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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

Sung Hye Kim, Hyun Kang, In-Jung Jun, Hye Won Park, Byung Hoon Yoo, Yun-Hee Lim, Kye-Min Kim

[Author information]
Sung Hye Kim, M.D.
Department of Anesthesiology and Pain Medicine, Inje University Sanggye Paik Hospital, Seoul, Korea
ORCID: https://orcid.org/0009-0004-6814-4761

Hyun Kang, M.D., Ph.D.
Department of Anesthesiology and Pain Medicine, Chung-Ang University College of Medicine, Seoul, Korea
ORCID: https://orcid.org/0000-0003-2844-5880

In-Jung Jun, M.D. Ph.D.
Department of Anesthesiology and Pain Medicine, Inje University Sanggye Paik Hospital, Seoul, Korea
ORCID: https://orcid.org/0000-0003-1386-3940
Hye Won Park
Inje University Medical Library, Busan, Korea.
ORCID: https://orcid.org/0000-0001-9374-7848

Byung Hoon Yoo, M.D., Ph.D
Department of Anesthesiology and Pain Medicine, Inje University Sanggye Paik Hospital, Seoul, Korea
ORCID: https://orcid.org/0000-0002-1958-8380

Yun-Hee Lim M.D., Ph.D
Department of Anesthesiology and Pain Medicine, Inje University Sanggye Paik Hospital, Seoul, Korea
ORCID: https://orcid.org/0000-0003-2399-4768

Kye-Min Kim, M.D., Ph.D.
Department of Anesthesiology and Pain Medicine, Inje University Sanggye Paik Hospital, Seoul, Korea
ORCID: https://orcid.org/0000-0003-1298-7642

[Running title]
IV ibuprofen vs. acetaminophen for pain

[Corresponding author]:

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Conceptualization: Sung Hye Kim, Kye-Min Kim

Study design: Sung Hye Kim, In-Jung Jun, Kye-Min Kim

Data acquisition: Sung Hye Kim, Hye Won Park, Kye-Min Kim

Analysis and interpretation of data: Sung Hye Kim, Hyun Kang, Kye-Min Kim

Writing—original draft: Sung Hye Kim, Hyun Kang, Kye-Min Kim

Writing—review & editing: Sung Hye Kim, Hyun Kang, Hye Won Park, In-Jung Jun, Byung Hoon Yoo, Yun-Hee Lim, Kye-Min Kim,
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[Author Names]

[Author affiliations]

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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

Running title: IV ibuprofen vs. acetaminophen for pain
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, I² = 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, I² = 65%) and 12 h (MD: –0.38, 95% CI [–0.68, –0.08], P = 0.01, I² = 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.
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.
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.

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)
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.
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,
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’ $I^2$, $\tau$ using the DerSimonian-Laird estimator, and prediction interval (PI) was used. If $\tau$ 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.
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
conducted using the TSA 0.9.5.10 beta software (Copenhagen Trial Unit, Center for Clinical Intervention Research).
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.
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 \([-2.20, -0.65]\), \(P = 0.0003, I^2 = 82\%, \tau = 0.77, 95\%\) PI \([-3.57, 0.73]\]) (Fig. 5A). In the sensitivity test, the heterogeneity disappeared after excluding one study [12] (MD: \(-1.04, 95\%\) CI \([-1.36, -0.72]\), \(P < 0.00001, I^2 = 0\%, \tau = 0.00\)). 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 \([-1.29, -0.37]\), \(P = 0.0004, I^2 = 65\%, \tau = 0.45, 95\%\) 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 \([-0.90, -0.35]\), \(P < 0.00001, I^2 = 0\%, \tau = 0.00\)). 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).
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, I² = 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, I² = 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, I² = 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, I² = 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).
**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], \( P = 0.08, I^2 = 25\% \), \( \tau = 0.38, 95\% \) PI [0.15, 1.63]) and vomiting (RR: 0.49, 95% CI [0.24, 0.99], \( P = 0.05, I^2 = 0\% \), \( \tau = 0.00 \)) 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 \([-0.07, 0.03]\), \( P = 0.42, I^2 = 58\% \), \( \tau = 0.1, 95\% \) 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 \([-0.12, 0.06]\), \( P = 0.52, I^2 = 67\% \), \( \tau = 0.14, 95\% \) 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
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.
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.
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
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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Table 1. Characteristics of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of surgery</th>
<th>Interventions</th>
<th>Timing of administration</th>
<th>Postoperative outcomes</th>
<th>Post-op pain measurement (VAS)</th>
<th>Rescue analgesics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Çelik 2018</td>
<td>Septorhinoplasty</td>
<td>IVB 800 mg (50)</td>
<td>Before induction</td>
<td>Tramadol</td>
<td>At recovery, 1, 6, 12, 24 h</td>
<td>Meperidine 25 mg</td>
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<td></td>
<td></td>
<td>IVA 1 g (50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erdogan Kayhan 2018</td>
<td>Laparoscopic</td>
<td>IVB 800 mg (40)</td>
<td>Before skin closure, q 6 h for postop 24 h</td>
<td>Morphine</td>
<td>Between 1 and 24, 6 and 24, 12 and 24 h</td>
<td>Tramadol 0.5 mg/kg</td>
</tr>
<tr>
<td>Ciftci 2019</td>
<td>Laparoscopic sleeve gastrectomy</td>
<td>IVB 800 mg (30)</td>
<td>After intubation, q 8 h for postop 24 h</td>
<td>Fentanyl</td>
<td>At recovery, 2, 4, 8, 12, 24 h</td>
<td>Meperidine 0.25 mg/kg</td>
</tr>
<tr>
<td>Demiroluk 2019</td>
<td>Laparoscopic</td>
<td>IVB 800 mg → 400 mg (20)</td>
<td>After creating a pneumoperitoneum, q 6 h for postop 24 h</td>
<td>Tramadol</td>
<td>At recovery, 6, 12, 24 h</td>
<td>Meperidine 20 mg</td>
</tr>
<tr>
<td></td>
<td>cholecystectomy</td>
<td>IVA 1 g (20)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Study Year</td>
<td>Procedure</td>
<td>Drug Type</td>
<td>Dose</td>
<td>Timing</td>
<td>Code</td>
<td>Dose</td>
</tr>
<tr>
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<tr>
<td>Ekinci 2020 [12]</td>
<td>Laparoscopic cholecystectomy</td>
<td>IVB 800 mg (30)</td>
<td>30 min preop, q 8 h for postop 24 h</td>
<td>Fentanyl</td>
<td>At recovery, Meperidine 0.25 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Akbas 2021 [25]</td>
<td>Lumbar disc surgery</td>
<td>IVB 800 mg (25)</td>
<td>At wound closure, q 6 h for postop 24 h</td>
<td>Morphine</td>
<td>Between 1 and 24, Morphine 2 mg</td>
<td></td>
</tr>
<tr>
<td>Mohammadian</td>
<td>Laparoscopic cholecystectomy</td>
<td>IVB 800 mg (30)</td>
<td>Intraop, postop 8 h, 16 h</td>
<td>Fentanyl</td>
<td>At 6, 12, 18, 24 h Meperidine 0.5 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Erdi 2022 [13]</td>
<td>Per cutaneous nephrolithotomy</td>
<td>IVB 800 mg (25)</td>
<td>Before skin closure, q 6 h for postop 24 h</td>
<td>Tramadol</td>
<td>At 0.5, 2, 4, 6, 12, 24 h No information about rescue analgesics, but the incidence is shown.</td>
<td></td>
</tr>
</tbody>
</table>

