Intravenous Ibuprofen in Postoperative Pain and Fever Management in Adults: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Pengxiang Zhou[1], Lu Chen[1], Ente Wang[2], Lanzhi He[3], Shuxia Tian[4], and Suo-Di Zhai[5]

[1]Affiliation not available
[2]Beijing Tongren Hospital, Capital Medical University
[3]Jiangbin Hospital of Guangxi Zhuang Autonomous Region
[4]Tianjin Nankai Hospital
[5]Peking University Third Hospital

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Abstract

Aims: Intravenous ibuprofen (IVIB) has been approved in the treatment of postoperative pain and fever in adults, but the application of multiple- or single- dosage IVIB remains divergent in clinical practice. This study aims to evaluate the efficacy and safety of IVIB in the management of postoperative pain and fever in adults who were unable to take oral medicine. Methods: A systematic review and meta-analysis was conducted based on randomized controlled trials (RCTs) regarding postoperative pain and fever management comparing IVIB with placebo, or other analgesic and antipyretic agents from 8 databases. Risk of bias and quality of evidence assessment were performed. The primary outcomes mainly included visual analogue scale (VAS) score within postoperative 24h and the reduction of temperature. Results: Twenty-three RCTs with 3716 participants were included. For postoperative pain, moderate-to-low certainty evidence indicated that IVIB was associated with lower postoperative VAS scores than placebo, with MD ranging between -3.53 (95% CI, -4.32 to -2.75) at 0 minute to -0.96 (95% CI, -1.35 to -0.57) at 24 hours. Compared to intravenous acetaminophen, IVIB appeared lower VAS scores (MD, -1.54 at 0min; -0.36 at 24h). For fever, IVIB appeared satisfactory antipyretic efficiency in a short period of time, but there was no difference between IVIB and intravenous acetaminophen. Moderate-to-low certainty evidence indicated that IVIB was well tolerated in both pain and fever management. Conclusions: Moderate-to-low certainty evidence supported that adults with postoperative pain and fever who were unable to take oral medicine would benefit from IVIB.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) play key roles both inpatient and outpatient postoperative pain and fever therapy (1). Uncontrolled postoperative pain is a "vital sign" since it leads to discomfort and a variety of impacts that can have a negative impact on perioperative outcomes (2). Unless contraindicated, acetaminophen and/or NSAIDs are strongly recommended to be a part of multimodal analgesia for the management of postoperative pain in patients according to clinical practice guidelines (3, 4). Non-opioid analgesics are frequently used in conjunction with opioid analgesics to treat postoperative pain. NSAIDs or acetaminophen are acknowledged as beneficial adjuncts to opioids that have the potential to significantly reduce the opioid consumption, resulting in avoidance of opioid-related adverse events (AEs) (5, 6). Previous systematic reviews revealed that NSAIDs could lessen the need for patients to use opioids as rescue analgesia, lowering the frequency and severity of opioid-induced adverse events (AEs) (7). Even though oral NSAIDs or acetaminophen have been utilized in the hospital setting for many years, a large percentage of patients are unable to take oral medications owing to intubation, tonsil surgery, dysphagia, coma, or unconsciousness

(8, 9). In contrast to the oral formulations, intravenous NSAIDs or acetaminophen can therefore be an appropriate option to present a convenient and fast-acting analgesic, resulting in rapid onset of pain relief and reduced time to maximal pain relief.

Ibuprofen is a non-selective NSAID that inhibits cyclooxygenase enzymes, reducing the formation of prostaglandins, which are responsible for pain, fever, and inflammation at the site of injury or disease (10, 11). Intravenous ibuprofen (IVIB) was approved for use in hospitals by the U.S. Food and Drug Administration in 2009 for the treatment of mild to moderate pain, moderate to severe pain when combined with the administration of opioids, and the reduction of adult fever. Previously, narrative reviews revealed that IVIB had a favorable safety profile and pain control (12). Nevertheless, prior systematic reviews only focused on the analgesic efficacy of single-dose IVIB (13, 14) and its use on pain reduction after third molar surgery (15). There lacks comprehensive synthesis evidence demonstrating the efficacy and safety of IVIB with multiple- or single- dosage in the management of pain and fever since the published body of knowledge on IVIB continues to grow.

