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Please cite this article as https://doi.org/10.4097/kja.24089

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Effect of perioperative intravenous ibuprofen versus acetaminophen on postoperative opioid consumption and pain after general anesthesia: a systematic review and meta-analysis with trial sequential analysis of randomized controlled trials

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IV ibuprofen vs. acetaminophen for pain

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[Previous presentation in conferences]: Not applicable.

[Conflict of Interest]: No potential conflict of interest relevant to this article was reported.

[Funding]: Not applicable.

[Acknowledgments]: Not applicable.

[IRB number]: Not applicable.

[Clinical trial registration number]:

PROSERO; https://www.crd.york.ac.uk/PROSPERO, no. CRD42023429275

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Effect of perioperative intravenous ibuprofen versus acetaminophen on postoperative opioid consumption and pain after general anesthesia: a systematic review and meta-analysis with trial sequential analysis of randomized controlled trials

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Running title: IV ibuprofen vs. acetaminophen for pain

Corresponding author:

Previous presentation in conferences: Not applicable

Conflict of interest: No potential conflict of interest relevant to this article was reported.

Funding: Not applicable

Acknowledgments: Not applicable

IRB number:

Clinical trial registration number: PROSPERO; no. CRD42023429275

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Abstract

Background: Ibuprofen and acetaminophen are widely used as adjuvant analgesics for postoperative pain. This meta-analysis compared the effects of intravenous (IV) ibuprofen and acetaminophen on postoperative opioid consumption and pain intensity after general anesthesia.

Methods: PubMed/MEDLINE, EMBASE, and Cochrane Library databases were searched to identify relevant studies published up to May 2023. Randomized controlled trials (RCTs) comparing the effects of perioperative IV ibuprofen and acetaminophen on postoperative opioid consumption and pain after general anesthesia were included in the meta-analysis and trial sequential analysis (TSA).

Results: Eight studies with 494 participants were included. Compared to IV acetaminophen, IV ibuprofen significantly reduced 24 h opioid consumption, presented as morphine equivalents (mean difference [MD]: –6.01 mg, 95% CI [–8.60, –3.42], $P < 0.00001$, $I^2 = 55\%$), and pain scores (on a scale of 0–10) at 4–6 h (MD: –0.83, 95% CI [–1.29, –0.37], $P = 0.0004$, $I^2 = 65\%$) and 12 h (MD: –0.38, 95% CI [–0.68, –0.08], $P = 0.01$, $I^2 = 11\%$) postoperatively. These results were statistically significant in TSA. Pain scores at 24 h postoperatively and side effects were not significantly different between the two groups in the meta-analysis, and TSA revealed that the sample size was too small to adequately evaluate the effects, requiring further studies for conclusive results.

Conclusions: Perioperative IV ibuprofen reduced 24 h opioid consumption and pain severity up to 12 h postoperatively compared to acetaminophen. Additional research is required to assess pain intensity beyond 12 h and side effects.

Keywords: Acetaminophen; General anesthesia; Ibuprofen; Meta-analysis; Opioid analgesics; Postoperative pain.

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Introduction

Postoperative pain management can affect the clinical outcomes and patient satisfaction after surgery [1]. While opioids traditionally play a crucial role in postoperative pain relief, there is an increasing tendency to minimize their usage owing to concerns regarding adverse effects and the risk of addiction [2,3]. In the same context, multimodal analgesia has become a standard practice for postoperative pain control, with acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) gaining popularity as adjunctive analgesics [4-6].

Acetaminophen (paracetamol) and NSAIDs exert their analgesic effects via different mechanisms. Acetaminophen primarily acts centrally by inhibiting the synthesis of prostaglandins via the cyclooxygenase (COX) pathway in the central nervous system, thereby exhibiting analgesic and antipyretic effects [7]. In contrast, NSAIDs have a peripheral effect by inhibiting both COX-1 and COX-2 enzymes, reducing the production of prostaglandins in damaged tissues, and showing analgesic, anti-inflammatory, and antipyretic effects [8]. Among the various types of NSAIDs, ibuprofen, a propionic acid derivative, has been preferred for its less unwanted adverse effects because of the low COX-1:COX-2 inhibition ratio [9].

Both acetaminophen and ibuprofen have been proven effective and safe for the treatment of postoperative pain since the introduction of their intravenous (IV) forms [10,11]. However, the results regarding which drug is more effective are inconsistent [12,13].

The aim of this meta-analysis with trial sequential analysis (TSA) of randomized controlled trials (RCTs) is to comprehensively evaluate and compare the effect of IV ibuprofen and IV acetaminophen on postoperative opioid consumption and pain after general anesthesia.

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Materials and methods

Study design

This systematic review and meta-analysis was designed in accordance with the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' guidelines (Supplement 1). This review was registered with the 'International Prospective Register of Systematic Reviews' (PROSPERO; https://www.crd.york.ac.uk/PROSPERO, no. CRD42023429275)

Information sources and search strategy

A literature search was conducted using the PubMed/MEDLINE, EMBASE, and Cochrane Library electronic databases. The search strategies were established by a librarian with extensive experience in searching for systematic reviews. The search terms included variants of terms, such as 'intravenous,' 'parenteral,' 'administration,' 'ibuprofen,' 'acetaminophen,' 'postoperative pain,' 'opioid,' 'morphine,' 'fentanyl,' 'analgesia,' and 'patient-controlled analgesia,' as well as Medical Subject Heading (MeSH) or EMBASE Subject Heading (EMTREE) terms (Supplement 1). The search was limited to RCTs conducted in humans. There were no restrictions on publication year or language. Grey literature was not excluded. The final search was completed on May 23, 2023.

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Study selection and eligibility criteria

Duplicates were removed after completing the literature search. Primary selection, based on titles and abstracts, was performed independently by two authors (KM and SH). For the final selection, the full texts of the first selection studies were independently assessed for eligibility by two authors (KM and SH). Any disagreements between the two authors were resolved through discussion with a third reviewer.

The inclusion criteria of this meta-analysis were as follows: (1) patients under general anesthesia; (2)

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adult patients; (3) studies comparing IV ibuprofen and IV acetaminophen; (4) perioperative administration of ibuprofen or acetaminophen; (5) appropriate postoperative outcomes (pain scores or opioid consumption) should be presented; and (6) the type of study should be RCTs.

There were no restrictions on the dosage frequency of ibuprofen or acetaminophen.

The exclusion criteria were as follows: (1) non-human studies, (2) type of anesthesia other than general anesthesia (e.g., local anesthesia, regional anesthesia, and sedation and analgesia), (3) pediatric or neonatal patients, (4) non-RCTs, (5) no appropriate postoperative outcomes, (6) non-IV administration of ibuprofen or acetaminophen, and (7) no comparison between ibuprofen and acetaminophen.

