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Preventive acetaminophen reduces postoperative opioid consumption, vomiting and pain scores following surgery: systematic review and meta-analysis.

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Abstract

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, they showed a reduction in 24-hour opioid consumption (SMD of -0.52; 95% CI -0.98 to -0.06), lower pain scores at 1 hour (MD -0.50; 95% CI -0.98 to -0.02), 2 hours (MD -0.34; 95% CI -0.67 to -0.01) and a lower incidence of postoperative vomiting (RR 0.50; 95% CI 0.31 to 0.83) in the preventive acetaminophen group. Current studies are limited by potential risk of bias.

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

Introduction

Postoperative pain is a common consequence of major surgery with an incidence of around 80%, with 39% of these patients experiencing severe or extreme pain.¹ Over half of patients are treated with intravenous opioids following 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 (COX) inhibition, serotonergic activation and/or cannabinoid (CB) 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% CI 3.4 to 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 choice for high-risk patients as an alternative to NSAIDs.

It has been suggested that preventive analgesia might improve postoperative pain¹⁰ and reduce the need for opioid analgesics after surgery. By providing early and adequate analgesia prior to surgical incision, it is hoped that preventive analgesia can reduce central sensitization resulting from surgical incision,¹¹ and provide more effective pain control in the postoperative period compared with the same analgesic given postincision.¹² Following initially promising results in animal models, two 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 non-steroidal anti-inflammatory drugs (NSAIDs), epidural analgesia, ketamine or intravenous opioids.¹³ A more recent review¹⁴ however found an opioid sparing effect of preventive epidural analgesia, local anaesthetic wound infiltration and NSAIDs. Other useful clinical endpoints such as reductions in opioid-related side effects or adverse events were not evaluated within either review.^{13 14}

However, the role of acetaminophen as a preventive analgesic is yet to be elucidated. Randomized controlled trials have been published over 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 comprising patients who had received postincision acetaminophen.

The study search was conducted in August 2014 by one of the study authors (BD). Electronic databases searched included MEDLINE (1946-2014), EMBASE (1974-2014), Cinahl (1981-2014), CENTRAL and AMED (1985-2003). 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 keywords 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 one hour before induction of anesthesia) versus postincision (any time between postincision and within 30 minutes from the end of surgery). We included patients over the age of 16. All types of surgery were considered.

We had no language restrictions in the search. Papers were translated if necessary using Google Translate. We excluded papers that focused on pediatric populations and papers that studied preventive acetaminophen versus placebo. Inclusion and exclusion criteria were independently assessed by two study authors (BD and JPW) and agreement 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 two study authors (BD and DR). 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 tool¹⁶ by two study authors (BD and DR) and agreement reached by consensus. Where outcome data were not available, authors were contacted to provide additional information. If no reply was received, data was 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 (MD). Pain scores were converted to a ten-point scale. Due to the different opioids used, 24-hour opioid consumption is presented as standardized mean differences (SMD). We regarded clinically significant SMD values as small >0.3, moderate >0.5 or large >0.7. Dichotomous data are presented as risk ratios (RR) and numbers needed to treat (NNT)

where appropriate. All results are presented with 95% confidence intervals (CI). Random-effects modeling was used due to significant clinical heterogeneity in the included studies.

Publication bias was assessed using a one-tailed Egger's linear regression test. Statistical heterogeneity was assessed using the I^2 statistic with p values derived from the chi-squared statistic. Investigation of heterogeneity was undertaken using 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, removing studies that used spinal anesthesia, those that gave additional postoperative doses and using one study-removed analysis. All analyses were undertaken using Comprehensive Meta-analysis 3¹⁸ 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 one study replied with information following searching of unpublished studies on clinical trial databases (Figure 1). Following 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 (60) and the active arm used paracetamol (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 due to 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 (Figure 2). Surgical procedures were diverse with each study focussing on different types of surgery²⁷ with varying degrees of postoperative opioid consumption (0.4mg-35mg). The percentage of female participants ranged from 15-100%. All studies used intravenous acetaminophen with two studies giving additional postoperative doses.^{21 24} Mean duration of surgery ranged from 60-135 minutes. The initial dose of acetaminophen was given 15-30 minutes before induction of anesthesia in 5 studies,^{20 21 22 24 26} 30 minutes pre-operatively in 1 study²³ and 10 minutes before incision in 1 study.²⁵

Postoperative analgesia

Six studies²⁰⁻²⁵ were included in the meta-analysis (Figure 3). Overall, they showed lower 24-hour opioid consumption in the preventive acetaminophen group with a 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 as there was no specified time frame over which opioid consumption was measured (47mg versus 51mg; $p=0.24$).

There was no evidence of publication bias ($p=0.32$). On meta-regression, morphine equivalent consumption in the control group predicting the majority of the heterogeneity between the studies ($R^2=58%$; $p=0.005$). Sensitivity analysis showed reductions in morphine were heavily influenced by one study²⁰ and analysis with studies at lower risk of bias resulted in lower opioid consumption (SMD -0.98; 95% CI -1.71 to -0.24). Removing the study that used spinal anesthesia²³ did not affect results. Excluding studies that gave additional postoperative doses led to 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 four 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 minutes to 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 (Figure 4) with a 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 (Figure 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 ($I^2=52\%$; $p=0.04$). 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 five postoperative vomiting^{20 22 24 25 26}. One study²⁶ 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 a RR of 0.78 (95% CI 0.43 to 1.41). There was evidence of publication bias ($p=0.03$). However, there was a lower risk of postoperative vomiting (Figure 6) in the preventive group, with a RR of 0.50 (95% CI 0.31 to 0.83) and a NNT of 11 (95% CI 6.1 to 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 as no events occurred in either group.²² The RR was 0.32 (95% CI 0.01 to 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 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 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 anaesthesia and local anaesthetic wound infiltration.¹⁴ Despite this, evidence for a potential role for other peri-operative 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 peri-operative acetaminophen administration could have important implications for postoperative pain management.

Preventive acetaminophen was found to reduce the risk of postoperative vomiting. The risk ratio for reductions in vomiting compared well with traditional antiemetics such as cyclizine, dexamethasone, metoclopramide and ondansetron.²⁹ The potential mechanism may include the reduction in morphine consumption in the preventive group. However, a meta-analysis of randomized controlled trials examining peri-operative acetaminophen in postoperative nausea and vomiting found 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 CB agonist anandamide.⁸

Our results with regards 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 two 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 0-2 hours postoperatively, and the duration of surgery between 60-135 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 2-4 hours in adults,⁴ any dose of acetaminophen given before surgery would more likely be sub-therapeutic 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 with this review. The major limitation relates to the risk of bias in the included studies (Figure 2). Only two studies described adequate allocation concealment, four described adequate randomisation and one described adequate blinding of outcome assessment. All have the potential to bias effect estimates in the preventive group.³⁰ Secondly, 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 higher control group opioid consumption predicted larger absolute reductions in opioid consumption, suggesting preventive acetaminophen might be more effective in more painful procedures, a finding consistent with previous research.^{31 32} Only one study in the review had a 24-hour morphine usage above 20mg, which may influence the clinical significance of results obtained. Thirdly, 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 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.

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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)]

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Legend to Figures

Figure 1: PRISMA flowchart for included studies

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

Figure 3: Forest plot for 24-hour opioid consumption

Figure 4: Forest plot for pain scores at 1 hour

Figure 5: Forest plot for pain scores at 2 hours

Figure 6: Forest plot for the incidence of postoperative vomiting

