Systematic Review and Meta-Analysis

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# Efficacy and safety of ibuprofen in children with musculoskeletal injuries

## A systematic review and meta-analysis of randomized controlled trials

Jianping Jin, MM, Xiaoqing Wang, MM, Jingjing Wang, MM, Zhanhai Wan, MM*

**Abstract**

**Objective:** To evaluate the analgesic efficacy and safety of ibuprofen in children with musculoskeletal injuries.

**Methods:** PubMed, EMBASE, Web of science, and the Cochrane Central register of Controlled Trials (CENTRAL) were systematically searched to identify eligible randomized controlled trials (RCTs) that compared ibuprofen with other analgesics for pain relief in children with musculoskeletal injuries. Primary outcomes included change of visual analog scale (VAS) scores from baseline to post-medication, the proportion of patients achieving adequate analgesia, and the proportion of patients requiring additional analgesia. Secondary outcome was the incidence of adverse effects. Data analysis was performed using RevMan 5.3 software.

**Results:** Five RCTs involving 1034 patients were included in this meta-analysis. Compared to the control group, change of VAS scores was greater in ibuprofen group at 60 min (standardized mean difference [SMD] = 0.28; 95% confidence intervals [CI], 0 to 0.57; $P = .05$), 90 min (SMD = 0.38; 95% CI, 0.17 to 0.59; $P = .0005$), and 120 min (SMD = 0.4; 95% CI, 0.23 to 0.57; $P < .00001$) after treatment. No difference was found in the change of VAS scores at 30 min (SMD = 0.07; 95% CI, -0.08 to 0.22; $P = .36$) after treatment. The proportion of patients who received adequate analgesia was higher in the ibuprofen group (risk ratios [RR] = 1.36; 95% CI, 1.20 to 1.56; $P < .00001$). The proportion of patients that required additional analgesia was lower in the ibuprofen group (RR = 0.7; 95% CI, 0.53 to 0.92; $P = .01$). The incidence of total adverse effects was lower in the ibuprofen group (RR = 0.59; 95% CI, 0.45 to 0.79; $P = .0002$).

**Conclusions:** Ibuprofen provides a better pain relief with a lower incidence of adverse effects in children with musculoskeletal injuries as compared to other analgesics.

**PROSPERO registration number:** CRD42021231975.

**Abbreviations:** CI = confidence intervals, NSAIDs = nonsteroidal anti-inflammatory drugs, RCTs = randomized controlled trials, RR = risk ratios, SMD = standardized mean difference, VAS = visual analog scale.

**Keywords:** analgesia, children, ibuprofen, meta-analysis, musculoskeletal injuries

## 1. Introduction

Musculoskeletal injuries, including fractures, bruises, and sprains, are one of the most common cause of children's visits to the emergency department for pain conditions.[1] Numerous studies indicate that analgesia is not adequately provided to these pediatric patients.[2–6] One study revealed that only 35% of children with a fracture or severe sprain were given the analgesics in emergency department.[7] The undertreatment of pain in pediatrics may be due to the limited evidence in pain management for children with musculoskeletal injuries or to the worry about adverse events induced by opioids as well as other analgesics.[4,5] Inadequate pain management in children may lead to detrimental effects, such as healing delay, anxiety, and hyperesthesia.[8,9] Previous studies suggest that nonsteroidal anti-inflammatory drugs (NSAIDs), are the most commonly-used analgesics in managing children's pain from musculoskeletal injuries in emergency department, of which ibuprofen is currently the standard first-line drug.[10,11] Other analgesics, such as acetaminophen,[10] codeine,[11] and morphine[12] are also widely prescribed for pain management in children with musculoskeletal injuries. A number of studies have compared the analgesic effects of ibuprofen with other analgesics,[12–16] but the results are

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inconsistent. A previous systematic review tried to synthesize the evidence regarding the effect of ibuprofen versus other analgesics on children's pain from musculoskeletal injuries but did not perform a meta-analysis for the consideration of variation of control protocols.[17] Moreover, the authors did not focus on the side effects of ibuprofen versus other analgesics.[17] Therefore, it is still necessary to conduct a meta-analysis to synthesize evidence regarding ibuprofen's effect and safety on children's pain management from musculoskeletal injuries.

## 2. Materials and methods

### 2.1. Ethical statements

No ethical approval is required because this is a literature-based study. This systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO; Registration NO. CRD42021231975) and was conducted in agreement with the PRISMA guideline.[18]

### 2.2. Search strategy

Two authors performed a comprehensive search for RCTs investigating the effect of ibuprofen on pediatric pain management from musculoskeletal injuries in a range of databases, namely, PubMed, EMBASE, CENTRAL, and Web of science, from inception to Jan 16, 2021 with restriction of English language. The key terms used in our systematic search include "ibuprofen", "children", "pediatric", "fracture" and "Musculoskeletal injury". We also tracked references for eligible studies that we may miss.

