Meta-Analysis

Effect of Preemptive Acetaminophen on Opioid Consumption: A Meta-Analysis

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Background: Strategies for reducing postoperative opioid consumption have been explored in many recent studies, due in large part to the recent opioid epidemic. Preemptive analgesia has been proposed as a potential method, but its use is still controversial.

Objectives: This review aimed to evaluate the efficacy of a single dose of acetaminophen as preemptive analgesia for patients undergoing general anesthesia.

Study Design: A meta-analysis of randomized controlled trials (RCTs).

Setting: The electronic databases of PubMed, EMBASE, Cochrane Library, and the Web of Science were searched. The protocol was previously registered in the PROSPERO database under the registration number CRD 42020165634.

Methods: We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. RCTs that compared preemptive acetaminophen with placebo in surgical patients receiving general anesthesia were included. The risk of bias for each included study was independently assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

Results: Six studies with 563 patients were included. Overall, the studies showed a reduction in 24-hour opioid consumption (standardized mean difference [SMD], –1.45; 95% confidence interval [CI], –2.36 to –0.55; $P = 0.002$), pain scores at 12 hours postoperatively (SMD, –0.86; 95% CI, –1.25 to –0.48; $P < 0.0001$), and a lower incidence of postoperative nausea (risk ratio [RR] 0.45; 95% CI, 0.34–0.58; $P < 0.001$) and vomiting (RR 0.39; 95% CI, 0.22–0.72; $P = 0.002$).

Limitations: The major limitation of this meta-analysis relates to the risk of bias in the limited number of included studies.

Conclusions: Preemptive acetaminophen administration significantly reduces opioid consumption within the initial 24 hours following general anesthesia, with lower pain scores at 12 hours after surgery, and less nausea and vomiting. However, well-conducted RCTs are still needed.

Key words: Acetaminophen, preemptive analgesia, perioperative pain management, postoperative opioid consumption, opioid-related side effects

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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). Clinicians are often faced with the challenge of tapering opioid prescriptions while simultaneously providing effective postoperative pain management, due in large part to the current opioid crisis (2). Although opioids are extremely effective in postoperative pain management, they have also been associated with somnolence, respiratory

depression, hypotension, nausea and vomiting (3). Thus alternative analgesia strategies to reduce opioid consumption should not be overlooked (1), as effective postoperative pain management has direct influences on surgical outcome and patient recovery (4).

Acetaminophen's analgesic effects rely on a sufficient concentration of acetaminophen at central sites and thus must rapidly, although passively, cross the blood–brain barrier to reach a threshold concentration in the cerebrospinal fluid (5). The exact route and timing of administration can vary from the preoperative, intraoperative, and postoperative periods. For perioperative pain management, acetaminophen is often part of a multimodal strategy that is recommended in many guidelines (6). Langford et al (7) have reported that peak plasma concentrations of acetaminophen were greater and were reached earlier after intravenous (IV) dosing than with oral (PO) dosing (Table 1). A recent meta-analysis reported that IV acetaminophen is effective for managing postoperative pain (8), but whether acetaminophen as preemptive analgesic could reduce postoperative opioid consumption effectively remains controversial.

Preemptive analgesia is an emerging analgesic mode that, according to the American Society of Anesthesiologists, when administered prior to the painful stimulus, may relieve postoperative pain and reduce analgesic consumption (9,17,20). The efficacy of preemptive analgesia remains unknown, as the results of clinical trials in humans have not consistently found benefit (10). Therefore this meta-analysis aimed to examine the use of acetaminophen as preemptive analgesic and its impact on postoperative opioid consumption, postoperative pain, and opioid-related side effects.

Table 1. *Pharmacokinetics table of acetaminophen IV vs. PO.*

Plasma	Acetaminophen 1g IV	Acetaminophen 1g PO
C_{max} (mg/L)	46.1 (21.7-99.7)	18.0 (2.8-30.8)
T_{max} (min)	15 (15-15)	120 (30-360)
AUC (total) (mg min/L)	3924 (2937-7323)	2659 (527-5616)
AUC (first hour) (mg min/L)	1688 (880-2992)	87 (0-907)
AUC (second hour) (mg min/L)	973 (437-1647)	283 (53-1775)

Data are presented as median (range).
Abbreviations: C_{max}, maximum concentration; T_{max}, time to C_{max}; AUC, area under the plasma curve.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for the reporting of meta-analyses of randomized controlled trials (RCTs). The protocol was previously registered in the PROSPERO database under the registration number CRD 42020165634.