Therefore, this study aimed to conduct a thorough systematic review and meta-analysis to validate the application of IVIB in postoperative analgesia and antipyretic management in adults, providing evidence-based support for clinical decision-making.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (Supplementary Table 1) for the development of the protocol in PROSPERO (CRD42021234764) and reported this review (16).

Search strategy and selection criteria

PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure, WanFang Database, and SinoMed database were searched from the inception dates to June 2022, without language restrictions, using the term "ibuprofen" and keywords shown in the Supplementary Table 2. We also searched clinicaltrials.gov and the World Health Organization clinical trials portal for ongoing or recently completed trials. We only identified randomized controlled trials (RCTs) in postoperative pain or fever adults comparing IVIB with placebo, or other analgesic and antipyretic agents. An additional search of the reference lists of relevant studies was performed to identify the eligible RCTs. Four reviewers (Z.P.X., C.L., H.L.Z., T.S.X.) independently screened the reports against pre-designed eligibility criteria, and any disagreements were resolved through discussion, consulting another reviewer (Z.S.D.).

For pain relief, the primary outcomes included the visual analogue scale (VAS) score within postoperative 24h and the difference in cumulative opioid medication consumption at postoperative 24h and 48h. Secondary outcomes included the incidence of adverse events (AEs) and the usage rate of rescue analgesic medication. For fever relief, we identified the change of temperature as the main outcome and the incidence of adverse events (AEs) as the secondary outcome.

Data Extraction

Three reviewers (Z.P.X., C.L., W.E.T) independently extracted data using standardized and piloted forms, which were finally checked by other reviewers (H.L.Z., T.S.X.). The baseline information was extracted, including the first author, the publication year, participants, samples, age, gender, the interventions and comparisons with dosage and usage, primary outcomes and secondary outcomes from each trial.

Risk of bias and quality of evidence assessment

Pairs of reviewers (Z.P.X., C.L.) independently appraised the risk of bias (ROB) for RCTs using the Cochrane Risk of Bias tool (17). Six domains, regarding selection, performance, attrition, detection, reporting, and other sources of bias were assessed. The quality of evidence for outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework (18). The GRADE approach results in an assessment of the quality of a body of evidence as high, moderate, low, or very low, according to five

categories, including risk of bias, imprecision, inconsistency, indirectness, and publication bias (19). Any discrepancies were resolved through discussion, or by a third reviewer (Z.S.D.).

Statistical analysis

We estimated intervention effects by calculating risk ratios (RR) for dichotomous outcomes or mean difference (MD) for continuous outcomes, with a 95% confidence interval (CI). Heterogeneity between studies was calculated using the I^2 statistic in Review Manager version 5.4.1. The data were considered substantial heterogeneity if I^2 was 50% or greater. When clinical and methodology heterogeneity were considered, subgroup analyses were conducted by the indications (pain or fever relief), the doses of treatment, the different types of AEs, and different dosing times, otherwise meta-analysis was performed using the random-effects model (20). All tests were 2-tailed and p-values < 0.05 was considered statistically significant. Descriptive analyses were conducted if there were insufficient similarity information to pool data. Sensitivity analysis and funnel plots (if more than 10 studies were included (21)) were performed to assess the possible bias.

RESULTS

Search results

The search strategy identified 1,969 trials, of which 32 studies met the inclusion criteria, with a total of 3,716 participants. The study selection process is illustrated in Figure 1. Overall, 3,090 participants were assigned to 18 types of surgery, mainly including laparoscopic cholecystectomy surgery, orthopedic surgery, abdominal surgery, orthognathic surgery, third molar surgery, septorhinoplasty, percutaneous nephrolithotomy, bunionectomy, and pancreaticoduodenectomy, etc. The baseline characteristics of each study were summarized in Table 1.

