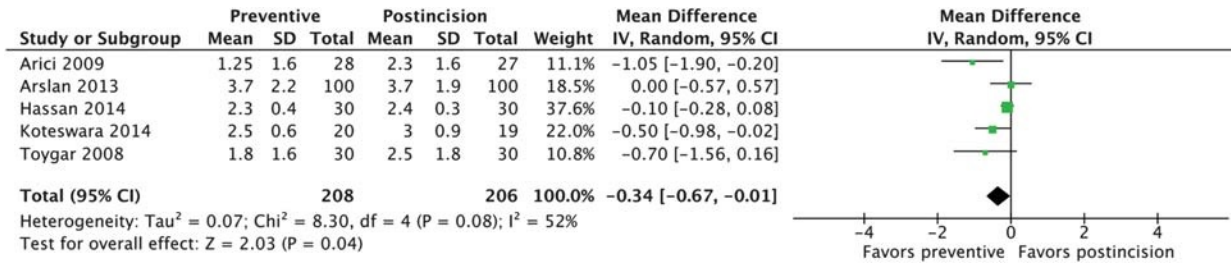

FIGURE 5. Forest plot for pain scores at 2 hours.

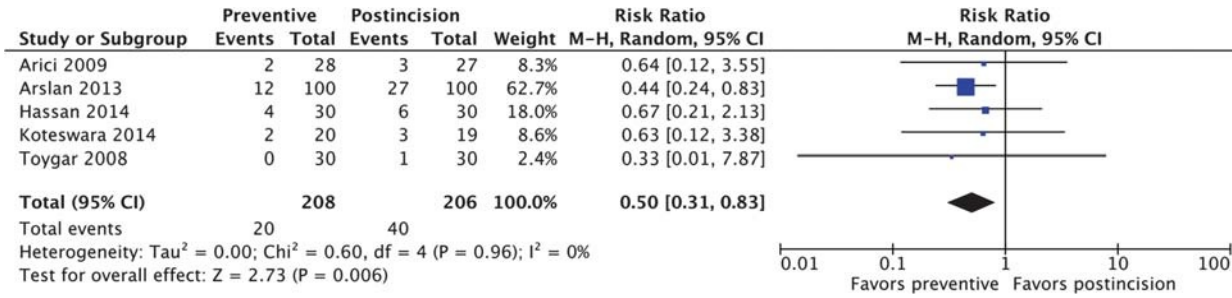

FIGURE 6. Forest plot for the incidence of postoperative vomiting.

preventive acetaminophen in more painful procedures to improve the absolute effects. However, the evidence currently suggests a potential role for preventive acetaminophen in reducing postoperative pain scores, opioid consumption, and postoperative vomiting. This is, to our knowledge, the first review to describe a possible preventive analgesic effect of acetaminophen.

ACKNOWLEDGMENT

The authors thank Lisa Lawrence, the clinical librarian who provided training to the study author conducting the electronic search strategy.