Data extraction

Two authors (KM and SH) independently extracted data from the text, tables, and graphs presented in each paper and confirmed that there was no missing or incorrect information. The collected information included the authors' name, publication year, study design, type of surgery, patient characteristics, dose of intervention drug, intervention method (such as the number of dosing and interval), and postoperative outcomes. Postoperative outcomes included 24 h cumulative opioid consumption, postoperative pain scores, side effects, and rescue analgesics.

The mean and standard deviation (SD) of 24 h opioid consumption and pain scores upon recovery from anesthesia, at 4–6 h, 12 h, and 24 h postoperatively were extracted. Pain scores at recovery included scores from emergence from anesthesia until 30 min after surgery. Regarding pain scores at 4–6 h postoperatively, priority was given to the scores at 6 h. If data were not available at 6 h, the data measured at 4 h were used as replacements. Pain was assessed using visual analog scale (VAS) scores and expressed on a scale of 0–10 in all studies except for one that used a scale of 0–100 [14]. In the present meta-analysis, pain scores were shown on a scale of 1–10.

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When outcome data were presented as medians with interquartile ranges [15], the sample mean and SD were estimated using the Box-Cox method recommended by McGrath et al. [16]. In cases where data were presented as graphs [13], two authors independently measured the values from the graphs, and the mean values from their measurements were used for the meta-analysis. When only the mean value was provided [13], the SD was estimated using the RevMan calculator (available at https://training.cochrane.org/resource/revman-calculator).

In addition, data on the number of patients experiencing adverse effects and the use of rescue analgesics were collected. For nausea and vomiting, only studies that separately reported the incidence of nausea or vomiting were included in the meta-analysis. When the results of the studies were insufficient or unclear, the study authors were contacted via email.

Risk of bias (ROB) assessment

In this meta-analysis, the quality of the studies was evaluated using the ROB 2.0 tool recommended by Cochrane for assessing the quality of randomized trials. Two authors (KM and SH) independently performed the evaluations. In cases of disagreements, a third author (H) was involved to resolve them. The ROB for a specific outcome was evaluated across five distinct domains: randomization process (domain 1), deviations from intended interventions (domain 2), missing outcome data (domain 3), measurement of the outcome (domain 4), and selection of the reported result (domain 5). Within each domain, responses to signaling questions determined the evaluations of 'low risk of bias,' 'some concerns,' or 'high risk of bias' [17]. Following the assessments across these five domains, the overall ROB for the specific outcome was determined.

The inter-rater reliability of the assessment of ROB was evaluated using Cohen's kappa, and its values were interpreted as follows: 0–0.20 indicating no agreement, 0.21–0.39 as minimal, 0.40–0.59 as weak,

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0.60–0.79 as moderate, 0.80–0.90 as strong, and values exceeding 0.90 representing almost perfect agreement [18].

Quality of evidence

The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach was used to evaluate the certainty level of evidence for each outcome. This is a systematic and transparent method used to assess and assign confidence levels to evidence in systematic reviews. It considers the ROB, inconsistency, indirectness, imprecision, and publication bias. The certainty level of the evidence was classified as very low, low, moderate, or high [19].

Statistical analysis

Due to the use of different types of opioids across studies, the 24 h opioid dose in each study was converted to morphine milligram equivalents (MME). The mean difference (MD) was calculated for 24 h opioid consumption and pain scores. For dichotomous variables, such as the incidence of side effects and the use of rescue analgesics, the risk ratio or risk difference was calculated using the Mantel-Haenszel estimation model. Outcomes with zero events were calculated using the risk difference. A 95% CI was calculated for all estimates.

Considering the variety in study designs, methodologies, and population characteristics, the random-effects model was applied for the meta-analysis of the effect estimate. To measure heterogeneity, Higgins' I^2, τ using the DerSimonian-Laird estimator, and prediction interval (PI) was used. If τ was 0.0, PI was not calculated. In cases with extensive heterogeneity [20], sensitivity tests were conducted using the leave-one-out analysis method. Publication bias was not evaluated in this meta-analysis because the number of included studies was less than 10.

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The meta-analysis was conducted using Review Manager (RevMan, [Computer program], Version 5.4, The Cochrane Collaboration, 2020.) and Comprehensive Meta-Analysis version 2.0 (Englewood, NJ, USA, 2008). Cohen's kappa for the evaluation of inter-rater reliability was calculated using IBM SPSS Statistics (IBM Corp.; Released 2017; IBM SPSS Statistics for Windows, Version 25.0: IBM Corp.).

TSA

Conventional meta-analyses are at a risk of random errors when dealing with limited data. TSA reduces this risk by calculating the required information size (RIS) for a meta-analysis with a threshold for statistical significance. This methodology provides controls for the potential false-positive and false-negative findings in meta-analyses [21]. In this study, we performed TSA to determine the RIS and evaluate the conclusiveness of our results. A cumulative Z curve was constructed using a random effects model. TSA was conducted to maintain an overall 5% risk of type I error.

The TSA results were interpreted by monitoring the cumulative Z curve. If the curve crossed the trial sequential monitoring boundary or entered the futility area, sufficient evidence existed to accept or reject the anticipated intervention effect, and further studies were not required. In contrast, if the Z curve failed to intersect any boundaries and the RIS was not attained, the evidence to form a conclusion was insufficient, underscoring the necessity for further studies [21].

For dichotomous outcomes, the RIS estimation considered the observed proportion of patients with an outcome in the acetaminophen group (IVA group), a relative risk reduction of 30% in the ibuprofen group (IVB group), a 5% alpha level, a beta of 20%, and the observed diversity in the trials in the meta-analysis.

For quantitative outcomes, the observed SD was used, along with the MD of the observed SD/3, a 5% alpha level, a beta of 10%, and the observed diversity from the trials in the meta-analysis. TSA was

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conducted using the TSA 0.9.5.10 beta software (Copenhagen Trial Unit, Center for Clinical Intervention Research).

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Results

Study selection and characteristics

A total of 6461 articles were identified through the initial database search of PubMed (n = 1491), EMBASE (n = 4293), and the Cochrane Library (n = 677). After removing 1250 duplicates, 5211 articles were screened. Two reviewers (KM and SH) excluded 5181 studies based on their titles and abstracts. Thereafter, the full texts of 30 articles were reviewed. Of the remaining 30 articles, 22 were excluded based on the exclusion criteria. Finally, eight studies (n = 494) were included in the meta-analysis (Fig. 1).

The characteristics of the selected studies are presented in Table 1. All the studies were RCTs conducted on surgical patients under general anesthesia. The types of surgeries varied, including septorhinoplasty [22], laparoscopic cholecystectomy [12,13,23], laparoscopic bariatric surgery [14], laparoscopic gastrectomy [24], lumbar disc surgery [25], and percutaneous nephrolithotomy [15]. The study drugs were injected intravenously, with ibuprofen administered at a dose of 800 mg and acetaminophen at 1000 mg per administration. In a study by Demiroluk et al. [23], the initial dose of ibuprofen was 800 mg, and the subsequent dose was 400 mg. In a study by Çelik et al., the study drugs were administered only once [22], while in others, they were administered multiple times at regular intervals [12-15,23-25].