Quality assessment of included studies

The assessment of the risk of bias was summarized in Figure 2, Figure 3, and Supplementary Table 3. 56.3% of trials (22-39) had an unclear risk of bias owing to insufficient information about random sequences, allocation concealment, and the blinding of participants, personnel, and outcome assessors. 28.1% of trials (40-48) showed a low risk of bias and 15.6% of trials (49-53) had a high risk of blinding of participants and personnel, selective reporting, or other bias.

Postoperative Analgesia Management

Primary outcomes

The VAS score at the different postoperative time

A total of 9 studies (599 patients) were included to compare the VAS score at different postoperative times between IVIB and placebo (25, 26, 29, 32, 37, 46-48, 53). The results indicated that IVIB was significant effective in reducing VAS scores at postoperative 0min (MD, -3.53; 95% CI, -4.32 to -2.75, 5 trials, low certainty), 1h (MD, -1.94; 95% CI, -2.66 to -1.22, 7 trials, moderate certainty), 2h (MD, -1.69; 95% CI, -2.29 to -1.09, 6 trials, low certainty), 4h (MD, -1.24; 95% CI, -1.80 to -0.68, 5 trials, low certainty), 8h (MD, -1.69; 95% CI, -2.65 to -0.73, 5 trials, low certainty), 12h (MD, -1.04; 95% CI, -1.63 to -0.45, 6 trials, low certainty), and 24h (MD, -0.96; 95% CI, -1.35 to -0.57, 8 trials, moderate certainty) (Figure 4, Supplementary Table 7). Subgroup analysis showed that IVIB (800 mg) was administered preoperatively and continued every 6 h or 8h postoperatively was associated with lower VAS scores (29, 46, 53) (Supplementary Figure 1). Additionally, five studies (25, 26, 32, 37, 48) reported the VAS score at different postoperative times between single-dose IVIB (800 mg) 30min preoperative group and placebo, the results did not change except for 4h and 8h (Supplementary Figure 2). Only one study (47) compared the single-dose IVIB (400 mg) with placebo, the results showed that IVIB was associated with lower pain scores in the postoperative 24h period. Subgroup analyses were further performed for different surgery types in the postoperative VAS score (Supplementary Table 4).

Four studies (26, 29, 31, 46) including 260 patients compared the VAS score at different postoperative times

between IVIB and intravenous acetaminophen. The results showed that VAS scores within postoperatively 24h were reduced in the IVIB group (Supplementary Figure 3). Although there were no statistical differences in terms of VAS scores at 1h (MD, -1.77; 95% CI, -3.98 to 0.45, 2 trials, low certainty) and 24h (MD, -0.36; 95% CI, -0.80 to 0.08, 4 trials, low certainty), the point estimates in IVIB group were associated with lower pain intensity.

Considering the differences in the effect indicators, including the area under the VAS pain curve (VAS-AUC), median value, and numeric rating scale (NRS), we conducted the descriptive analyses to show the results. Compared with placebo, Southworth et al (52) reported that IVIB (800 mg) q6h was associated with significant reduction in postoperative pain across three time periods (VAS-AUC, 1-24h, 6-24h, 12-24h, $P < 0.01$), while IVIB (400 mg) provide effectively pain relieve within 6-24h and 12-24h periods. Three studies (33, 39, 45) compared the postoperative analgesic effect of IVIB (800 mg) versus acetaminophen (1000 mg). Viswanath et al showed that the median postoperative pain scores in the IVIB group were significantly lower than those in the IV acetaminophen group at 4 hours ($P = 0.004$) and 24 hours ($P = 0.019$), respectively (33). Kayhan et al indicated that the usage of IVIB was associated with a reduction in pain at 1-24h and 12-24h (VAS-AUC, $P < 0.05$) (45). However, Ucar et al (39) indicated that there were no differences in pain intensity between IVIB and acetaminophen ($P = 0.428$). Additionally, Lubis et al found the pain score in the walking phase based on NRS in the IVIB group was lower than that in the acetaminophen group (5.6 ± 0.5 vs 7.3 ± 1.2, $P < 0.001$), while there is no significant difference in the resting state (38). Dwarica et al reported that there was no statistically significant difference in the pain VAS scores within postoperative 24h between IVIB and intravenous ketorolac group (at rest: 2.30 ± 2.10 vs 2.68 ± 2.34, $P = 0.20$; at ambulation: 3.94 ± 2.57 vs 4.16 ± 2.73, $P = 0.57$, respectively) (51).

