Systematic Review and Meta-Analysis

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Comparison of intravenous and oral acetaminophen for pain control after total knee and hip arthroplasty

A systematic review and meta-analysis

Lixin Sun, MM[a], Xiaopei Zhu, MM[a], Jianhong Zou, MB[b], Yongchun Li, MD, PhD[c], Wei Han, MD, PhD[c,*]

Abstract

Objective: To evaluate the efficacy between intravenous and oral acetaminophen as adjunct to multimodal analgesia regimens for pain management after total knee and hip arthroplasties.

Methods: We conduct electronic searches of Medline (1966–2017.09), PubMed (1966–2017.09), Embase (1980–2017.09), ScienceDirect (1985–2017.09), and the Cochrane Library. Only randomized controlled trials (RCTs) are included. The quality assessment is performed according to the Cochrane systematic review method. Fixed/random effect model is adopted according to the heterogeneity tested by I^2 statistic. Meta-analysis is performed using Stata 11.0 software.

Results: Two RCTs are included involving 236 patients. The present meta-analysis demonstrated that there were no significant differences between groups regarding pain scores at 12, 24, or 48 hours. No significant differences were observed in terms of opioid consumption at 12, 24, or 48 hours after arthroplasties.

Conclusion: Intravenous acetaminophen to multimodal analgesia dose not demonstrate a significant benefit in reducing pain and opioid consumption compared oral formulation after total knee arthroplasty and total hip arthroplasty. Higher-quality RCTs are required for further research.

Abbreviations: CI = confidence interval, RCT = randomized controlled trial, RD = risk difference, THA = total hip arthroplasty, TKA = total knee arthroplasty, VAS = visual analog scale, WMD = weighted mean difference.

Keywords: acetaminophen, meta-analysis, pain control, total hip arthroplasty, total knee arthroplasty

1. Introduction

Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are popular surgical procedures for the treatment of end-stage of osteoarthritis.[1,2] However, the process is associated with postoperative pain ranging from mild to severe which leads to discomfort and stress. It is reported that there were more than 700 thousand TKAs and 400 thousand THAs are performed in the USA annually.[3,4] Pain control after major orthopedic surgery is a huge challenge. Inadequate pain management after surgery may cause potential complications, such as a higher risk of myocardial infarction, hypostatic pneumonia, anxiety, and depression. Numerous methods have been implemented to manage postoperative pain including peripheral nerve block, local infiltration analgesia, patient-controlled analgesia, and epidural analgesia.[5–8] However, each method has its limitations. The optimal analgesic strategy remains controversial and pain management is an interesting topic in the field of arthroplasties. Recently, multimodal analgesia regimens have been recommended for patients undergoing TKA and THA.

Acetaminophen is a nonsteroidal anti-inflammatory drugs which is widely used for pain management.[9] The mechanism of action of acetaminophen is not completely understood. It does appear to selectively inhibit COX activities in the brain, which may contribute to its ability to treat fever and pain. This activity does not appear to be direct inhibition by blocking an active site, but rather by reducing COX, which must be oxidized to function.[10] Published studies have confirmed that intravenous acetaminophen as adjunct to multimodal analgesia regimens was effective and safe for reducing pain and opioid consumption.[11] Oral acetaminophen is cheaper and more convenient than intravenous formulation. However, bioavailability in the cerebrospinal fluid and plasma is superior with the intravenous formulation. Currently, the efficacy of intravenous versus oral acetaminophen for pain control in TKA and THA has been in controversy. Therefore, we conduct a systematic review and meta-analysis from randomized controlled trials (RCT) to

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JHZ and HW conceived of the design of the study. YCL performed and collected the data and contributed to the design of the study. LXS and XPZ finished the manuscript. All authors read and approved the final manuscript.

LS and, XZ equally contributed to this study.

The authors declare that they have no competing interests.

[a] Department of Anesthesiology, Qingdao Municipal Hospital, [b] Department of Lab, Center for Disease Control and Prevention of Shibei District of Qingdao, [c] Department of Pulmonary Medicine, Qingdao Municipal Hospital, Qingdao, China.

[*] Correspondence: Wei Han, Department of Pulmonary Medicine, Qingdao Municipal Hospital, Qingdao 266011, China (e-mail: 3591939980@qq.com).

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evaluate the efficacy between intravenous and oral acetaminophen as adjunct to multimodal analgesia regimens for pain management after TKA and THA.