RCTs that evaluated the effect of preemptive acetaminophen on postoperative opioid consumption were considered eligible for the systematic review. Included RCTs evaluated preemptive administration, defined as before incision, of acetaminophen as compared with placebo in patients older than age 16 years undergoing inpatient surgeries under general anesthesia. RCTs reporting postoperative use of acetaminophen, whether alone or in addition to a preoperative administration, were excluded from the analysis. Inclusion and exclusion criteria were independently assessed by 2 study authors (CX and DW), and agreement was reached by consensus.

Search Strategy

Electronic databases searched included PubMed, Cochrane Library, EMBASE, and the Web of Science. Search terms included the free text words within the title or abstract "preemptive" or the medical subject headings (MeSH) "acetaminophen" AND MeSH "pain, postoperative." No search was performed for unpublished studies, nor was a minimum sample size required for inclusion in the meta-analysis.

Two authors independently evaluated the full manuscripts of all included trials and performed data extraction using a standardized data collection form specifically developed for this review. Data extraction included administration, sample size, follow-up period, type of surgery, pain scores (Visual Analog Scale [VAS]), cumulative opioid consumption, and adverse events. The pain VAS was converted to an 11-point (0 to 10) Numeric Rating Scale. Individual authors were contacted to provide additional information when outcome data were not available, and data were extracted from graphs if no reply was received. The primary outcome was opioid cumulative consumption during the initial postoperative period (24 hours). Other outcomes assessed included postoperative pain scores, nausea and vomiting.

Assessment of Bias

The risk of bias for each included study was independently assessed using the criteria outlined in

the Cochrane Handbook for Systematic Reviews of Interventions (11). This included assessment of random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), blinding of the outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other types of biases. There are 3 bias assessment criteria for each point, namely "low," "high," and "unclear." Given that the number of RCTs included in this analysis was less than 10, we did not perform an assessment of publication bias. This is consistent with previous studies in which approaches for detection of publication bias would have exhibited limited efficacy (16).

Statistical Analysis

A fixed-effect model and a random-effects model were used following an evaluation of the heterogeneity in the included RCT. Statistical heterogeneity was assessed using the I^2 statistic and Cochran's Q statistic. Although a fixed-effect model was utilized in the absence of heterogeneity, a random-effects model was used when there existed heterogeneity. Heterogeneity was assumed to be present when the *P* value was < 0.05 or the I^2 exceeded 50%. Results for cumulative consumption of opioids during the initial 24 hours following surgery are reported as a standardized mean difference (SMD) and their associated 95% confidence intervals (CI). The incidence of secondary outcomes including nausea and vomiting are reported as relative risks and their associated 95% CIs. For all analyses, a 2-tailed *P* value < 0.05 was considered statistically significant. All analyses were taken using Review Manager (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) (13).

Results

A total of 14,202 relevant citations were identified using the search strategy, of which 3,675 were duplicate studies (Fig. 1). After review of the abstracts, 57 studies were identified as potentially relevant to the research question. Studies were excluded because of the study outcome (n = 20), did not include general anesthesia (n = 12), received multimodel analgesia with other medications (n = 7), were retrospective (n = 6), did not include a comparison with placebo (n = 5), or those for which we were unable to extract data (n = 1). The final analysis included a total of 6 RCTs including a total of 563 patients. Of the 563 patients, 280 received preemptive acetaminophen, whereas the remaining 283 received a control (Table 2). There were no opioids utilized by patients prior to the day of surgery, and there was no report of home opioids for discharge.