Cumulativeconsumption of opioid medication

Fifteen studies (26, 27, 29, 31, 32, 34, 35, 37, 42, 46-48, 50, 52, 53) and six studies (26, 29, 31, 35, 45, 46) compared the differences in the cumulative opioid consumption between IVIB and placebo or acetaminophen during postoperative 24h, respectively. The opioids include tramadol, fentanyl, and morphine. As shown in Figure 5, compared to placebo, IVIB (800 mg) could significantly reduce fentanyl (MD, -0.23 mg; 95% CI, -0.39 to -0.07, 4 trails, low certainty) and morphine consumption (MD, -10.14 mg; 95% CI, -15.33 to -4.95, 6 trails, moderate certainty), but could not reduce tramadol consumption (MD, -45.03 mg; 95% CI, -132.00 to 41.94, 3 trails, low certainty).There was no statistically significance between IVIB (400 mg) and placebo in terms of morphine consumption (MD, -5.76 mg; 95% CI, -13.60 to 2.07, 3 trails, moderate certainty). Only two studies (42, 47) reported that IVIB (400 mg) reduced fentanyl consumption compared with placebo (553.00 μg $\pm$ 257.04 vs 303.33 μg $\pm$ 132.08, $P<0.001$ (47); median consumption: 12.5 μg vs 37.5 μg, $P = 0.004$ (42)).

When compared to acetaminophen, IVIB (800 mg) was associated with lower fentanyl (MD, -0.09 mg; 95% CI, -0.17 to -0.01, 2 trails, low certainty) and morphine (MD, -5.49 mg; 95% CI, -7.04 to -3.94, 2 trails, moderate certainty) consumption, except for tramadol (MD, -33.28 mg; 95% CI, -67.30 to 0.74, 2 trails, moderate certainty) (Supplementary Figure 4, Supplementary Table 7). Two studies reported the median opioid consumption after postoperative 24h. Ucar et al (39) found IVIB (800 mg) was associated with lower tramadol consumption than intravenous acetaminophen (195 mg vs 325 mg, $P = 0.031$). Lubis et al (38) indicated that no statistical difference was found in the median total morphine consumption between IVIB (800 mg) and acetaminophen group (9.0 mg vs 15.0 mg, $P = 0.391$). Only one study (42) reported IVIB (400 mg) was associated with lower fentanyl consumption than acetaminophen (12.5μg vs 32.5μg, P=0.016).

In terms of the cumulative opioid consumption during postoperative 48h, IVIB (800 mg) group was associated with lower fentanyl (255.45 ± 171.429 μg and 748.85 ± 155.645 μg, $P < 0.001$) (44) and morphine (MD, -20.65 mg; 95% CI, -28.06 to -13.24, 2 trials, moderate certainty) (28, 34) consumption than the placebo group, respectively (Supplementary Figure 5).