Postoperatively, opioids were administered via patient-controlled analgesia (PCA) without baseline infusion. The opioids used in the PCA included tramadol [15,22,23], morphine [14,25], and fentanyl [12,13,24]. In cases where pain was not adequately relieved by PCA (e.g., VAS 4 or higher), rescue analgesics were administered. In general, the rescue opioid used differed from the opioid included in the PCA, except in one study in which both the PCA and rescue opioid were morphine and the amount of rescue analgesics was included in the 24 h total morphine consumption [25].

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The pain scores were reported at several time points in each study (Table 1).

ROB

For the final eight studies included in the meta-analysis, the ROB was evaluated for each of the four outcomes (Fig. 2). In the randomization process, four studies [13-15,24] were evaluated as 'some concerns' because of unclear descriptions of the randomization process. In the domain of deviation from the intended intervention, two studies [13,14] were rated as having 'some concerns' because they were analyzed 'per protocol' rather than with 'intention-to-treat.' All trials were assessed as having low risk in the missing outcome data domain. For the measurement of the outcome, one study [13] was rated as 'high risk' on the outcome of side effects, because of the unclear definition of PONV scoring system and the description of the results. In the selection of the reported results, one study [25] was assessed as 'high risk' for the outcome of pain scores due to the potential distortion of the results. The others were assessed as low risk.

In the ROB assessment, Cohen's kappa value for the results of the two reviewers was 0.912, indicating almost perfect agreement.

Meta-analysis and TSA

Twenty-four hours opioid consumption

In a meta-analysis of eight studies [12-15,22-25], 24 h opioid consumption, presented as morphine milligram equivalent, was significantly lower in the IVB group than in the IVA group (MD: –6.01 mg, 95% CI [–8.60, –3.42], $P < 0.00001$, $I^2 = 55\%$, $\tau = 2.46$, 95% PI [–11.82, –0.20]) (Fig. 3). In the sensitivity analysis excluding one study [12], the heterogeneity disappeared (MD: –5.08 mg, 95% CI [–6.40, –3.76], $P < 0.00001$, $I^2 = 0\%$, $\tau = 0.00$) with maintained direction and significance of the results.

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TSA indicated that only 41.3% (494 of 1196 patients) of the RIS was accrued. The cumulative Z curve (blue curve) crossed both the conventional test boundary (dashed red line) and the trial sequential monitoring boundary (red curve) (Fig. 4A).

Severity of postoperative pain

VAS at recovery

A meta-analysis comparing five studies [12,15,22-24] showed that pain scores measured at recovery were lower in the IVB group (MD: –1.42, 95% CI [–2.20, –0.65], P = 0.0003, I^2 = 82%, τ = 0.77, 95% PI [–3.57, 0.73]) (Fig. 5A). In the sensitivity test, the heterogeneity disappeared after excluding one study [12] (MD: –1.04, 95% CI [–1.36, –0.72], P < 0.00001, I^2 = 0%, τ = 0.00). Although there was a reduction in the effect size, the direction and significance of the results remained.

TSA indicated that only 15.8% (310 of 1958 patients) of the RIS was accrued. The cumulative Z curve crossed the conventional test boundary but not the trial sequential monitoring boundary (Supplement).

VAS at 4–6 h postoperatively

Five studies [12,13,15,22-24] assessed pain scores at 4–6 h postoperatively. The IVB group showed lower pain intensity than the IVA group (MD: –0.83, 95% CI [–1.29, –0.37], P = 0.0004, I^2 = 65%, τ = 0.45, 95% PI [–1.98, 0.32]) (Fig. 5B). In the sensitivity analysis, the exclusion of one study [12] resulted in an improvement in heterogeneity (MD: –0.62, 95% CI [–0.90, –0.35], P < 0.00001, I^2 = 0%, τ = 0.00). The effect size decreased; however, the direction and statistical significance of the results remained consistent.

TSA indicated that only 37.1% (370 of 997 patients) of the RIS was accrued. The cumulative Z curve (blue curve) crossed both the conventional test boundary (dashed red line) and the trial sequential monitoring boundary (red curve) (Fig. 4B).

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VAS at 12 h postoperatively

A meta-analysis of five studies [13,15,22-24] demonstrated that the VAS score at 12 h postoperatively was lower in the IVB group than in the IVA group (MD: –0.38, 95% CI [–0.68, –0.08], P = 0.01, I^2 = 11%, τ = 0.1, 95% PI [–0.70, –0.06]) (Fig. 5C).

TSA indicated that only 85.6% (310 of 362 patients) of the RIS was accrued. The cumulative Z curve (blue curve) crossed both the conventional test boundary (dashed red line) and the trial sequential monitoring boundary (red curve) (Fig. 4C).

VAS at 24 h postoperatively

A meta-analysis of five studies [12,13,15,22-24] showed no significant difference in the pain scores at 24 h postoperatively between the two groups (MD: –0.26, 95% CI [–0.61, 0.10], P = 0.16, I^2 = 76%, τ = 0.37, 95% PI [–1.22, 0.70]) (Fig. 5D). In the sensitivity analysis, the exclusion of one study [12] resulted in an improvement in heterogeneity with no significant changes in the results compared to the pooled analysis (MD: –0.13, 95% CI [–0.32, 0.07], P = 0.20, I^2 = 6%, τ = 0.00).

TSA indicated that only 27.1% (370 of 1364 patients) of the RIS was accrued. The cumulative Z curve did not cross the conventional test boundary (Supplement 2).

Rescue analgesics

Seven studies [12-15,22-24] were included in the meta-analysis of the effects of both analgesics on the use of rescue analgesics. The requirement for rescue analgesics was significantly lower in the IVB group than in the IVA group (RR: 0.40, 95% CI [0.21, 0.74], P = 0.004, I^2 = 39%, τ = 0.41, 95% PI [0.15, 1.09]) (Supplement 2).

TSA indicated that only 19.7% (444 of 2256 patients) of the RIS was accrued. The cumulative Z curve crossed the conventional test boundary but not the trial sequential monitoring boundary (Supplement 2).

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Nausea, vomiting

Four studies [12,22-24] reported the results of postoperative nausea and vomiting separately. Patients in the IVB group had a significantly lower risk of nausea (RR: 0.49, 95% CI [0.22, 1.08], P = 0.08, I^2 = 25%, τ = 0.38, 95% PI [0.15, 1.63]) and vomiting (RR: 0.49, 95% CI [0.24, 0.99], P = 0.05, I^2 = 0%, τ = 0.00) than patients in the IVA group (Supplement 2).

TSA indicated that only 14.5% (260 of 1796 patients) and 8.7% (260 of 2988 patients) of the RIS was accrued for nausea and vomiting, respectively. The cumulative Z curves for nausea and vomiting did not cross the conventional test boundaries (Supplement 2).