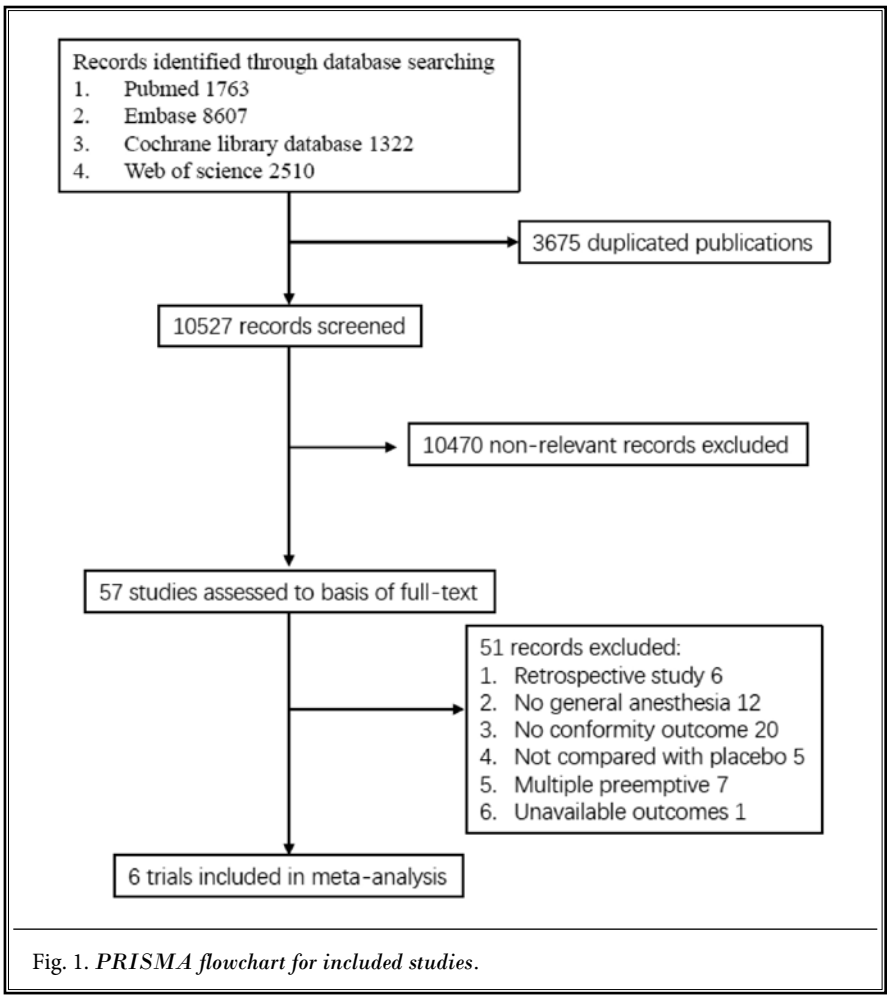

Fig. 1. *PRISMA flowchart for included studies.*

Literature Quality Evaluation

When assessing the risk of bias, 4 trials (67%) mentioned random sequence generation, 3 (50%) trials were double-blind clinical studies, and 3 trials (50%) were unclear of blinding. Only one study (21) was at "high" risk of an incomplete outcome bias. Other biases of all 6 trials were unclear, as shown in Fig. 2. No studies were excluded according to the result of this evaluation.

Preemptive Acetaminophen Effects on Opioid Consumption

Only 12-hour opioid consumption was reported in one study (23), so it was excluded for the 24-hour opi-

Table 2. *Characteristics of included studies.*

Study	Gender	Sample size	Mean age	Surgery duration (min)	Intervention	Surgery	Outcome	Opioid dosage and interval
Semih Arici 2009 (18)	100%	55	50.1	118	1.0 g intravenous acetaminophen 30 min before induction	Elective abdominal hysterectomy	Pain score, sedation, morphine consumption, nausea, vomiting, respiratory depression, pruritus, constipation, length of stay	PCA with morphine: 1mg/ml morphine with a PCA device programmed for a 2mg bolus with a 10 min lockout period and a 0.4mg/kg 4-h limit.
Young-Eun 2011 (24)	100%	71	45	145.3	2.0 g intravenous acetaminophen 30 min before induction	Elective abdominal hysterectomy	Pain score, hydromorphone consumption, nausea, vomiting, sedation, respiratory depression, pruritus, requiring antiemetics	PCA with hydromorphone: 0.2 mg of hydromorphone with a lock-out of 10 min and no continuous infusion. Ketorolac 30 mg IV injection was suppled if postoperative analgesia was felt to be inadequate.
Mustafa 2013 (19)	66%	200	42.9	94	1.0 g intravenous acetaminophen 10 min before incision	Laparoscopic cholecystectomy	Pain scores, tramadol consumption, nausea, vomiting, respiratory depression, pruritus, rash, allergy, stomach irritation, diarrhea, constipation, headache, sedation, dry mouth, sweating, hypotension, patient satisfaction	In case of inadequate analgesia, patients of all groups received tramadol, IV 100 mg of starting dose and the same dose was repeated with a maximum dose of 400 mg daily.
Vida Ayatollahi 2014 (23)	100%	60	28.3	NR	1.0 g intravenous paracetamol 20 min before induction	Elective cesarean section	Pain score, pethidine consumption, systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, time of first analgesic	If VAS was ≥ 5, 0.5 mg/kg IV pethidine was administrated.
Erkan Cem Celik 2018 (20)	54%	100	26.1	133.9	1.0 g intravenous paracetamol before surgery	Open septorhinoplasty	Pain score, tramadol consumption, breathing depression, sedation, urinary retention, nausea, vomiting, pruritus, constipation, bleeding, dyspepsia	PCA with a demanded dose of 20 mg tramadol, and a 20 min lockout interval. If VAS was ≥ 4, 25mg meperidine was given to patients.
Lindsay 2019 (21)	100%	101	61.2	NR	1.0 g intravenous acetaminophen 10-30 min before incision	Laparoscopic or robotic route	Pain score, morphine milligram equivalents consumption, nausea, drowsiness, itching, dizziness	Did not report precisely.