### 2.3. Eligible criteria

A study was eligible, if

1. study design was RCT,
2. study participants were pediatric patients (< 18 years) with musculoskeletal injuries,
3. the study focused on the comparison between oral medication with ibuprofen only and oral medication with other analgesics for pain management, and
4. any of the following outcomes of interest were reported: change of visual analog scale (VAS) from baseline, proportion of patients achieving adequate analgesia or requiring additional analgesia, and adverse effects (e.g., nausea, vomiting, drowsiness, dizziness and constipation).

### 2.4. Study selection and data extraction

Two authors independently identified the eligible studies by screening title and abstract first and then reviewing full-text of potentially eligible articles. Two authors independently extracted the following information from included studies: authors, publication year, sample size, study participants' age and weight, interventions, controls, and outcomes. Since several scales for measuring severity of pain were used in included studies, we converted the results of pain measurement from different scales to a 0–100 mm VAS (VAS, 0: no pain, 100: worst imaginable pain). We attempted to contact corresponding authors for original data if the results of pain measurement were presented by median and range. If there was no response, we would convert median and range to mean and standard deviation according to the methods described by Hozo and colleagues.[19] Disagreements were resolved by discussion with a third author.

### 2.5. Risk of bias assessment

Two authors independently assessed the quality of included studies using the Cochrane Collaboration's tool for risk of bias[20] with six items:

1. random sequence generation (selection bias);
2. allocation concealment (selection bias);
3. blinding of participants and personnel (performance bias);
4. blinding of outcome assessment (detection bias);
5. incomplete outcome data (attrition bias); and
6. selective reporting (reporting bias).

The estimated risk of bias for each item was rated as 'low', 'high', or 'unclear'. Disagreements were discussed with a third author.

### 2.6. Statistical analysis

We calculated standardized mean differences (SMD) and risk ratios (RR) with 95% confidence intervals (CI) for continuous and dichotomous outcomes, respectively. To consider clinical heterogeneity (e.g., type of injury, kind of analgesics, and the method of pain measurements), we applied random-effect model to synthesize results from included studies. Statistical heterogeneity was assessed using the $I^2$ test. Significant heterogeneity was considered to be present when $I^2$ statistic was $> 50\%$. $P < .05$ was considered to be statistically significant.

## 3. Results

### 3.1. Characteristics of included studies

A total of 266 studies were identified initially, of which we excluded 56 duplicates, 169 non-RCTs, 12 conference abstracts, 14 on-going RCTs and 9 irrelevant studies by reviewing title, abstract and full-text. Finally, a total of 6 RCTs were included, of which 5 studies[12–16] involving 1034 patients were included into meta-analysis (Fig. 1). 424 patients received ibuprofen and 610 patients received other analgesics, including acetaminophen, codeine, and morphine.

The characteristics of the included studies were present in Table 1. The risk of bias of the included studies was present in Table 2.

### 3.2. Results of meta-analysis

**3.2.1. Change of pain scores after treatment.** Four studies[7,9,21,22] reported change of VAS scores after treatment. Pooled results showed that the change of VAS scores was higher in ibuprofen group compared with control group (SMD = 0.27; 95% CI, 0.15 to 0.38; $I^2 = 55\%$; $P < .00001$) (Fig. 2).

Subgroup analysis was conducted according to the time of pain measurements. No significant difference was found in the change of VAS scores at 30 min after treatment in the ibuprofen group compared with the control group (SMD = 0.07; 95% CI, -0.08 to 0.22; $I^2 = 17\%$; $P = .36$). However, a higher change of VAS scores was found at 60 min (SMD = 0.28; 95% CI, 0 to 0.57; $I^2 = 71\%$; $P = .05$), 90 min (SMD = 0.38; 95% CI, 0.17 to 0.59; $I^2 = 40\%$; $P = .0005$), and 120 min (SMD = 0.4; 95% CI, 0.23 to 0.57; $I^2 =$