Other side effects

Pruritus was reported in seven studies [12,14,15,22-25], and the meta-analysis showed no significance (Risk Difference: –0.02, 95% CI [–0.07, 0.03], P = 0.42, I^2 = 58%, τ = 0.1, 95% PI [–0.26, 0.22]) (Supplement 2). TSA indicated that only 13.1% (434 of 3302 patients) of the RIS was accrued. The cumulative Z curve did not cross the conventional test boundary (Supplement 2).

Dyspepsia was investigated in three studies [12,14,22], and the meta-analysis revealed no significant difference between the two groups (Risk Difference: –0.03, 95% CI [–0.12, 0.06], P = 0.52, I^2 = 67%, τ = 0.14, 95% PI [–0.63, 0.58]) (Supplement 2). TSA indicated that only 4.8% (260 of 5445 patients) of the RIS was accrued. The trial sequential monitoring boundary was ignored owing to insufficient information. The cumulative Z curve did not cross the conventional test boundary (Supplement 2).

As for other side effects, despite being evaluated in several studies, the reported incidence frequently remained zero. Respiratory depression assessed in four studies [12,14,22,23] showed zero incidence. Constipation assessed in two studies [12,22] showed zero incidence. Confusion/sedation, evaluated in three studies [12,14,22], showed an incidence of 0 out of 35 in the IVB group and 2 out of 39 in the IVA

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group in only one study [14]. Urinary retention, observed in four studies [12,22,23,25], was reported in only one study [25] with an incidence of 2 out of 25 in the IVB group and 1 out of 25 in the IVA group. Bleeding was assessed in three studies [12,22,23], with one study [22] reporting an incidence of 2 out of 50 in the IVB group and 1 out of 50 in the IVA group. Headache, evaluated in two studies [14,23], showed an incidence of 7 out of 35 in the IVB group and 7 out of 39 in the IVA group in a single study [14]. Meta-analysis of confusion/sedation, urinary retention, bleeding, and headache showed no significant results (Supplement 2).

Certainty level of evidence from GRADE

The quality of evidence from this meta-analysis for each outcome is presented in a summary of findings table (Table 2). The certainty level for pain scores at 12 h was assessed as high. The 24 h opioid consumption and vomiting was considered moderate. However, the certainty levels for pain scores at 4–6 and 24 h, rescue analgesics, and nausea were low.

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Discussion

Although the roles of IV ibuprofen and acetaminophen as postoperative adjuvant analgesics are well established, there is insufficient evidence regarding the comparative efficacy of these two drugs for postoperative pain after general anesthesia. This meta-analysis confirmed that postoperative opioid consumption at 24 h and pain intensity up to 12 h postoperatively were significantly lower with IV ibuprofen than with acetaminophen, and this statistical significance was maintained with TSA. However, the TSA revealed that the sample size of the meta-analysis was insufficient to assess the effects of the study drugs on pain scores at 24 h postoperatively, rescue analgesic requirements, and side effects.

The results of this study regarding the effect on opioid consumption and pain scores are in line with those of a recent meta-analysis by Zhou et al., who evaluated the analgesic and antipyretic effects of IV ibuprofen compared with those of placebo and acetaminophen [26]. However, the studies included by Zhou et al. were more heterogeneous than ours; the anesthetic types varied from local anesthesia to regional and general anesthesia, and endoscopic procedures were also included. Furthermore, the effect on opioid consumption has not been adequately assessed, as the opioid-sparing effects of ibuprofen and acetaminophen were evaluated for each type of opioid (tramadol, fentanyl, and morphine). We consider it more reasonable to comprehensively analyze all opioids together based on morphine equivalent doses, as in our study.

In our study, the 24 h opioid consumption was lower in the IVB group by approximately 6 mg in MME (MD: –6.01, $P < 0.00001$) than in the IVA group. Despite the reduced amount of opioids, the postoperative pain scores were significantly lower in the IVB group for up to 12 h postoperatively, suggesting the superiority of ibuprofen over acetaminophen for postoperative pain relief. Furthermore, the need for rescue analgesics was significantly lower in the IVB group, although these results were not confirmed in TSA.

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The MD in pain scores between IVB and IVA, on a scale of 10 points, showed a decreasing trend over time, with –0.83 points at 4–6 h, –0.38 points at 12 h, and no significant difference between the two groups at 24 h. Although the effects on pain intensity at 24 h postoperatively are inconclusive based on the TSA results, the effect appears to diminish over time, and this may be associated with the decreasing intensity of postoperative pain over time.

As the opioid dose was significantly lower in the IVB group, opioid-related side effects, such as nausea and vomiting, could be reduced in this group [27]. However, this finding was not confirmed by the present meta-analysis. Considering their pharmacological effects, the incidence of gastrointestinal problems and bleeding tendencies may differ between ibuprofen and acetaminophen. Nevertheless, it has been suggested that ibuprofen does not increase these side effects [28,29], and the frequency of adverse effects was very low in our study. Despite the small sample size in this meta-analysis, ibuprofen did not appear to significantly increase gastrointestinal or hemorrhagic complications in a postoperative setting.

This study had some limitations. First, the meta-analysis of opioid consumption and pain scores showed moderate-to-substantial heterogeneity, except for pain scores at 12 h. Because the type of surgery can influence postoperative opioid consumption [30], various types of surgeries could contribute to this heterogeneity. Moreover, variations in the timing of the administration of the study drugs or the types of opioids used could be potential causes. Interestingly, in the sensitivity analysis, excluding the study by Ekinci et al. [12], the heterogeneity significantly decreased. Upon review, the study by Ekinci et al. [12] did not seem to be significantly different compared to other studies in terms of study design, demographic characteristics, dosing frequency, and intervals, making it difficult to identify the specific cause of heterogeneity. If there was one minor difference compared to other studies, the MD in the VAS scores between the IVB and IVA groups was reported to be particularly large. Second, due to the limited number of studies included in this meta-analysis and variations in administration timing across studies, it was not

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possible to compare the effects of the study drugs based on administration timing, such as preoperative, intraoperative, or postoperative administration. Third, various types of surgery were included in this meta-analysis. According to a network meta-analysis by Carter et al. [31], the effects of ibuprofen and acetaminophen on the reduction of postoperative pain intensity can vary depending on the type of surgery. However, in the study by Carter et al., the number of included studies was too small to draw conclusions.

In summary, the perioperative administration of IV ibuprofen demonstrated a superior analgesic effect compared with that of IV acetaminophen up to 12 h postoperatively, leading to a reduction in 24 h opioid consumption. Further studies are required to assess the effects on pain intensity beyond 12 h, rescue analgesic requirements, and side effects. We anticipate that ibuprofen may be a beneficial adjuvant analgesic for postoperative pain.