Abbreviations: NR, not reported; PCA, patient-controlled analgesia.

oid consumption report. The 24-hour opioid consumption was reported in the other 5 trials among patients in the acetaminophen (n = 250) and control groups (n = 253). Significant heterogeneity was observed between trials (I^2 = 95%), therefore results of the random-effects model are reported. Compared with the control group, administration of preemptive acetaminophen was associated with a statistically significant decrease in cumulative opioid consumption (SMD, –1.45; 95% CI, –2.36 to –0.55; *P* = 0.002; Fig. 3). To explore the stability of this result, sensitivity analyses were performed by removing one study at a time and recalculating the pooled SMD results did not find substantial modification of cumulative opioid consumption after exclusion of any individual study (Supplement 1).

Pain Scores

When assessing postoperative pain scores, there was evidence of considerable statistical heterogeneity (I^2 = 59% and 88% for 12 and 24 hours, respectively), thus the random-effects model was reported. Pain scores were significantly lower in the preemptive acetaminophen group compared with the placebo group at 12 hours (Fig. 4A), with a mean difference of –0.86 points (95% CI, –1.25 to –0.48). Results of the sensitivity analysis demonstrated that the pain score at 12 hours remained consistent after removing the trials one by one.

At 24 hours (Fig. 4B), the pain scores of patients in the preemptive acetaminophen group were not statistically different than patients in the placebo group (–0.54, 95% CI, –1.17 to 0.09), with considerable statistical heterogeneity. Sensitivity analyses showed that pain scores at 24 hours were heavily influenced by Mustafa 2013 (19) or Erkan 2018 (20). Removing each study showed that preemptive acetaminophen administration lowers pain scores compared with the placebo group (SMD –0.99; 95% CI, –1.26 to –0.17 and –0.22; 95% CI, –0.42 to –0.02 for Mustafa and Erkan, respectively). Further, once removed, the analysis of studies at a lower risk of bias resulted in lower pain scores (Mustafa 2013 removed: –0.99; 95% CI, –1.26 to –0.17, Erkan 2018 removed: –0.22; 95% CI: –0.42 to –0.02). These results are presented using