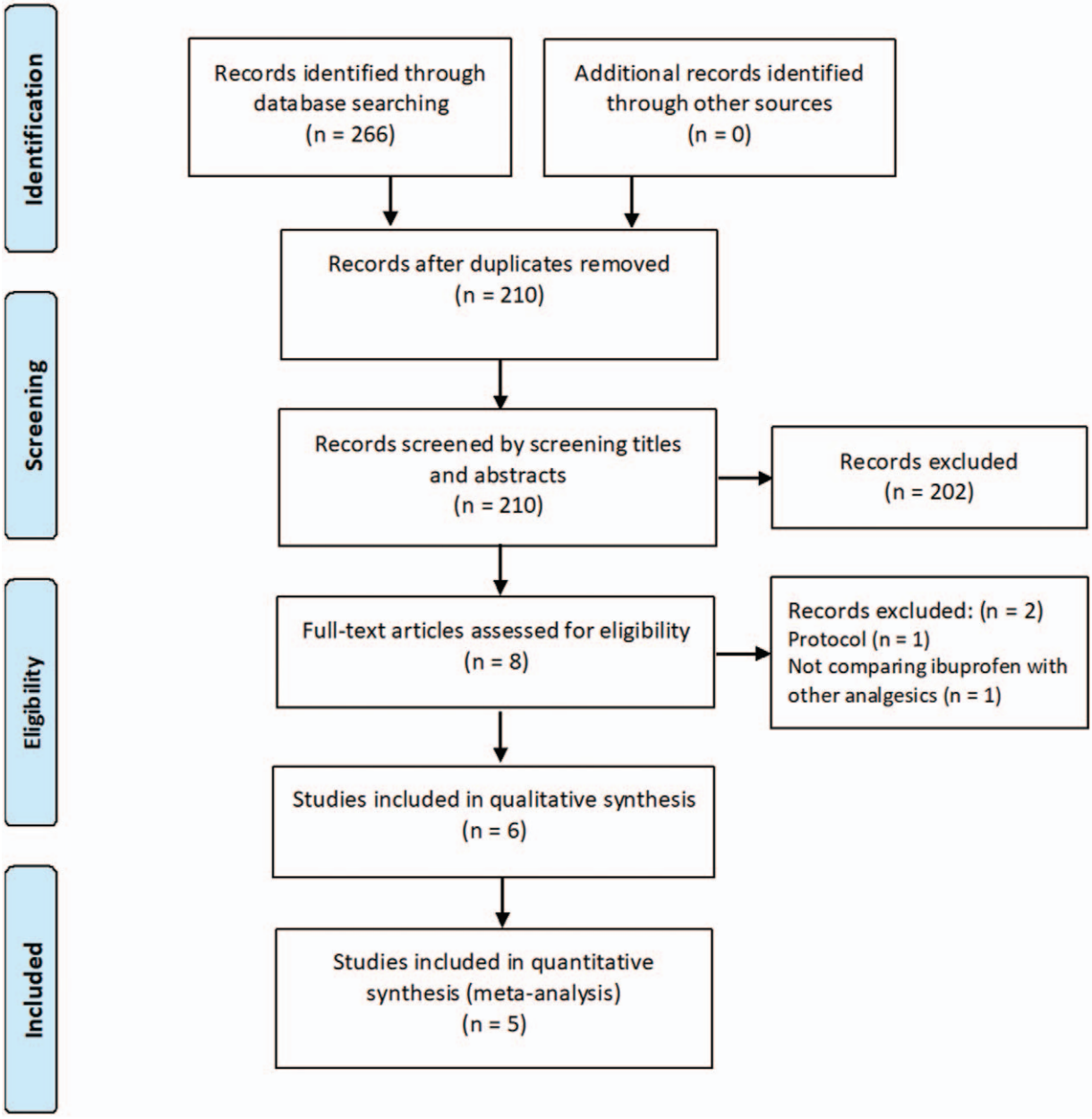


**Figure 1.** The flow diagram of study selection.

0%; $P < .00001$) in the ibuprofen group compared with the control group.

Subgroup analysis was also conducted according to the pain medication. Compared with morphine, the effect of ibuprofen was similar on the change of VAS scores at 30 min after treatment (SMD = -0.04; 95% CI, -0.25 to 0.18; $I^2 = 13\%$; $P = .75$).

### 3.3. Adequate analgesia

Two studies[7,9] reported the proportion of adequate analgesia. Pooled results showed that 36% more children in ibuprofen group achieved adequate analgesia than the control group (RR = 1.36; 95% CI, 1.20 to 1.56; $I^2 = 2\%$; $P < .00001$) (Fig. 3).

Subgroup analysis was conducted according to the time of pain measurements. The results showed a higher proportion of adequate analgesia at 60 min (RR = 1.30; 95% CI, 1.07 to 1.57; $I^2 = 0\%$; $P = .007$), and 120 min (RR = 1.45; 95% CI, 1.13 to 1.86; $I^2 = 45\%$; $P = .003$) in the ibuprofen group compared with the control group.

### 3.4. Requiring additional analgesia (Failure of analgesia)

Four studies[9,21–23] reported the proportion of failure of analgesia. Pooled results showed that the proportion of failure of analgesia was lower in the ibuprofen group compared with the control group (RR = 0.7; 95% CI, 0.53 to 0.92; $I^2 = 0\%$; $P = .01$) (Fig. 4).

Subgroup analysis was conducted according to the pain medication. Compared with acetaminophen-codeine, the proportion of failure of analgesia was lower but with no statistical significance after ibuprofen treatment (RR = 0.67; 95% CI, 0.44 to 1.02; $I^2 = 0\%$; $P = .06$).