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References

1. Kehlet H, Holte K. Effect of postoperative analgesia on surgical outcome. Br J Anaesth 2001; 87: 62-72.
2. Hah JM, Bateman BT, Ratliff J, Curtin C, Sun E. Chronic opioid use after surgery: implications for perioperative management in the face of the opioid epidemic. Anesth Analg 2017; 125: 1733-40.
3. Kumar K, Kirksey MA, Duong S, Wu CL. A review of opioid-sparing modalities in perioperative pain management: methods to decrease opioid use postoperatively. Anesth Analg 2017; 125: 1749-60.
4. Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. Curr Opin Anaesthesiol 2009; 22: 588-93.
5. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain 2016; 17: 131-57.
6. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 2012; 116: 248-73.
7. Smith HS. Perioperative intravenous acetaminophen and NSAIDs. Pain Med 2011; 12: 961-81.
8. Cashman JN. The mechanisms of action of NSAIDs in analgesia. Drugs 1996; 52(Suppl 5): 13-23.

Epub ahead of print

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9. Vane JR, Botting RM. Mechanism of action of nonsteroidal anti-inflammatory drugs. Am J Med 1998; 104: 2S-8S.
10. Jahr JS, Lee VK. Intravenous acetaminophen. Anesthesiol Clin 2010; 28: 619-45.
11. Smith HS, Voss B. Pharmacokinetics of intravenous ibuprofen: implications of time of infusion in the treatment of pain and fever. Drugs 2012; 72: 327-37.
12. Ekinci M, Ciftci B, Celik EC, Köse EA, Karakaya MA, Ozdenkaya Y. A randomized, placebo-controlled, double-blind study that evaluates efficacy of intravenous ibuprofen and acetaminophen for postoperative pain treatment following laparoscopic cholecystectomy surgery. J Gastrointest Surg 2020; 24: 780-5.
13. Mohammadian Erdi A, Arabzadeh A, Isazadehfar K, Masoumzadeh M, Bahadoram M. Comparing the efficacy and side effects of intravenous ibuprofen and acetaminophen in pain control following laparoscopic cholecystectomy. World J Plast Surg 2022; 11: 117-24.
14. Erdogan Kayhan G, Sanli M, Ozgul U, Kirteke R, Yologlu S. Comparison of intravenous ibuprofen and acetaminophen for postoperative multimodal pain management in bariatric surgery: a randomized controlled trial. J Clin Anesth 2018; 50: 5-11.
15. Ucar M, Erdogan MA, Sanlı M, Colak YZ, Aydogan MS, Yucel A, et al. Efficacy of intravenous ibuprofen and intravenous paracetamol in multimodal pain management of postoperative pain after percutaneous nephrolithotomy. J Perianesth Nurs 2022; 37: 540-4.
16. McGrath S, Zhao X, Steele R, Thombs BD, Benedetti A. Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. Stat Methods Med Res 2020; 29: 2520-37.
17. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898.

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18. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb) 2012; 22: 276-82.
19. Granholm A, Alhazzani W, Møller MH. Use of the GRADE approach in systematic reviews and guidelines. Br J Anaesth 2019; 123: 554-9.
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-60.
21. Kang H. Trial sequential analysis: novel approach for meta-analysis. Anesth Pain Med (Seoul) 2021; 16: 138-50.
22. Çelik EC, Kara D, Koc E, Yayik AM. The comparison of single-dose preemptive intravenous ibuprofen and paracetamol on postoperative pain scores and opioid consumption after open septorhinoplasty: a randomized controlled study. Eur Arch Otorhinolaryngol 2018; 275: 2259-63.
23. Demiroluk Ö, Abitağaoğlu S, Göçmen DK, Özcabi Y, Ari DE. Comparison of analgesic effects of paracetamol and ibuprofen after laparoscopic cholecystectomy. Turkiye Klinikleri J Med Sci 2019; 39: 278-84.
24. Ciftci B, Ekinci M, Celik EC, Kaciroglu A, Karakaya MA, Demiraran Y, et al. Comparison of intravenous ibuprofen and paracetamol for postoperative pain management after laparoscopic sleeve gastrectomy. A randomized controlled study. Obes Surg 2019; 29: 765-70.
25. Akbas S, Ozkan AS, Durak MA, Yologlu S. Efficacy of intravenous paracetamol and ibuprofen on postoperative pain and morphine consumption in lumbar disc surgery: prospective, randomized, double-blind, placebo-controlled clinical trial. Neurochirurgie 2021; 67: 533-9.

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26. Zhou P, Chen L, Wang E, He L, Tian S, Zhai S. Intravenous ibuprofen in postoperative pain and fever management in adults: a systematic review and meta-analysis of randomized controlled trials. Pharmacol Res Perspect 2023; 11: e01123.
27. Roberts GW, Bekker TB, Carlsen HH, Moffatt CH, Slattery PJ, McClure AF. Postoperative nausea and vomiting are strongly influenced by postoperative opioid use in a dose-related manner. Anesth Analg 2005; 101: 1343-8.
28. Bjarnason I. Ibuprofen and gastrointestinal safety: a dose-duration-dependent phenomenon. J R Soc Med 2007; 100(Suppl 48): 11-4.
29. Kelley BP, Bennett KG, Chung KC, Kozlow JH. Ibuprofen may not increase bleeding risk in plastic surgery: a systematic review and meta-analysis. Plast Reconstr Surg 2016; 137: 1309-16.
30. Kim KM, Kim HS, Lim SH, Cheong SH, Choi EJ, Kang H, et al. Effects of genetic polymorphisms of OPRM1, ABCB1, CYP3A4/5 on postoperative fentanyl consumption in Korean gynecologic patients. Int J Clin Pharmacol Ther 2013; 51: 383-92.
31. Carter JA, Black LK, Sharma D, Bhagnani T, Jahr JS. Efficacy of non-opioid analgesics to control postoperative pain: a network meta-analysis. BMC Anesthesiol 2020; 20: 272.

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Table 1. Characteristics of the included studies

Study	Type of surgery	Interventions (No. of patients)	Timing of administration	Postoperative outcomes		
				Post-op opioid used in PCA	Post-op pain measurement (VAS)	Rescue analgesics
Çelik 2018 [22]	Septorhinoplasty	IVB 800 mg (50) IVA 1 g (50)	Before induction	Tramadol	At recovery, 1, 6, 12, 24 h	Meperidine 25 mg
Erdogan Kayhan 2018 [14]	Laparoscopic bariatric surgery	IVB 800 mg (40) IVA 1 g (40)	Before skin closure, q 6 h for postop 24 h	Morphine	Between 1 and 24, 6 and 24, 12 and 24 h	Tramadol 0.5 mg/kg
Ciftci 2019 [24]	Laparoscopic sleeve gastrectomy	IVB 800 mg (30) IVA 1 g (30)	After intubation, q 8 h for postop 24 h	Fentanyl	At recovery, 2, 4, 8, 12, 24 h	Meperidine 0.25 mg/kg
Demiroluk 2019 [23]	Laparoscopic cholecystectomy	IVB 800 mg → 400 mg (20) IVA 1 g (20)	After creating a pneumoperitoneum, q 6 h for postop 24 h	Tramadol	At recovery, 6, 12, 24 h	Meperidine 20 mg