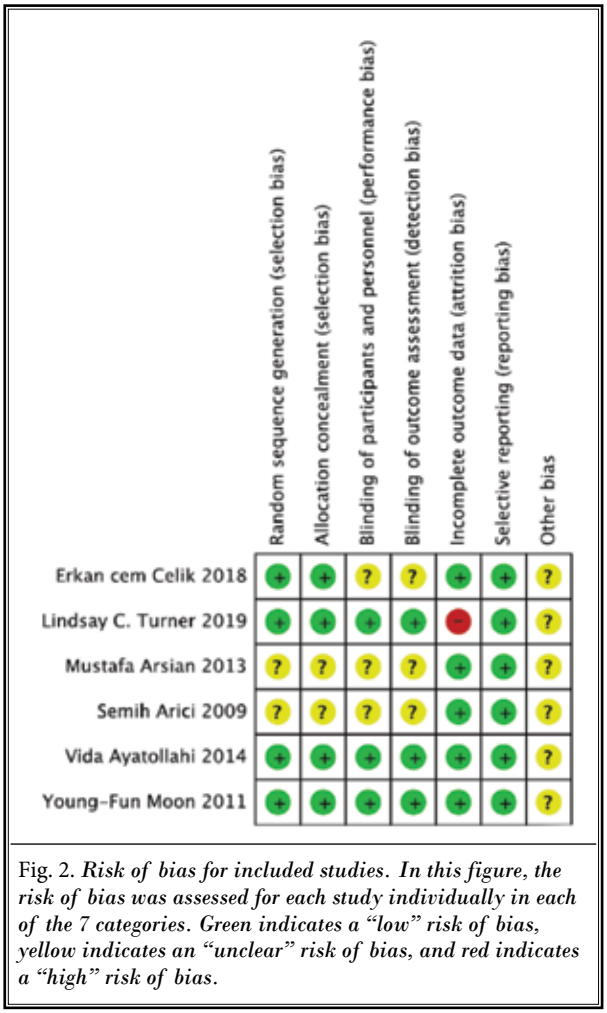

Fig. 2. *Risk of bias for included studies. In this figure, the risk of bias was assessed for each study individually in each of the 7 categories. Green indicates a "low" risk of bias, yellow indicates an "unclear" risk of bias, and red indicates a "high" risk of bias.*

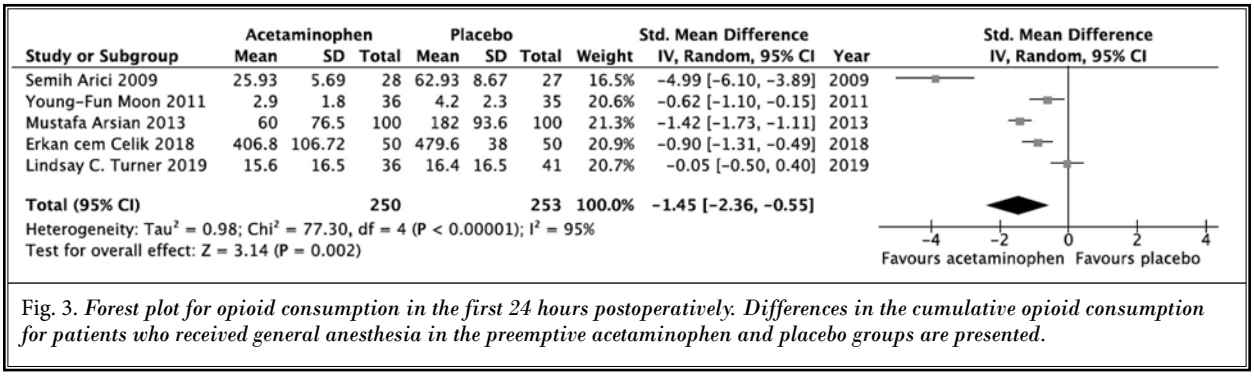

Fig. 3. *Forest plot for opioid consumption in the first 24 hours postoperatively. Differences in the cumulative opioid consumption for patients who received general anesthesia in the preemptive acetaminophen and placebo groups are presented.*