**Table 1**

**Study characteristics.**

| Study | Countries | Patients | Age (years) | Weight (kg) | Pain cause | Interventions | Comparisons | Outcomes | Pain measurements |
|---|---|---|---|---|---|---|---|---|---|
| Clark 2007 | Canada | 311 | 11.8 (2.8) vs 12.0 (2.9) vs 12.2 (3.1)* | NA. | extremities, neck, or back injuries | ibuprofen (10 mg/kg, orally, n=103) | acetaminophen (15 mg/kg, orally, n=103) or codeine (1 mg/kg, orally, n=105), | change of pain scores; the number of patients requiring additional analgesia; the number of patients achieving adequate analgesia; adverse events | Visual analog scale |
| Drendel 2009 | America | 244 | 7.4 (4.0–17.9) vs 8.2 (4.2–14.9)† | 27.9 (14.4–60.0) vs 29.4 (13.8–59.2)† | the radius, ulna, or humerus fractures | ibuprofen 10 mg/kg, orally (n=128) | acetaminophen with codeine (1 mg/kg, orally, n=116) | the proportion of requirement for rescue medication; pain medication use; pain scores; functional outcomes; satisfaction; adverse effects | The modified Bieri Faces Pain Scale |
| Friday 2009 | America | 66 | 10.6 (3.4) vs 10.1 (3.4)* | 47.3 (22.8) vs 43.0 (18.6)* | extremity injuries | ibuprofen (10mg / kg, orally, n=34) | acetaminophen with codeine (1 mg / kg, orally, n=32) | change of pain scores; requirement for additional analgesia; adverse effects | The Color Analog Scale |
| Le May 2017 | Canada | 456 | 12.2 (2.6) vs 11.7 (2.7) vs 12.0 (2.7)* | NA. | upper or lower limb injuries | ibuprofen (10 mg/kg, orally, n=91) | morphine (0.2 mg/kg, orally, n=188) or morphine (0.2 mg/kg, orally) with ibuprofen (10 mg/kg, orally, n=177) | pain score < 30 mm at 60 min after treatment; adverse effects | Visual analog scale |
| Poonai 2014 | England | 134 | 10.8 (3.1) vs 10.7 (3.3)* | NA. | uncomplicated extremity fractures | ibuprofen (10 mg/kg, orally, n=68) | morphine (0.5 mg/kg, orally, n=66) | change of pain scores; the number of participants who required acetaminophen; adverse effects | Faces Pain Scale |
| Koller 2007 | America | 66 | 11.1 (3.6) vs 10.9 (2.8) vs 12.0 (2.6)* | 56.1 (25.7) vs 51.3 (19.9) vs 66.6 (26.7)* | closed fractures or injuries | ibuprofen (10 mg/kg, orally, n=22) | oxycodone (0.1 mg/kg, orally, n=22) or oxycodone (0.1 mg/kg, orally) with ibuprofen (10 mg/kg, orally, n=22) | change of pain scores at 30, 60, 90, and 120 min after medication; adverse effects | Faces Pain Scale and Visual Analog Scale |

* Data are present as mean with standard deviation.

† Data are present as mean with range. NA=Not applicable.

**Table 2**

**Risk of bias of included trials.**

| Study | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting |
|---|---|---|---|---|---|---|
| Clark 2007 | Low | Low | Unclear | Low | Unclear | Low |
| Drendel 2009 | Low | Low | Low | Low | Low | Low |
| Friday 2009 | Low | High | Low | Low | Low | Low |
| Le May 2017 | Low | Low | Low | Low | Low | Low |
| Poonai 2014 | Low | Low | Low | Low | Low | Low |
| Koller 2007 | Unclear | High | Low | Low | Low | Low |

High = high risk of bias, Low = low risk of bias, Unclear = unclear risk of bias.

### 3.5. Adverse effects

Five studies[7,9,21–23] reported the incidence of adverse effects. Pooled results showed that ibuprofen group had 41% lower risk of adverse events than control group (RR = 0.59; 95% CI, 0.45 to 0.79; $I^2 = 21\%$; $P = .0002$) (Fig. 5). Specifically, children using ibuprofen had 75% lower risk of nausea (RR = 0.25; 95% CI, 0.13 to 0.48; $I^2 = 0\%$; $P < .0001$), 77% lower risk of vomiting (RR = 0.23; 95% CI, 0.09 to 0.57; $I^2 = 0\%$; $P = .002$), and 35% lower risk of drowsiness (RR = 0.65; 95% CI, 0.46 to 0.91; $I^2 = 0\%$; $P = .01$) compared to the control. No difference was found in the incidence of dizziness (RR = 0.62; 95% CI, 0.27 to 1.38; $I^2 = 0\%$; $P = .24$) and constipation (RR = 0.64; 95% CI, 0.12 to 3.47; $I^2 = 32\%$; $P = .61$) between ibuprofen group and control group (Fig. 6).

Subgroup analysis was conducted according to the pain medication. Compared with morphine, the incidence of adverse effects was lower after ibuprofen treatment (RR = 0.47; 95% CI, 0.28 to 0.79; $I^2 = 35\%$; $P = .004$). Compared with acetaminophen-codeine, the incidence of total adverse effects was lower after ibuprofen treatment (RR = 0.58; 95% CI, 0.42 to 0.80; $I^2 = 0\%$; $P = .0008$).