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Ekinci 2020 [12]	Laparoscopic cholecystectomy	IVB 800 mg (30) IVA 1 g (30)	30 min preop, q 8 h for postop 24 h	Fentanyl	At recovery, 1, 2, 4, 8, 16, 24 h	Meperidine 0.25 mg/kg
Akbas 2021 [25]	Lumbar disc surgery	IVB 800 mg (25) IVA 1 g (25)	At wound closure, q 6 h for postop 24 h	Morphine	Between 1 and 24, 6 and 24, 12 and 24 h	Morphine 2 mg → included in 24 h total morphine consumption
Mohammadian Erdi 2022 [13]	Laparoscopic cholecystectomy	IVB 800 mg (30) IVA 1 g (30)	Intraop, postop 8 h, 16 h	Fentanyl	At 6, 12, 18, 24 h	Meperidine 0.5 mg/kg
Ucar 2022 [15]	Percutaneous nephrolithotomy	IVB 800 mg (25) IVA 1 g (25)	Before skin closure, q 6 h for postop 24 h	Tramadol	At 0.5, 2, 4, 6, 12, 24 h	No information about rescue analgesics, but the incidence is shown.

IVA: intravenous acetaminophen, IVB: intravenous ibuprofen, PCA: patient-controlled analgesia, VAS: visual analog scale

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Table 2. Summary of findings

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants	ROB	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty of the evidence (GRADE)
	Risk with IV acetaminophen	Risk with IV ibuprofen								
24 h opioid consumption (morphine equivalent)	The mean 24 h opioid consumption: 37.97 mg	MD: –6.01 mg (–8.6, –3.42)		494 (8 RCTs)	Not serious	Serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ Moderate†
VAS at 4–6 h	The mean VAS:	MD: –0.83		370 (6 RCTs)	Not serious	Serious	Not serious	Serious	Undetected	⊕⊕◯◯ Low†,‡

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	3.29	(–1.29, –0.37)							
VAS at 12 h	The mean VAS: 2.60	MD: –0.37 (–0.64, –0.1)	310 (5 RCTs)	Not serious	Not Serious	Not serious	Not serious	Undetected	⊕⊕⊕⊕ High
VAS at 24 h	The mean VAS: 1.22	MD –0.26 (–0.61, 0.1)	370 (6 RCTs)	Not serious	Serious	Not serious	Serious	Undetected	⊕⊕◯◯ Low[†,§]
Rescue analgesic	263 per 1,000	108 per 1,000 (74 to 163)	RR 0.41 (0.28 to 0.62)	444 (7 RCTs)	Not serious	Serious	Not serious	Serious	Undetected	⊕⊕◯◯ Low[†,§]

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Nausea	223 per 1,000	107 per 1,000 (60 to 194)	RR 0.48 (0.27 to 0.87)	260 (4 RCTs)	Not serious	Serious	Not serious	Serious	Undetected	⊕⊕◯◯ Low[†,§]
Vomiting	169 per 1,000	80 per 1,000 (39 to 157)	RR 0.47 (0.23 to 0.93)	260 (4 RCTs)	Not serious	Not serious	Not serious	Serious	Undetected	⊕⊕⊕◯ Moderate[§]

Rescue analgesic, nausea, and vomiting were evaluated for postoperative 24 h.

CI: confidence interval, GRADE: Grading of Recommendations, Assessment, Development, and Evaluations, IV: intravenous, MD: mean difference, PI: prediction interval, RCTs: randomized controlled trials, ROB: risk of bias, RR: risk ratio, VAS: visual analog scale.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

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Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

[*]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[†] The 95% PI is significantly wider than the 95% CI.

[‡] The 95% PI crosses the line of identity in contrast to the 95% CI.

[§] The optimal information size criterion is not met.