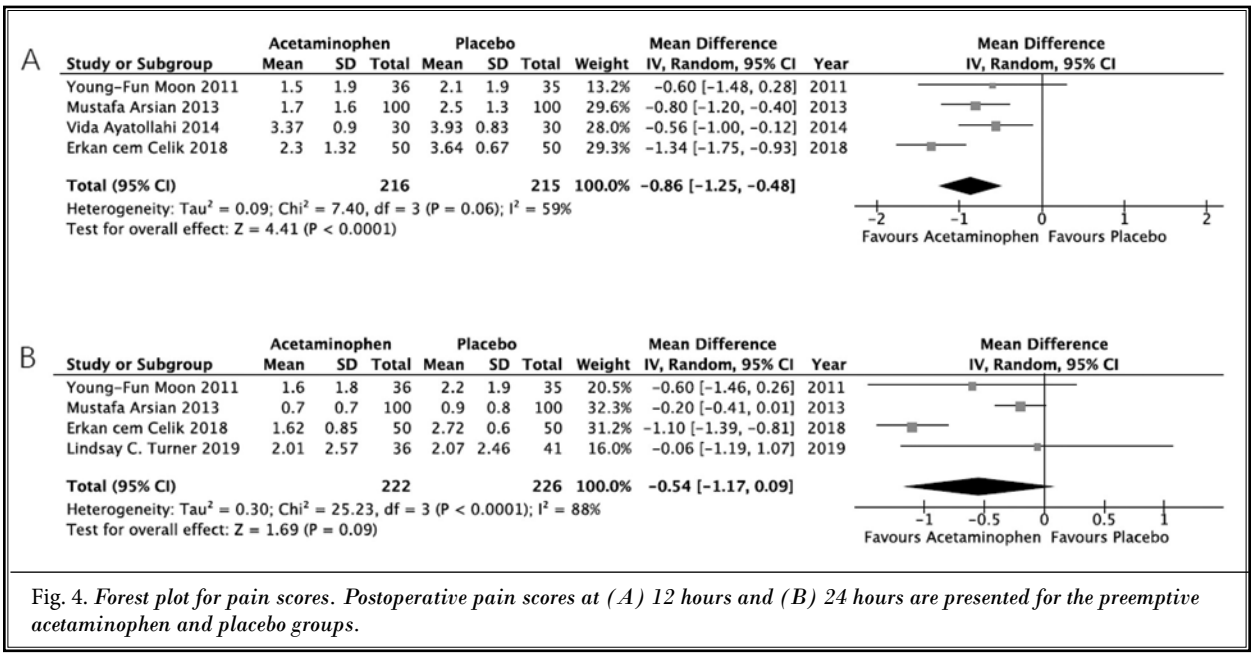

Fig. 4. *Forest plot for pain scores. Postoperative pain scores at (A) 12 hours and (B) 24 hours are presented for the preemptive acetaminophen and placebo groups.*

the fixed-effects model because of the lack of statistical heterogeneity (I^2 = 49% or I^2 = 0%, respectively). Thus the effect of preemptive acetaminophen on 24-hour pain scores should be cautiously interpreted.

Opioid-Related Side Effects

Nausea and vomiting incidence rates were reported in 4 (67%) of the 6 trials and were thus analyzed. No statistically significant heterogeneity was observed in this analysis of nausea; thus the fixed-effects model results are presented (I^2 = 50%, P = 0.11). A statistically significant decrease in the incidence of nausea was observed between the acetaminophen and placebo groups (risk ratio [RR], 0.45; 95% CI, 0.34–0.58) in the meta-analysis (Fig. 5A). Similarly, a lower incidence of postoperative vomiting was observed in the preemptive group, with an RR of 0.39 (95% CI, 0.22–0.72; Fig. 5B).

Discussion

In this systematic assessment regarding the effects of preemptive acetaminophen, a reduced cumulative postoperative opioid consumption was observed when compared with placebo. The use of preemptive acetaminophen analgesia also resulted in a significantly reduced incidence of postoperative nausea and vomiting. Further, preemptive analgesia resulted in lower pain scores at 12 hours postoperatively, however, its effect at 24 hours could not definitively be determined.

Acetaminophen has long been theorized to decrease opioid consumption due to enhancement of pain control. Preemptive analgesia is a safe and potentially inexpensive intervention that has commonly been used as a part of multimodal analgesia regimens to improve postoperative pain control, decrease opioid use and related side effects, and improve the length of stay required for postoperative recovery (10,19-21). A meta-analysis by De Oliveira et al (11) showed that systemic acetaminophen used as a single-use preventive regimen was an effective intervention to improve postoperative pain outcomes, but the meta-regression analysis failed to detect the association between acetaminophen dose and cumulative opioid consumption. Another meta-analysis study indicated that preventive acetaminophen reduced 24-hour opioid consumption (SMD, –0.52; 95% CI, –0.98 to –0.06) compared with acetaminophen given after incision (12). Our study indicated that, compared with placebo, the preemptive acetaminophen significantly decreased cumulative opioid consumption after general anesthesia. Both of the previous studies included all types of anesthesia, however, we only included patients undergoing general anesthesia in this review because preemptive acetaminophen administration may have various clinical effects on different types of anesthesia, thus removing this potential critique of the previous literature.

The results of Doleman's meta-analysis (12) demonstrated that preventive acetaminophen compared with acetaminophen given after incision resulted in lower