IVA: intravenous acetaminophen, IVB: intravenous ibuprofen, PCA: patient-controlled analgesia, VAS: visual analog scale
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants</th>
<th>ROB</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Impact of publication bias</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk with IV acetaminophen</td>
<td>24 h opioid consumption (morphine equivalent)</td>
<td>The mean 24 h opioid consumption: 37.97 mg (equivalent) 6.01 mg</td>
<td>494</td>
<td>Not serious</td>
<td>Serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Undetected</td>
<td>Moderate†</td>
<td></td>
</tr>
<tr>
<td>VAS at 4–6 h</td>
<td>The mean VAS: 0.83</td>
<td>370</td>
<td>Not serious</td>
<td>Serious</td>
<td>Not serious</td>
<td>Serious</td>
<td>Undetected</td>
<td>Low‡‡</td>
<td></td>
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</tbody>
</table>

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3.29 \((-1.29, -0.37)\)

VAS at 12 h The mean MD: – 310 Not serious Not Serious Not serious Not serious Undetected ⭐⭐⭐⭐
VAS: 0.37 (5 RCTs)
2.60 \((-0.64, -0.1)\)

VAS at 24 h The mean MD: – 370 Not serious Serious Not serious Serious Undetected ⭐⭐
VAS: 0.26 (6 RCTs)
1.22 \((-0.61, 0.1)\)

Rescue analgesic 263 per 1,000 108 per RR 0.41 444 Not serious Serious Not serious Serious Undetected ⭐⭐⭐
(74 to 0.62) (74 to 163)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence per 1,000</th>
<th>Incidence per 1,000</th>
<th>RR (95% CI)</th>
<th>GRADE</th>
<th>Severe</th>
<th>Not Severe</th>
<th>GRADE</th>
<th>Severe</th>
<th>Not Severe</th>
<th>GRADE</th>
<th>Severe</th>
<th>Not Severe</th>
<th>GRADE</th>
<th>Severe</th>
<th>Not Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>223</td>
<td>107</td>
<td>0.48</td>
<td>(0.27 to 0.87)</td>
<td>Low†§</td>
<td>Undetected</td>
<td>Not serious</td>
<td>Serious</td>
<td>Not serious</td>
<td>Serious</td>
<td>Undetected</td>
<td>3</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(60 to 194)</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Vomiting</td>
<td>169</td>
<td>80</td>
<td>0.47</td>
<td>(0.23 to 0.93)</td>
<td>Moderate§</td>
<td>Undetected</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious</td>
<td>Undetected</td>
<td>3</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(39 to 157)</td>
<td></td>
<td></td>
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</tbody>
</table>

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


**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.
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.
Figure legends

Fig. 1. Flow diagram of study selection

Articles searched from databases
- PubMed (n=1491)
- Embase (n=4293)
- Cochrane (n=677)

Duplicates removed (n=1250)

Screened by title & abstract (n=5211)

Articles excluded (n=5181)

Screened by full-text (n=30)

Full-text articles excluded, with exclusion criteria (n=22)
- Types of anesthesia other than general anesthesia (n=6)
- Non-randomized controlled trials (n=6)
- No appropriate postoperative outcomes (n=2)
- No comparison between ibuprofen and acetaminophen (n=8)

Studies included in quantitative synthesis (meta-analysis) (n=8)
Fig. 2. Risk of bias

(A) 24 h opioid consumption, (B) Postoperative pain scores, (C) Use of rescue analgesics, (D) Side effects
Fig. 3. Forest plot: effect of ibuprofen and acetaminophen on 24 h opioid consumption.
**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.
**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.