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Figure legends

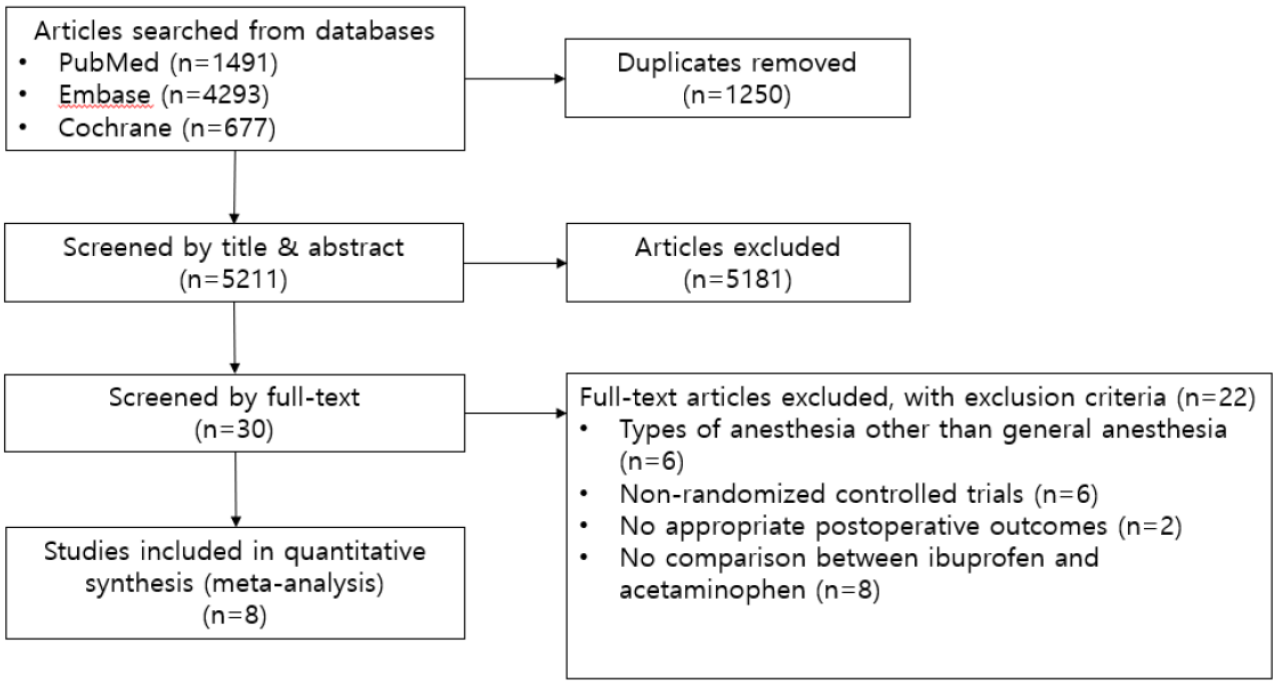

Fig. 1. Flow diagram of study selection

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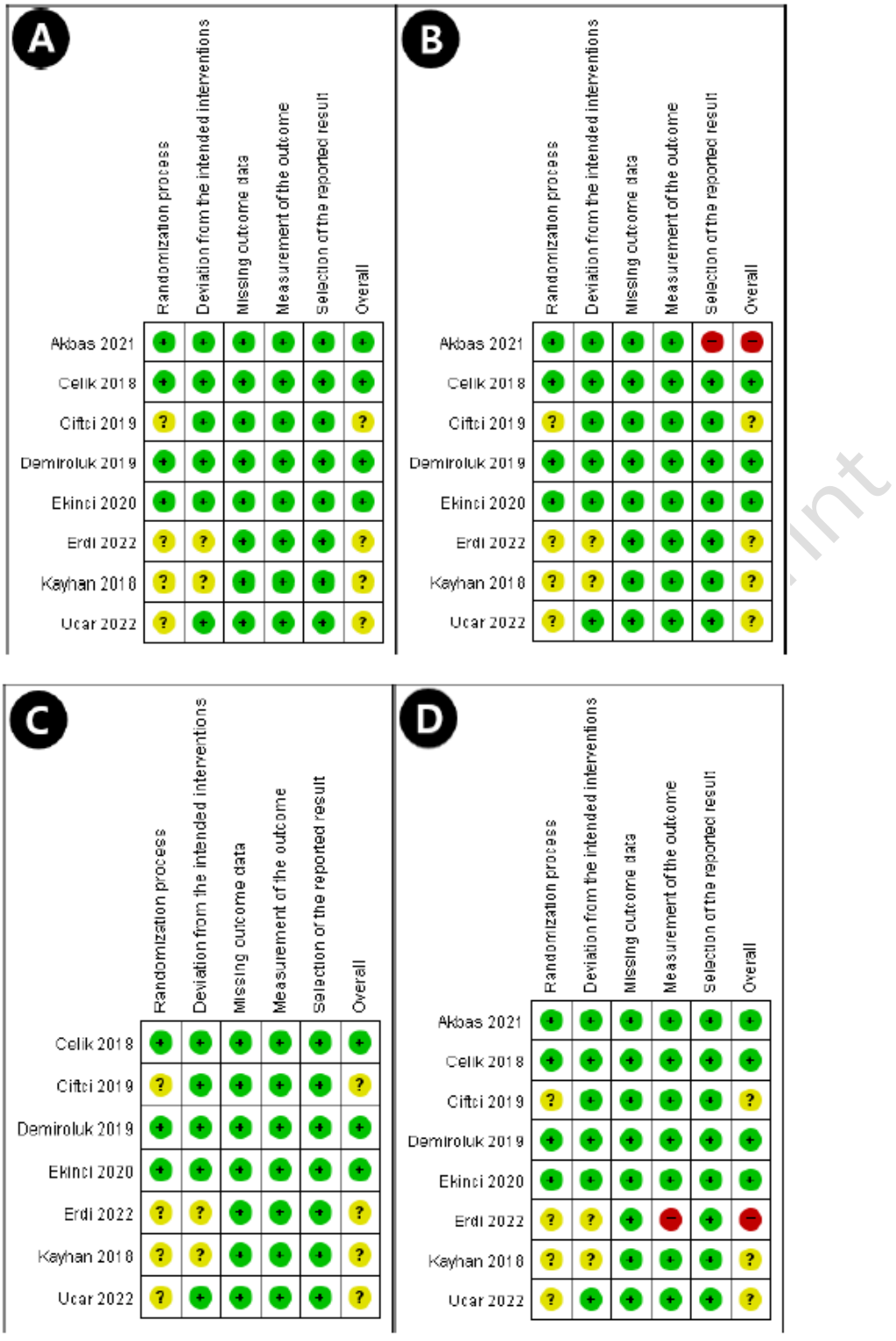

Fig. 2. Risk of bias

(A) 24 h opioid consumption, (B) Postoperative pain scores, (C) Use of rescue analgesics, (D) Side effects

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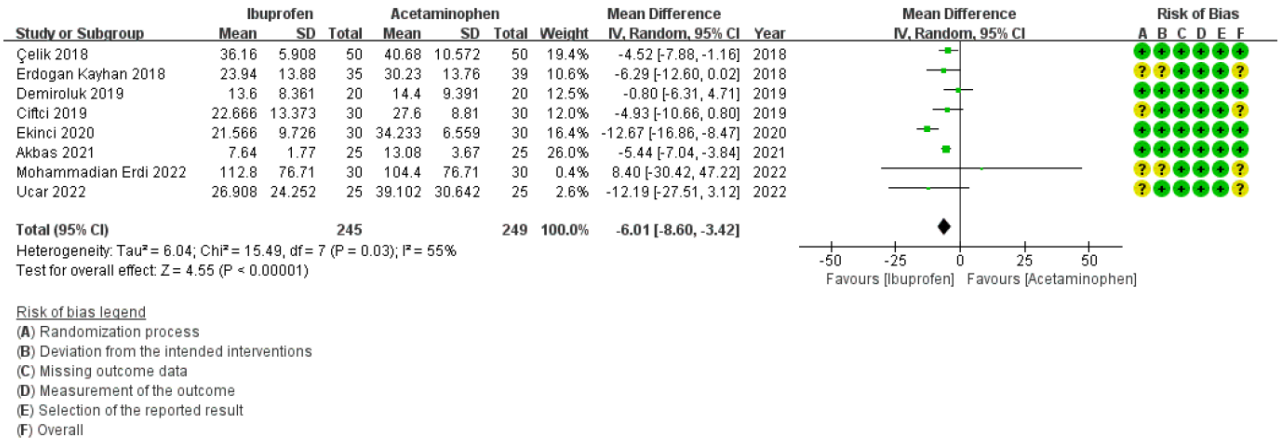

Fig. 3. Forest plot: effect of ibuprofen and acetaminophen on 24 h opioid consumption.