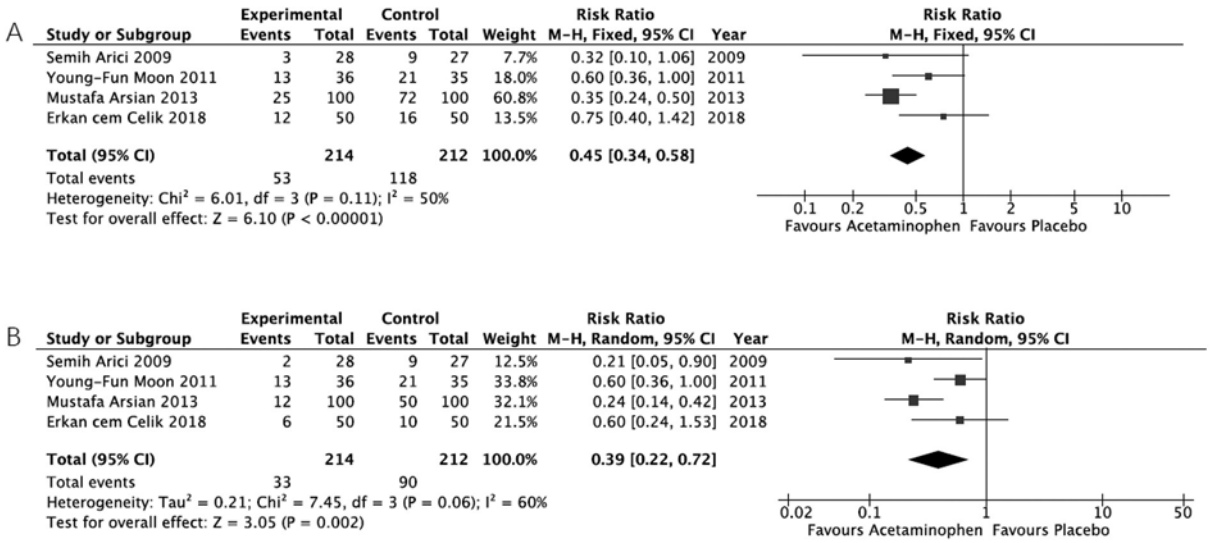

Fig. 5. *Forest plot for the postoperative nausea and vomiting. The incidence of (A) nausea and (B) vomiting are presented.*

postoperative pain scores up to 2 hours postoperatively. In our study, compared with placebo, preemptive acetaminophen administration could reduce pain score at 12 hours postoperatively. However, some well-conducted RCTs are necessary to indicate the effect of preemptive acetaminophen on pain scores outside of the immediate postoperative period. In addition, there was a significant difference in the risk of postoperative nausea and vomiting in the preemptive group, suggesting that acetaminophen could be used as preemptive analgesia to both improve opioid consumption and reduce opioid-related side effects.

The common routes of acetaminophen administration are IV and PO. In this study, the preemptive acetaminophen was given intravenously, thus the effect of PO acetaminophen could not be detected. A previous study suggested that there was no statistically significant difference in pain scores and opioid consumption between preemptive PO and IV acetaminophen use (14). In another study of patients undergoing regional anesthesia, patients did not have a significant difference in pain scores and postoperative side effects after receiving preoperative PO or IV acetaminophen (15). Given the increased cost associated with an IV route, administration of PO acetaminophen may become an attractive economic selection for preemptive analgesia. However, more generalizable studies with increased power are needed to truly elucidate the clinical effects of PO acetaminophen.

For perioperative pain management, considering using IV acetaminophen is recommended in many guidelines as a part of multimodal strategy. The high cost of the IV dosage form has limited its use (approximately 300 times more expensive than the same PO dose). However, the Hansen et al (22) retrospective study indicated that IV acetaminophen is associated with shorter length of hospital stay and less total hospitalization costs compared with PO acetaminophen.

Potential Biases in the Review Process

There are several limitations in this review. The major limitation relates to the risk of bias in the included studies. Only 3 studies described adequate randomization and blinding of patients and outcome assessment; thus they have the potential to bias-effect estimates in the preventive group. Further limiting our interpretation is the small sample size of most included RCTs (< 50 patients per group). Only one study included over 100 patients per group, which presents challenges in generalizing these conclusions and may impact the effect of acetaminophen on some rare side effects of opioid. Although we limited the type of intervention (single-dose acetaminophen undergoing general anesthesia), we observed high heterogeneity in some of the analyses. Finally, the publication bias and meta-regression was not calculated and evaluated due to the small number of included studies. Performance of more high-quality and well-conducted RCTs are needed.

Conclusions

Preemptive acetaminophen administration significantly reduces opioid consumption within the initial 24 hours following general anesthesia, with lower pain scores at 12 hours after surgery, and less nausea and vomiting. Future rigorously conducted and reported RCTs examining preemptive effect of acetaminophen on postoperative opioid consumption are needed, ensuring that publication bias is avoided.