Data from one study[24] were not suitable for quantitative synthesis. The authors reported that oxycodone, ibuprofen, and the combination provided a comparable decrease in pain scores at

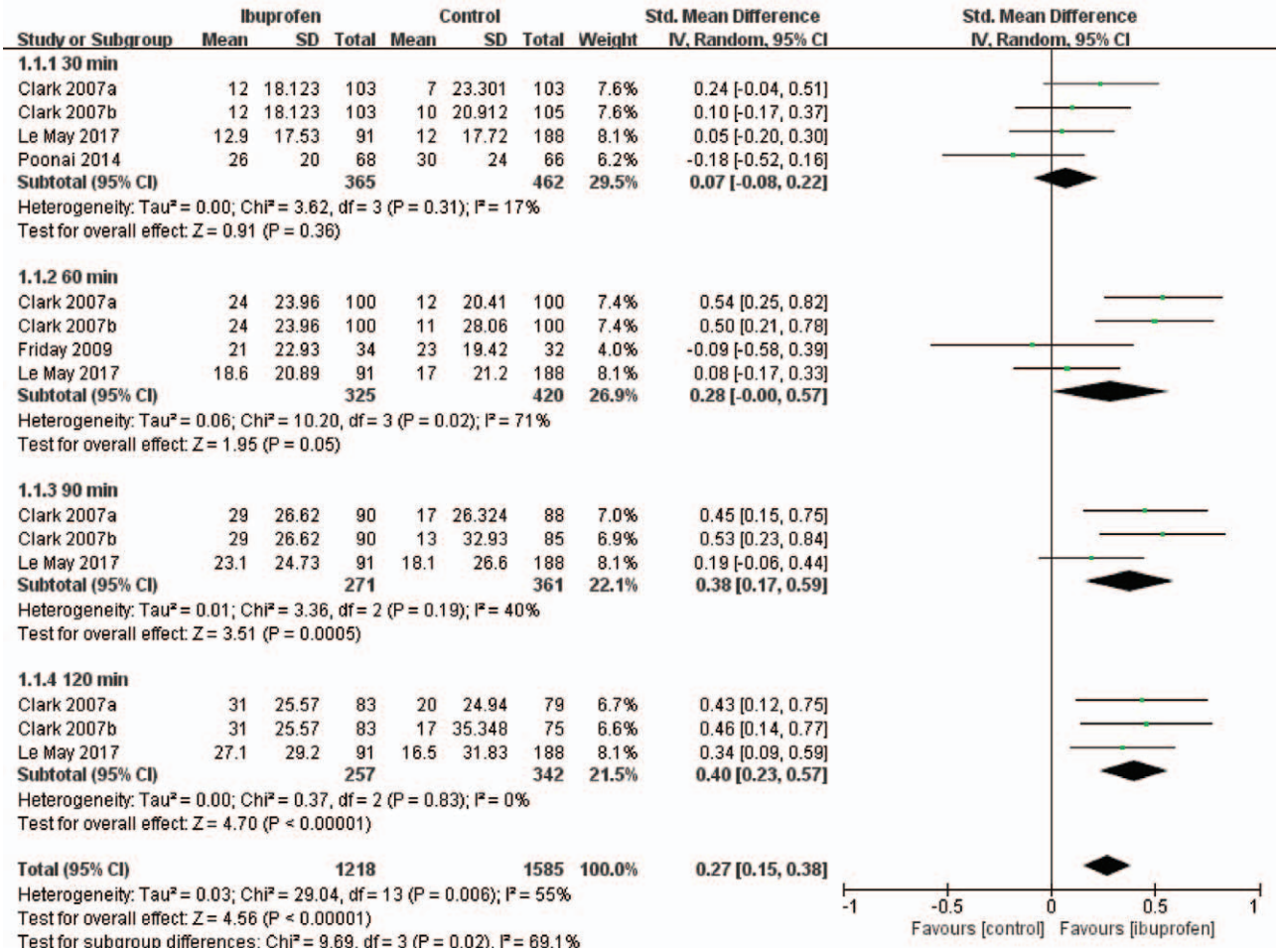


**Figure 2.** Meta-analysis of the change of VAS scores from baseline to post-medication.

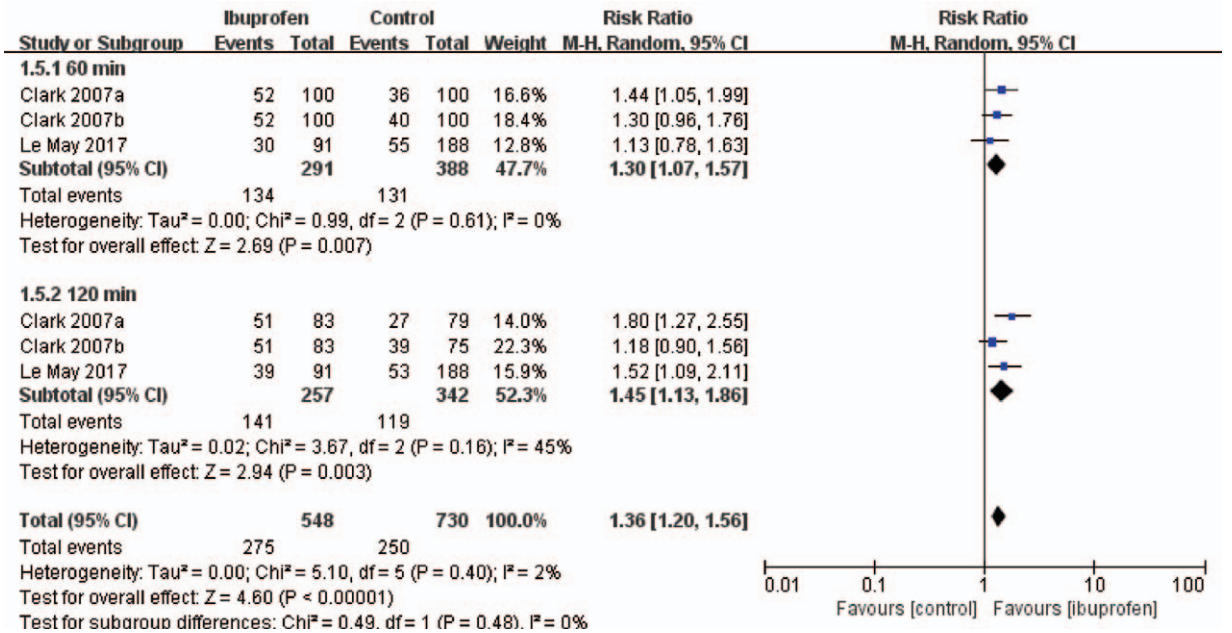


**Figure 3.** Meta-analysis of the proportion of patients achieving adequate analgesia.

30, 60, 90, and 120 min after medication. However, patients in the combination treatment group had more side effects.

### 3.6. Publication bias

Funnel plots for publication bias could not be reliably tested because of the small number of included studies.

## 4. Discussion

In this meta-analysis, we found that oral intake of ibuprofen produced a better analgesic effect than other analgesics for children with musculoskeletal injuries at 60 min, 90 min, and 120 min after medication. The analgesic effect was comparable between ibuprofen and other analgesics at 30 min after