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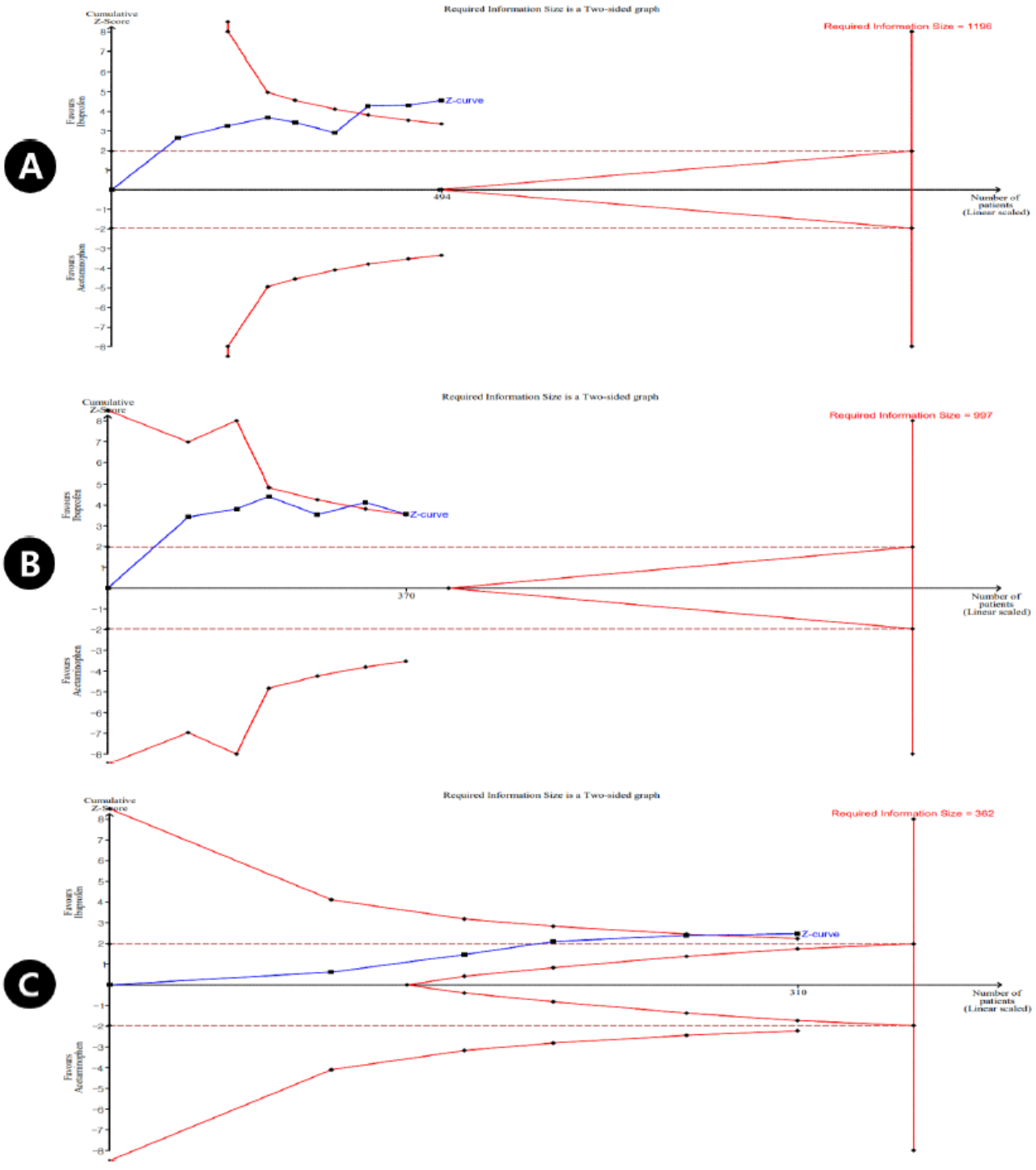

Fig. 4. Trial sequential analysis

(A) 24 h opioid consumption, (B) VAS at 4–6 h postoperatively, (C) VAS at 12 h postoperatively.

VAS: visual analog scale.

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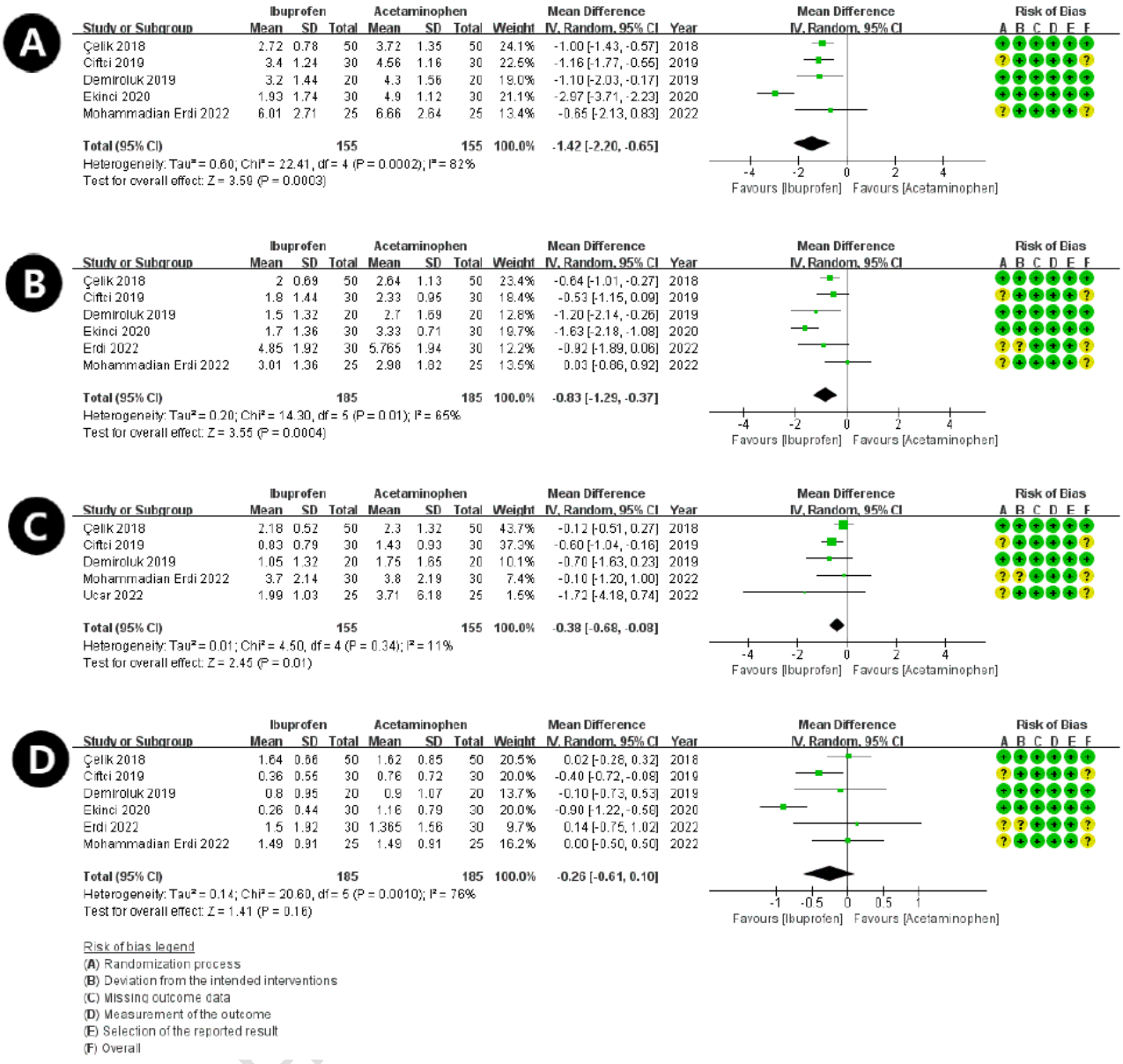

Fig. 5. Forest plot: effect of ibuprofen and acetaminophen on postoperative pain scores.

(A) VAS at recovery, (B) VAS at 4–6 h postoperatively, (C) VAS at 12 h postoperatively, (D) VAS at 24 h postoperatively. VAS: visual analog scale.

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