Author Contributions

Chengluan Xuan helped in writing the abstract, introduction, data acquisition, analysis and interpretation, discussion, and revising the final manuscript. Wen Yan helped design the study, retrieve the data, and analyze the data. Dan Wang helped design the study, retrieve the data, and analyze the data. Ariel Mueller helped with the data analyses and interpretation and revising the final manuscript. Haichun Ma helped with the conception and design, analysis, and interpretation. Jingping Wang helped with the conception and design, analysis and interpretation, revising the final manuscript, and approval of the final submitted manuscript.

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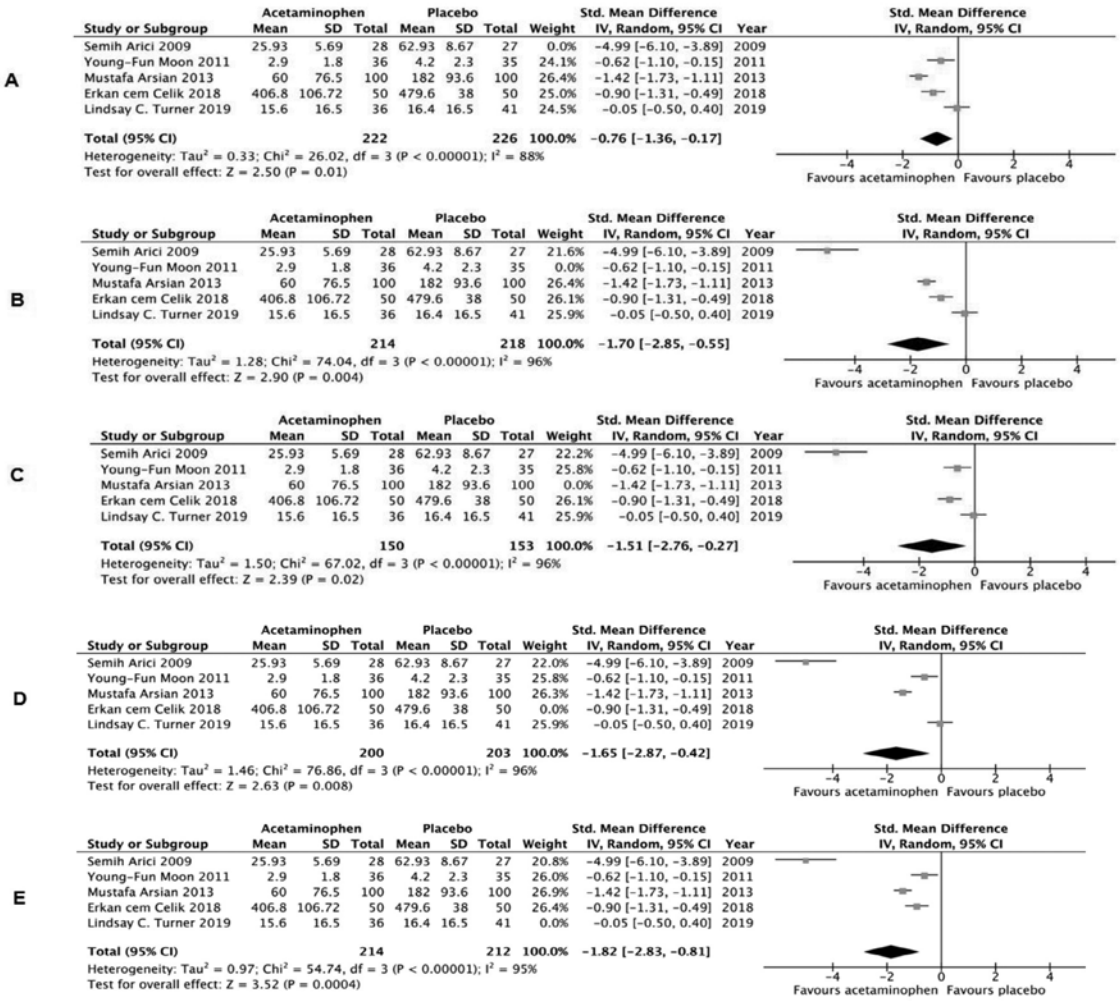

Supplement 1. *A: Sensitivity analysis of opioid consumption for removing study of Semih Arici 2009. B: Sensitivity analysis of opioid consumption for removing study of Young-Fun Moon 2011. C: Sensitivity analysis of opioid consumption for removing study of Mustafa Arsian 2013. D: Sensitivity analysis of opioid consumption for removing study of Erkan cem Celik 2018. E: Sensitivity analysis of opioid consumption for removing study of Lindsay C. Turner 2019.*