REFERENCES

1. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg*. 2003;97:534–540.
2. Benhamou D, Berti M, Brodner G, et al. Postoperative Analgesic THerapy Observational Survey (PATHOS): a practice pattern study in 7 central/southern European countries. *Pain*. 2008;136:134–141.
3. White PF, Kehlet H. Improving postoperative pain management: what are the unresolved issues? *Anesthesiology*. 2010;112:220–225.
4. Oscier CD, Milner QJ. Perioperative use of paracetamol. *Anaesthesia*. 2009;64:65–72.
5. Hyllested M, Jones S, Pedersen JL, Kehlet H. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. *Br J Anaesth*. 2002;88:199–214.
6. McNicol ED, Tzortzopoulou A, Cepeda MS, Francia MB, Farhat T, Schumann R. Single-dose intravenous paracetamol or propacetamol for prevention or treatment of postoperative pain: a systematic review and meta-analysis. *Br J Anaesth*. 2011;106:764–775.
7. Bandolier. Oxford League Table of Analgesic Efficacy. 2007. Available at: http://www.medicine.ox.ac.uk/bandolier/booth/painpag/acutrev/analgesics/lftab.html. Accessed November 20, 2014.
8. Apfel CC, Turan A, Souza K, Pergolizzi J, Hornuss C. Intravenous acetaminophen reduces postoperative nausea and vomiting: a systematic review and meta-analysis. *Pain*. 2013;154:677–689.
9. Barden J, Edwards J, Moore A, McQuay H. Single dose oral paracetamol (acetaminophen) for postoperative pain. *Cochrane Database Syst Rev*. 2004;1:CD004602.
10. Dahl JB, Kehlet H. The value of pre-emptive analgesia in the treatment of postoperative pain. *Br J Anaesth*. 1993;70:434–439.
11. Woolf CJ, Chong MS. Preemptive analgesia-treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg*. 1993;77:362–379.
12. Dahl JB, Moiniche S. Pre-emptive analgesia. *Br Med Bull*. 2004;71:13–27.
13. Møiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. *Anesthesiology*. 2002;96:725–741.
14. Ong CK, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. *Anesth Analg*. 2005;100:757–773.
15. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264–269.
16. Higgins J, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
17. Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester: Wiley-Blackwell; 2008.
18. *Comprehensive Meta-analysis Version 3*. Englewood, NJ: Biostat; 2015.
19. The Cochrane Collaboration. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre; 2012.
20. Arici S, Gurbet A, Turker G, Yavaşcaoğlu B, Sahin S. Preemptive analgesic effects of intravenous paracetamol in total abdominal hysterectomy. *Agri*. 2009;21:54–61.
21. Ayogen H, Dogru K, Erdem S, Bicer C, Aksu R, Boyaci A. The effect of IV paracetamol on the hemodynamic indices, liver functions and the postoperative analgesia in the patients underwent major orthopaedic surgery. *Erciyes Medical J*. 2008;30:71–77.
22. Koteswara CM, Sheetal D. A study on pre-emptive analgesic effect of intravenous paracetamol in functional endoscopic sinus surgeries: a randomized, double-blinded clinical study. *J Clin Diagn Res*. 2014;8:108–111.
23. Khalili G, Janghorbani M, Saryazdi H, Emaminejad A. Effect of preemptive and preventive acetaminophen on postoperative pain score: a randomized, double-blind trial of patients undergoing lower extremity surgery. *J Clin Anesth*. 2013;25:188–192.
24. Toygar P, Akkaya T, Ozkan D, Ozel O, Uslu E, Gumus H. Does IV paracetamol have preemptive analgesic effect on lumber disc surgeries? [In Turkish]. *Agri*. 2008;20:14–19.
25. Arslan M, Celep B, Cicek R, Kalender HU, Yilmaz H. Comparing the efficacy of preemptive intravenous paracetamol on the reducing effect of opioid usage in cholecystectomy. *J Res Med Sci*. 2013;18:172–177.
26. Hassan HI. Perioperative analgesic effects of intravenous paracetamol: preemptive versus preventive analgesia in elective cesarean section. *Anesth Essays Res*. 2014;8:339–344.
27. Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. *Anesthesiology*. 2009;111:657–677.
28. Doleman B, Heinink TP, Read D, Faleiro RJ, Lund JN, Williams JP. A systematic review and meta-regression analysis of prophylactic gabapentin for postoperative pain. *Anaesthesia*. 2015;70:1186–1204.
29. Carlisle JB, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev*. 2006;3:CD004125.
30. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*. 1995;273:408–412.

31. Averbuch M, Katzper M. Severity of baseline pain and degree of analgesia in the third molar post-extraction dental pain model. *Anesth Analg*. 2003;97:163–167.

32. Bjune K, Stubhaug A, Dodgson MS, Breivik H. Additive analgesic effect of codeine and paracetamol can be detected in strong, but not moderate, pain after caesarean section. *Acta Anaesthesiol Scand*. 1996;40:399–407.

33. Espitalier F, Tavernier E, Remérand F, Laffon M, Fusciardi J, Giraudeau B. Heterogeneity in meta-analyses of treatment of acute postoperative pain: a review. *Br J Anaesth*. 2013;111:897–906.

34. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924–926.

APPENDIX 1.

1	MEDLINE	Paracetamol.ti,ab
2	MEDLINE	Acetaminophen.ti,ab
3	MEDLINE	Ofirmev.ti,ab
4	MEDLINE	Perfalgan.ti,ab
5	MEDLINE	1 OR 2 OR 3 OR 4
6	MEDLINE	exp SURGICAL PROCEDURES, OPERATIVE/
7	MEDLINE	Surgery.ti,ab
8	MEDLINE	6 OR 7
9	MEDLINE	5 AND 8
10	MEDLINE	9 (Limit to: Humans and [Age Groups All Adult 19 plus years] and [Publication Types Clinical Trial, All or Clinical Trial or Controlled Clinical Trial or Journal Article or Meta Analysis or Multicenter Study or Pragmatic Clinical Trial or Randomized Controlled Trial or Review or Systematic Reviews])

The Pharmacokinetics of Preventive Acetaminophen

Accepted for publication: January 6, 2016.