Secondary outcomes

The usage rate of rescue analgesia

Eleven studies (26, 29-32, 37, 43-46, 48) compared results for participants receiving rescue analgesia between IVIB group and placebo or acetaminophen group. IVIB (RR, 0.27; 95% CI, 0.15 to 0.47, 11 trials, low certainty) was found to be associated with a lower usage rate of rescue analgesia compared with other treatments. However, the further subgroup analysis showed that there was no significant difference between the IVIB group and the placebo group (RR, 0.16; 95% CI, 0.02 to 1.29, 9 trials, moderate certainty), and acetaminophen group (RR, 0.30; 95% CI, 0.06 to 1.35, 6 trials, moderate certainty), respectively (Supplementary Figure 6, Supplementary Table 7).

Safety

A total of 18 studies (23, 26-29, 31, 32, 34, 35, 42, 43, 45-50, 52) reported adverse events, mainly including nausea or vomiting, pruritus, dizziness, headache, flatulence, and dyspepsia. 15 studies (23, 26, 27, 29, 32, 34, 35, 42, 43, 46-48, 50, 52) with 1,746 participants compared IVIB with placebo. Meta-analysis showed that IVIB was associated with a lower incidence of nausea or vomiting (RR, 0.71; 95% CI, 0.56 to 0.91, 14 trials, moderate certainty). There was no significant difference in the incidence of pruritus (RR, 0.94; 95% CI, 0.67 to 1.32, 8 trials, moderate certainty), dizziness (RR, 0.77; 95% CI, 0.25 to 2.39, 7 trials, moderate certainty), headache (RR, 0.82; 95% CI, 0.43 to 1.58, 4 trials, moderate certainty), dyspepsia (RR, 0.87; 95% CI, 0.33 to 2.32, 4 trials, moderate certainty), or flatulence (RR, 1.08; 95% CI, 0.76 to 1.54, 4 trials, moderate certainty) (Figure 6, Supplementary Table 7).

Ten studies (26, 29, 31, 35, 39, 42, 43, 45, 46, 49) consisting of 670 participants reported the difference in the safety between IVIB and acetaminophen. As a result, IVIB was associated with a lower incidence of nausea or vomiting (RR, 0.65; 95% CI, 0.51 to 0.83, 9 trials, moderate certainty). There was no significant difference in the incidence of pruritus (RR, 0.64; 95% CI, 0.22 to 1.84, 3 trials, moderate certainty) or headache (RR, 0.98; 95% CI, 0.48 to 2.00, 3 trials, moderate certainty) (Supplementary Figure7, Supplementary Table 7).

Antipyretic Management

Five RCTs (22, 24, 36, 40, 41) discussed the antipyretic efficacy of IVIB in adult patients with severe (malaria and burns) or non-severe illnesses (tonsillopharyngitis and emergency fever). Three of the studies (22, 24, 40) compared the efficacy and safety of IVIB with placebo, and we conducted descriptive analysis only. Krudsood et al (22) reported the area under the temperature curve (AUC-T°) for ibuprofen (400 mg q6h) at 24h post-treatment, with a more significant reduction in temperature in the IVIB group compared to the placebo group (7.49 ± 7.94 vs. 16.44 ± 11.60, P = 0.002). Promes et al (24) reported that the AUC-T° for ibuprofen (800 mg q6h) during 24 hours post-treatment was associated with a lower value than the placebo group (9.19 ± 7.6 vs 16.09 ± 11.5, P = 0.008). Morris et al (40) investigated the antipyretic effect of IVIB (400 mg q4h) and discovered that the proportion of patients whose temperature dropped below 101.0 °F within 4 hours was significantly higher in the IVIB group than in the placebo group (24 patients: 77% vs. 9 patients: 32%, P = 0.0005). Promes et al (24) and Morris et al (40) also reported AEs and severe adverse events (SAEs), but all SAEs were not related to the drug. There were no statistical differences in the incidence of AEs between the two groups.