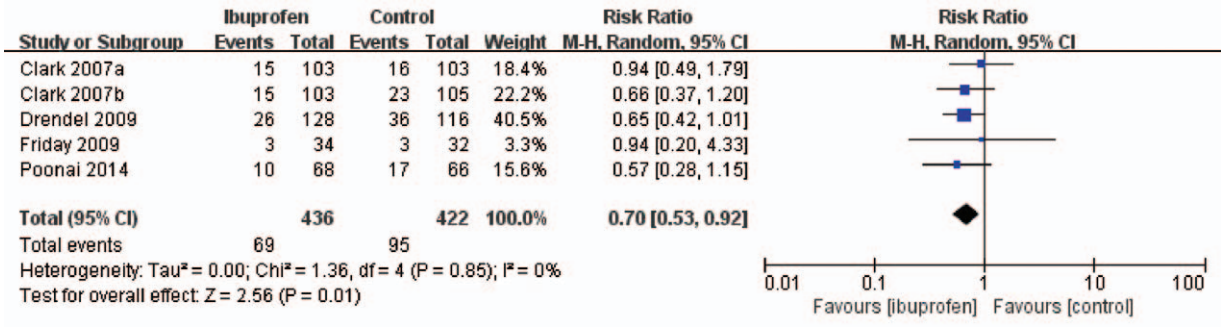


**Figure 4.** Meta-analysis of the proportion of patients requiring additional analgesia.

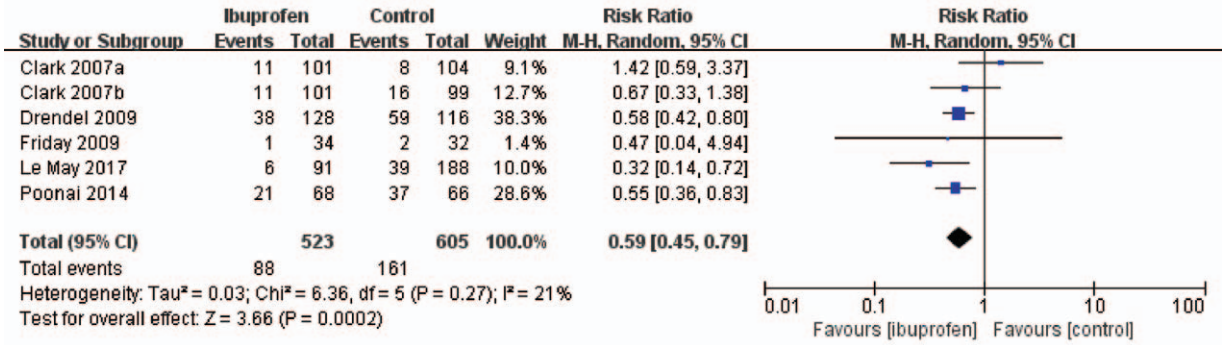


**Figure 5.** Meta-analysis of the incidence of total adverse effects.

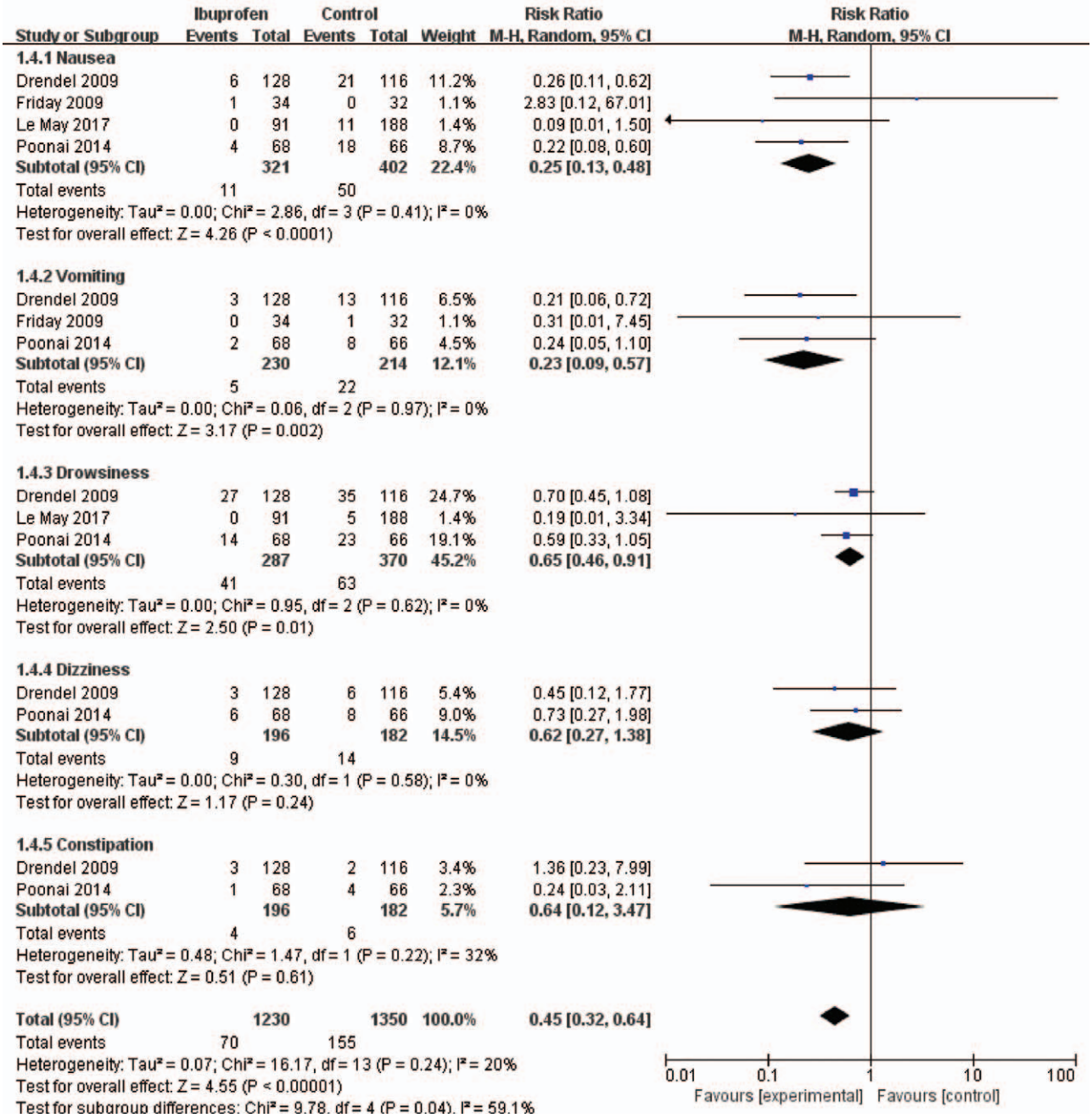


**Figure 6.** Meta-analysis of the incidence of specific adverse effects.

medication. Compared with other analgesics, ibuprofen had higher proportion of patients that achieved adequate analgesia and lower proportion of patients that required additional analgesia. In addition, ibuprofen had a lower incidence of adverse effects than other analgesics.

Painful condition is commonly seen in children with musculoskeletal injury that remains undertreated in emergency department.[4,8] Inadequate analgesia may cause detrimental effects in children.[8] It is essential to adequately assess pain and provide effective analgesia treatment in these pediatric population. The ideal drug should adequately alleviate pain symptoms with minimal adverse effects and no long-term addiction potential.[25] Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually recommended for acute pain management in patients with musculoskeletal injuries due to their non-inferior analgesic effect and low possibility of adverse effects.[25]

Traditionally, opioids are commonly prescribed for pain relief after acute injuries.[23] Unfortunately, opioids may lead to significant adverse events (e.g., somnolence, delirium, respiratory depression, abuse, dependence and addiction), creating a need for better alternatives.[21] Several studies demonstrate that NSAIDs provide analgesia comparable to that of opioids for both adult and pediatric patients with musculoskeletal injuries.[6,16,22] Consistently, pooled results in our meta-analysis showed that ibuprofen was equivalent with morphine in pain relief but generated fewer adverse effects. Therefore,

ibuprofen is a reasonable option for children with musculoskeletal injuries.