To the Editor:

I read with great interest the systematic review and meta-analysis on the efficacy of preventive acetaminophen in the perioperative period by Doleman and colleagues[1] published in the November/December 2015 issue of *Regional Anesthesia and Pain Medicine*. I commend the authors for addressing the role of preventive acetaminophen use, which was previously elucidated in a systematic review and meta-analysis by Apfel and colleagues.[2] I was slightly surprised when Doleman and colleagues reported that their findings of preventive acetaminophen on analgesia postoperatively for surgical times ranging from 60 to 135 minutes did not align with the expected pharmacokinetics of acetaminophen. They had expected therapeutic plasma levels to peak almost immediately after intravenous acetaminophen, and that the therapeutic effects of preventive acetaminophen would not be evident after 1 to 2 hours of surgery. I humbly disagree.

Acetaminophen diffuses passively across the blood–brain barrier to act centrally. Singla and colleagues[3] conducted a pharmacokinetic study assessing the cerebrospinal fluid concentration of acetaminophen after intravenous, oral, and rectal administrations of acetaminophen. Their data suggest the effect-site C_{max} for acetaminophen is reached 2 hours after plasma C_{max} for acetaminophen is achieved for all preparations of acetaminophen. In other words, the effect-site T_{max} for acetaminophen lags 2 hours behind the plasma T_{max} for acetaminophen. On the basis of the aforementioned pharmacokinetic study, the results reported by Doleman and colleagues correspond to the pharmacokinetics of acetaminophen.

Amanda Jane Cheng Yee Yap, BSc, MBBS
Department of Anesthesiology
University of Vermont Medical Center
Burlington, VT

The author declares no conflict of interest.

REFERENCES

1. Doleman B, Read D, Lund JN, Williams JP. Preventive acetaminophen reduces postoperative opioid consumption, vomiting, and pain scores after surgery: systematic review and meta-analysis. *Reg Anesth Pain Med*. 2015;40:706–712.
2. Apfel CC, Turan A, Souza K, Pergolizzi J, Hornuss C. Intravenous acetaminophen reduces postoperative nausea and vomiting: a systematic review and meta-analysis. *Pain*. 2013;154:677–689.
3. Singla NK, Parulan C, Samson R, et al. Plasma and cerebrospinal fluid pharmacokinetic parameters after single-dose administration of intravenous, oral, or rectal acetaminophen. *Pain Pract*. 2012;12:523–532.

Reply to Dr Yap

Accepted for publication: February 5, 2016.

To the Editor:

We thank Dr Yap[1] for her interest in our article. The aim of our review was to identify whether preventive acetaminophen is more effective at reducing postoperative pain when compared with postincision acetaminophen.[2] As alluded to in her letter, during the discussion we speculate on the preventive effects of acetaminophen concerning the pharmacokinetics of the drug. The pharmacokinetics to which we were referring were plasma concentrations, which, using data from the study quoted by Dr Yap,[3] would be consistent (median T_{max} of 15 minutes). However, we agree that cerebrospinal fluid (CSF) concentrations lag behind plasma concentrations and that using CSF pharmacokinetics to explain this effect would not be consistent with our discussion. Despite this, using this as the basis on which to base the clinical effects of acetaminophen may be flawed. We will highlight these points hereafter.

First, although the median T_{max} of intravenous acetaminophen in CSF was 2 hours in the cited study,[3] smaller concentrations of acetaminophen were detectable much sooner and in much higher concentrations when compared with oral administration. Indeed, the C_{max} for oral acetaminophen (T_{max} 4 hours) is reached via the intravenous route within 1 hour.[3] To assume clinical effects occur only at T_{max} would be misleading. At present, to our knowledge, it is unknown at what concentration the analgesic effects of acetaminophen occur in relation to CSF concentrations, although using experience from clinical practice we can assume this would occur much sooner than the C_{max}. To illustrate using an example from the literature, intravenous acetaminophen was used in 1 randomized controlled trial to reduce acute traumatic limb pain.[4] Clinically significant reductions in mean visual analog scale scores occurred 30 minutes after administration rather than the later time point of 2 hours. Therefore, lower CSF concentrations may produce clinical effects before reaching the C_{max}.