Two studies (36, 41) compared the antipyretic effect of a single dose of IVIB (400 mg) with that of acetaminophen (1000 mg), both of which showed a better antipyretic effect and a significant reduction in temperature from baseline (Can et al, P = 0.001; Oncel et al, P < 0.001). However, Can et al (36) found that there was no difference in the antipyretic effect between IVIB and intravenous acetaminophen 30 minutes after administration (P = 0.980). Additionally, Oncel et al (41) found that IVIB was more effective in reducing temperature than intravenous acetaminophen at 15 minutes after administration (median: 0.60 vs 0.40, P = 0.036), whereas there was no difference in the changes of the fever at 60 minutes (median: 1.5 vs 1.5, P = 0.350). No drug-related AEs were reported in either study.

Publication Bias of Included Studies

The analyses produced asymmetric funnel plots for the incidence of the nausea or vomiting (Supplementary Figure 8), and the Egger's test indicated no publication bias for the included studies (P = 0.181). However,

we could not detect potential publication bias for remaining outcomes owing to a lack of data for individual outcome measure.

Sensitivity Analysis

For pooled results with substantial heterogeneity, the sensitivity analysis was conducted by excluding trials for each outcome. We found the heterogeneity significantly decreased. For the outcome of the usage of rescue analgesia, there were statistically significant difference between the IVIB and placebo (RR, 0.16; 95% CI, 0.08 to 0.34, 8 trials, moderate certainty) or acetaminophen (RR, 0.26; 95% CI, 0.14 to 0.49, 5 trials, high certainty) when excluding Daniels et al (43) (300mg IVIB), which was lower than that in other studies. The results were not changed in remaining outcomes (Supplementary Table 5). The robustness of results was also carried out by removing trials of overall high risk of bias, and no material change was observed in each outcome results (Supplementary Table 6).

DISCUSSION

We found moderate-to-low certainty evidence that preoperative IVIB could reduce the pain intensity within 24 hours after various surgeries compared with placebo, regardless of single-dose or administrated every 6 hours or 8 hours. Furthermore, compared with intravenous acetaminophen, IVIB was basically associated with lower pain scores within postoperative 24h. IVIB (800 mg) could reduce morphine consumption at both 24h and 48h postoperatively, whereas IVIB (400 mg) showed no benefit. IVIB (400mg or 800mg) could reduce the need for rescue analgesics compared with placebo and intravenous acetaminophen. In another hand, IVIB appeared satisfactory antipyretic efficiency in a short period of time in adults, but there was no difference between IVIB and intravenous acetaminophen. In terms of safety, IVIB was well tolerated in both pain and fever management, and was associated with a lower incidence of nausea or vomiting compared with placebo or intravenous acetaminophen. As a result, IVIB represents an effective and well tolerated agent for the treatment of acute perioperative analgesic when oral agents may be impractical or when rapid onset with predictable therapeutic dosing is needed in hospitalized patients.

Implications for IVIB in clinical practice

Treatment of postoperative pain continues to be a challenge. Appropriate implications of perioperative multimodal analgesia may contribute to the relieve of psychological distress, anxiety, sleeplessness and helplessness, impaired postoperative rehabilitation, potentially long-term psychological consequences, and the possibility of chronic postsurgical pain (54-56). Acetaminophen and NSAIDs have been evaluated as a fundamental part of multimodal analgesia in patients also receiving opioids without contraindications (such as patients undergoing coronary artery bypass graft surgery, with a history of active peptic ulcers, bleeding, or gastrointestinal bleeding or perforation following the use of NSAIDs) (3, 57, 58).

Several studies have indicated that there was no obvious difference between intravenous and oral administration in acetaminophen and NSAIDs (59, 60). Intravenous route, with a higher cost, is preferred in appropriate patients who were unable to take anything by mouth early in the perioperative period (61). In a regional investigation of the United Kingdom, intravenous NSAIDs administration was the preferred route of analgesics in the perioperative period largely owing to its reliability and speed of onset (62).