Although this meta-analysis showed ibuprofen is more effective in offering adequate analgesia than other analgesics, two studies reported only 52%[13] and 29.9%[6] of children achieved adequate analgesia at 60 min after treatment, suggesting that ibuprofen alone is not adequate for pain relief in all children with musculoskeletal injury. However, the combination of ibuprofen with codeine or oxycodone as well as morphine did not significantly improve the proportion of children that achieved adequate analgesia, but led to more adverse events.[12,24,26] Therefore, pain management provided by current medications remains suboptimal for most patients.

There have been concerns prescribing ibuprofen for children with musculoskeletal injuries because of negative effects of NSAIDS on fracture healing. Animal studies suggest that NSAIDS, such as indomethacin, aspirin, and ibuprofen affect fractures healing in rats,[27,28] but there is no conclusive evidence in human studies.[29] Retrospective studies of pediatric patients showed no cases with NSAIDS use have delayed bone healing.[30,31] One RCT reported no significant delay in healing of Colle's fractures in adults by piroxicam.[32] For children, RCTs also reported ibuprofen did not affect fracture healing.[14,33] However, long-term use of indomethacin for 6 weeks increased the risk of nonunion of acetabular fractures.[34] Nevertheless, there is no evidence that a short-term use of ibuprofen is associated with delayed fracture healing in humans.

Acetaminophen-codeine and ibuprofen are commonly prescribed oral analgesics. However, this combination does not provide better pain relief but lead to more side effects than ibuprofen in pediatrics.[35] Our pooled results showed that the proportion of analgesia failure was lower but with no statistical significance after ibuprofen treatment compared with acetaminophen-codeine. Moreover, the incidence of total adverse effects was lower after ibuprofen treatment. In addition, administration of codeine-containing analgesics may be difficult to perform prior to adequate evaluation, initial prescription of ibuprofen for children with acute injuries is thus recommended.

Musculoskeletal pain persists in children after discharge from emergency department. Currently, limited clinical trials evaluate analgesia situation in children with musculoskeletal injuries in the outpatient setting. One included study in this meta-analysis found that ibuprofen produced comparable rates of successful analgesia with acetaminophen-codeine for children with arm fractures.[14] However, functional outcomes, such as play, were better in children receiving ibuprofen. Moreover, fewer adverse effects and more satisfaction were seen in children receiving ibuprofen. Therefore, ibuprofen appears to be preferable to acetaminophen-codeine for children with musculoskeletal pain in an outpatient setting. Another RCT indicated that both ibuprofen and paracetamol can effectively alleviate children's pain from an acute fracture in the outpatient setting.[36] However, analgesic effects and side effects are comparable between ibuprofen and paracetamol. Therefore, either drug appears to be a reasonable option for pediatric acute limb fracture after discharge from the emergency department.

Antidepressants are generally first-line medications for chronic pain associated with musculoskeletal injuries in adults, such as back pain and osteoarthritis pain.[37] A recent systematic review and meta-analysis showed that serotonin-noradrenaline reuptake inhibitors (SNRIs) could reduce back pain and osteoarthritis pain, but tricyclic antidepressants (TCAs) and other antidepressants did not reduce back pain.[38] In this meta-analysis, we mainly focused on the effects of ibuprofen or other analgesics on the acute pain from musculoskeletal injuries in children. A substantial number of patients with acute pain might turn into chronic pain patients with musculoskeletal injuries. However, the evidence that regarding the efficacy of antidepressants in children with acute/chronic pain from musculoskeletal injuries were limited.[39,40] Therefore, the large sample multi-center randomized controlled trials are needed to determine the definitive effects of antidepressants on acute/chronic pain from musculoskeletal injuries in children.

Some limitations exist in this meta-analysis. Firstly, only six studies are included in and the sample size is relatively small. Secondly, the different conditions among included studies, including type of injury, the control analgesics, the method of pain measurement that may increase the clinical heterogeneity.

## 5. Conclusions

Ibuprofen can provide a better pain relief with fewer adverse effects in children with musculoskeletal injuries as compared to other analgesics. This meta-analysis supports ibuprofen as the first-line drug for children with musculoskeletal injuries.

## Author contributions

**Conceptualization:** Jianping Jin, Zhanhai Wan.
**Data curation:** Xiaoqing Wang, Jingjing Wang.
**Formal analysis:** Jianping Jin, Xiaoqing Wang, Jingjing Wang.
**Methodology:** Jianping Jin, Jingjing Wang.
**Validation:** Jianping Jin, Zhanhai Wan.
**Writing – original draft:** Jianping Jin.
**Writing – review & editing:** Zhanhai Wan.

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