Second, to focus solely on CSF concentrations as the basis on which to judge clinical efficacy may neglect alternative mechanisms of action of acetaminophen. Although the most likely mechanisms of action of acetaminophen are central (such as central cyclooxygenase inhibition, serotonergic, and cannabinoid pathways), peripheral inhibition of cyclooxygenase 2 may also be a potential mechanism of action.[5] Therefore, plasma pharmacokinetics may be relevant in the context of explaining peripheral efficacy on the basis of C_{max} concentrations. So in regard to the points made previously, as the clinical effects of intravenous acetaminophen are observed within 30 minutes, even if we assume that preventive acetaminophen was therapeutic in the early postoperative period, this may not be sufficient to explain the lower pain scores observed up to 2 hours postoperatively and the reduction in 24-hour opioid consumption. At the very least, it is safe to assume that postincision C_{max} would occur later in the postoperative period when compared with preventive administration (for single-dose studies).

Ultimately, our review was aimed at answering the clinical question: Is preventive acetaminophen more effective than postincision acetaminophen at reducing pain and opioid consumption postoperatively, whatever the mechanism? We thank Dr Yap for her contribution to the discussion of the potential mechanisms for this, which at this point remain speculative. Certainly, using the timings of CSF C_{max} concentrations does correlate with our observed pain score reductions, which may be the subject of future research. However, we hope our review will stimulate clinical research in this area, which improves on the flaws of those published previously.

Brett Doleman, MBBS(Hons), BSc(Hons)
David J. Read, BMBS
Jonathan N. Lund, DM
John P. Williams, PhD
University of Nottingham
Derby, United Kingdom

Conflicts of interest: B.D., J.N.L., and J.P.W. are undertaking a randomized controlled trial of preventive acetaminophen for postoperative pain and a Cochrane Review on preventive analgesia for postoperative pain. D.J.R. declares no conflict of interest.

REFERENCES

1. Yap AJCY. The pharmacokinetics of preventive acetaminophen. *Reg Anesth Pain Med*. 2016;41:413.

2. Doleman B, Read D, Lund JN, Williams JP. Preventive acetaminophen reduces postoperative opioid consumption, vomiting, and pain scores after surgery: systematic review and meta-analysis. *Reg Anesth Pain Med*. 2015;40:706–712.
3. Singla NK, Parulan C, Samson R, et al. Plasma and cerebrospinal fluid pharmacokinetic parameters after single-dose administration of intravenous, oral, or rectal acetaminophen. *Pain Pract*. 2012;12:523–532.
4. Craig M, Jeavons R, Probert J, Benger J. Randomised comparison of intravenous paracetamol and intravenous morphine for acute traumatic limb pain in the emergency department. *Emerg Med J*. 2012;29:37–39.
5. Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *FASEB J*. 2008;22:383–390.

Species Variation in Effects of Intrathecal κ-Opioid Receptor Agonist on Morphine-Induced Itch and Antinociception

Accepted for publication: December 16, 2015.

To the Editor:

We read with great interest the article by Sakakihara and colleagues,[1] entitled "Effects of intrathecal κ-opioid receptor agonist on morphine-induced itch and antinociception in mice," published in *Regional Anesthesia and Pain Medicine.* They describe the rationale of their study, "Research suggested that systemically administered κ-opioid receptor (KOR) agonists inhibit intrathecal morphine-induced itch in primates. However, serious adverse effects induced by systemically administered KOR agonists may restrict their usefulness in humans." The authors demonstrated that intrathecal KOR agonists exert antipruritic effects on intrathecal morphine-induced itch without affecting sedation, and that combination of intrathecal morphine and intrathecal KOR agonists produces more potent antinociceptive effects against a thermal stimulus when compared with morphine alone.

Nearly 3 decades ago, Pfeiffer and colleagues[2] suggested that agonism of the KOR elicits dysphoric and psychotomimetic effects in humans. They reasoned that, in humans, μ agonists produce euphorigenic actions which seem to be opposed to the dysphoric effects of the κ agonist (ie, the endogenous opioid systems associated with μ and κ receptors may serve opposite functions in processes affecting emotional and perceptual experiences).[2] In the paper by Pfeiffer et al, the psychotomimetic effects which subjects experienced included racing thoughts, feelings of body distortion, disturbances in the perception of space and time, abnormal visual experiences such as moving lines or walls or color phenomena, and uncontrolled laughter. We question how, and if, such psychotomimetic experience is manifested in the murine model of Sakakihara et al using intrathecal KOR agonists along with intrathecal morphine.