The effect of antipyretic and analgesic of ibuprofen primarily by inhibiting cyclooxygenase (COX), and ibuprofen has varying degrees of reversible and competitive inhibitory effects on COX-1 (88.7%) and COX-2 (71.4%) (63). IVIB has a higher (twice) maximum blood concentration and shorter time to peak (0.11h vs. 1.5h) than oral dosage forms, but the elimination half-life of IVIB and oral ibuprofen did not differ (approximately 2 hours) (64-66). IVIB thereby plays a vital role in patients requiring acute analgesia and rapid hypothermia. Nevertheless, considering the limited types of intravenous acetaminophen and NSAIDs on the market, there is lack of head-to-head studies comparing the efficacy and safety among them. Our review found that IVIB might benefit analgesic management in pain control, rescue analgesics, and the risk of nausea and vomiting, which fill in the gap in this area.

Safety Evaluation of IVIB

All NSAIDs contain label warnings and precautions regarding the risk of gastrointestinal bleeding or ulceration, cardiovascular risks, renal and hepatic injury, and bleeding related to platelet dysfunction (67, 68). Nevertheless, these AEs are predominantly connected to long-term drug use, whereas acute perioperative use of NSAIDs is considered relatively safe. Overall, IVIB had not demonstrated increased risk of SAEs, including hematological and renal system, in pain and fever management according to our analyses. It showed a decreased risk of nausea or vomiting, probably owing to the lower cumulative consumption of opioid medication in multimodal analgesia management (69). Furthermore, the elderly patients who received IVIB also experienced far fewer AEs overall (59%) than did those receiving placebo (94%) (*50*). In pediatric population, the majority of AEs were mild to moderate, and there was no significant difference between IVIB and intravenous acetaminophen (70, 71).

It is worth mentioning that several studies have investigated the safety of single and multiple doses of IVIB administered over 5 to 10 minutes other than 30 minutes recommended for the treatment of postoperative pain in health adults. They found that 22%˜29% of patients experienced AEs, and the most common AE was infusion site pain (11%˜15%). No deaths or IVIB-related SAEs were reported (72, 73). Also, studies assessed the safety and acceptability of 5- to 10-minute infusion of IVIB and found that it appeared a faster efficacy in reducing fever compared to acetaminophen administered at a regular pace (41, 66). IVIB rapid infusion was therefore proved be well tolerated and proved additional benefits in the perioperative period and emergent situations.

Strength and Limitations

To our best knowledge, this is the first comprehensive systematic review to summarize the efficacy and safety of IVIB for postoperative pain and fever management in adults, with thorough consideration on multiple- (Q6h or Q8h) or single- dosage of IVIB without limitation on surgery types. Considering the heterogeneity of pain intensity, we only synthesized the data except for non-molar surgery studies in efficacy evaluation. It could strengthen the applicability of our review findings to patients with differing illness in various clinical settings.

This study has several limitations. First, more than 70% of trials included fewer than 60 patients per group, which may bring imprecision in synthesized results and publication bias due to small sample size. Second, there were insufficient trials to preform funnel plot to evaluate the publication bias, which may result in downgrade in the certainty of evidence. Third, considering insufficient data in some outcome measures, we were unable to identify high homogenous through subgroup analyses. Future studies should focus on the appropriateness of oral versus intravenous ibuprofen, patients' compliance and economic evaluation, as well as its rational use in pediatrics and the elderly.

CONCLUSIONS

Moderate-to-low certainty evidence indicated that adults with postoperative pain and fever who were unable to take oral medicine would benefit from IVIB in comparison to placebo or intravenous acetaminophen.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

CONTRIBUTORS

Conceptualization and design: Z.P.X., C.L., Z.S.D.; Methodology and registration: Z.P.X.; Literature search, selection and data extraction: Z.P.X., C.L., W.E.T., T.S.X., H.L.Z.; Risk of bias and evidence certainty evaluation: Z.P.X., C.L.; Drafting of the manuscript: Z.P.X., C.L.; Supervision: Z.S.D.; Revision of the manuscript: Z.P.X., C.L., Z.S.D.; All authors have approved the final version of this manuscript.

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DATA AVAILABILITY STATEMENT

All relevant data are within the article and supplementary materials.

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