Further, the antipruritic effect of κ agonists may involve peripheral KOR as well.[3] μ-Opioid receptor (MOR) and KOR are expressed in the skin and central nervous system (CNS).[4] μ-Opioid receptor and KOR mediate different effects. Activation of MOR inhibits pain, whereas activation of KOR inhibits itch.[3] κ-Opioid receptors participate in the pathophysiology of pruritus not only by their expression in the CNS but also by their presence in the skin.[3] Phan and colleagues[3] suggested that the application of KOR agonists as systemic, and probably also topical, agents is a promising therapeutic approach to chronic pruritus. Despite many observations and treatments, it is extremely difficult, if not impossible, to differentiate peripheral KOR effects from activity within the CNS.[5] Phan and colleagues[4] further suggested that pruritus might arise from an imbalance of the MOR and KOR system activity in either the skin or CNS.

We previously encountered a case of intractable itching in a 56-year-old woman, being treated for failed back surgery syndrome, while undergoing an outpatient epidural hydromorphone infusion trial.[6] Our patient had been taking longstanding oxycodone extended-release 40 mg twice a day, before her epidural infusion trial, without experiencing any itching, nor did she experience any itching with oral methadone at 20 mg twice a day after the hydromorphone epidural infusion trial. Yet, she experienced intractable pruritus while receiving a minimal dose of hydromorphone epidural infusion (0.72 mg daily during a 7-day trial).[6] We performed a focused literature review and hypothesized that the centrally located MOR plays a major role in opioid-induced pruritus, whereas κ-opioid activity antagonizes opioid-induced pruritus.

Because psychotomimetic effects are centrally mediated, one would intuit that central KOR plays a most dominant role, if not an exclusive one. In this regard, intrathecal κ agonist infusion in humans may potentially (at least in theory) lead to dysphoric and psychotomimetic effects. Thus, we question the clinical utility of centrally administering κ-receptor agonist in humans. However, the work of Sakakihara et al showing improved analgesia and reduced itching in mice, when intrathecal KOR agonists and morphine (MOR agonists) are coadministered is not only enlightening but also deserving of further investigation.

Xiulu Ruan, MD
Department of Anesthesiology
Louisiana State University Health Science Center
New Orleans, LA

Gary W. Bumgarner, PhD
McWhorter School of Pharmacy
Samford University
Birmingham, AL

Alan David Kaye, MD, PhD
Department of Anesthesiology
Louisiana State University Health Science Center
New Orleans, LA

The authors declare no conflict of interest.

REFERENCES

1. Sakakihara M, Imamachi N, Saito Y. Effects of intrathecal κ-opioid receptor agonist on morphine-induced itch and antinociception in mice. *Reg Anesth Pain Med*. 2016;41:69–74.
2. Pfeiffer A, Brantl V, Herz A, Emrich HM. Psychotomimesis mediated by kappa opiate receptors. *Science*. 1986;233:774–776.
3. Phan NQ, Lotts T, Antal A, Bernhard JD, Ständer S. Systemic kappa opioid receptor agonists in the treatment of chronic pruritus: a literature review. *Acta Derm Venereol*. 2012;92:555–560.
4. Phan NQ, Bernhard JD, Luger TA, Ständer S. Antipruritic treatment with systemic μ-opioid receptor antagonists: a review. *J Am Acad Dermatol*. 2010;63:680–688.
5. Bigliardi PL, Bigliardi-Qi M. Peripheral opioids. In: Carstens E, Akiyama T, eds. *Itch: Mechanisms and Treatment*. Boca Raton, FL: CRC Press/Taylor & Francis; 2014. Chapter 18. Available at: http://www.ncbi.nlm.nih.gov/books/NBK200922/.
6. Ruan X, Ma L, Couch JP, Chen T, Bumgarner GW. Intractable pruritus during outpatient epidural hydromorphone infusion: a case report and a focused review of the literature. *J Opioid Manag*. 2015;11:184.

Reply to Dr Ruan

Accepted for publication: January 27, 2016.

To the Editor:

We thank Ruan et al[1] for their great interest in our study, which demonstrated the effects of an intrathecal κ-opioid