2. Methods

This article is reported according with the guideline of PRISMA statement. Ethical approval is not required because it is a meta-analysis of previously published studies.

2.1. Search strategy

We conduct electronic searches of Medline (1966–2017.09), PubMed (1966–2017.09), Embase (1980–2017.09), ScienceDirect (1985–2017.09), and the Cochrane Library. The following keywords are used on combination with Boolean operators AND or OR: "total knee arthroplasty OR replacement," "total knee arthroplasty OR replacement," "acetaminophen" and "pain control OR pain management OR analgesia." Details search for Embase and Pubmed are shown in Tables 1 and 2. References of the included studies are also scanned for potentially relevant articles. No restrictions are placed on the publication language. Two reviewers independently assess the titles and abstracts of all the reports identified by the electronic and manual searches. Subsequently, the full text of the potential articles which meet the inclusion criteria are screened, and a final decision is made. Disagreement is resolved by consulting an additional reviewer.

2.2. Inclusion criteria and study selection

(1) Participants: Published studies enrolling adult human subjects who prepare for TKA and THA are included in the meta-analysis; (2) Interventions: The intervention groups receive intravenous infusion of acetaminophen as adjunct to multimodal analgesia regimens in the setting of postoperative pain; (3) Comparisons: The control groups receive oral acetaminophen; (4) Outcomes: The primary outcomes are visual analog scale (VAS) scores at 12, 24, and 48 hours; opioid consumption at 12, 24, and 48 hours. The secondary outcomes contain length of stay and postoperative complications (nausea, vomiting, and pruritus); (5) Study design: RCTs are regarded as eligible in our study. The exclusion criteria are as follows: (1) insufficient clinical outcome data and (2) reviews, case report, letters, or conference articles.

2.3. Date extraction

Two of the authors independently extract the data from each full-text report using a standard data extraction form. The following data are extracted: article titles, first author names, publication year, samples size, population, age, sex, intervention procedures, duration of follow-up, and outcome parameters. Corresponding authors are consulted to obtain any required information that is missing. The clinical outcomes include VAS scores and opioid consumption, length of stay, and postoperative complications (nausea, vomiting, and pruritus).

Table 1

EMBASE search strategy.

1. 'pain*':ti,ab, 2. 'control'/exp, 3. 'management '/exp, 4. 'analgesia'/exp, 5. 2 or 3 or 4
6, 1, and 5
7. 'acetaminophen *':ti,ab, 8. knee*:ti,ab, 9. arthroplasty/exp, 10. replacement/exp
11., 9, or 10
12., 8, and 11
13. hip*:ti,ab, 14. arthroplasty/exp, 15. replacement/exp
16., 14, or 15
17., 13, and 6
18., 6, and 7
19., 12, and 18
20., 17, and 18
21., 19, or 20

Table 2

PubMed and Medline search strategy.

(((knee[Title] and (replacement[Title] OR arthroplasty[Title])) OR (hip[Title] and (replacement[Title] OR arthroplasty[Title]))) AND (pain[Title] OR analgesia[Title])) AND ((Acetaminophen[Title]) AND (pain[Title] OR analgesia[Title]))

2.4. Assessment of methodological quality

Quality assessment of the included RCTs is performed by 2 authors according to the *Cochrane Handbook for Systematic Reviews of Interventions 5.0*. We perform the assessing the "risk of bias" table, which includes the following key domains: adequate sequence generation, allocation of concealment, blinding, incomplete outcome data, free of selective reporting, and free of other bias. Each item is recorded by "Yes," "No," or "Unclear." Each risk of bias item is presented as a percentage across all included articles. The percentage indicates the proportion of different levels of risk of bias for each item.

2.5. Evidence synthesis

The evidence grade for the main outcomes is assessed using the guidelines of the Recommendations Assessment, Development and Evaluation (GRADE) system[12] including the following items: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The recommendation level of evidence is divided into the following categories: (1) high, which means that further research is unlikely to change confidence in the effect estimate; (2) moderate, which means that further research is likely to significantly change confidence in the effect estimate but may change the estimate; (3) low, which means that further research is likely to significantly change confidence in the effect estimate and to change the estimate; and (4) very low, which means that any effect estimate is uncertain. The evidence quality was graded using the GRADEpro Version 3.6 software.

2.6. Data analysis

We perform all of the meta-analysis with the Stata 11.0 software (The Cochrane Collaboration, Oxford, UK). Statistical heterogeneity is tested depending on the value of P and I^2 using the standard chi square test. When there is no statistical evidence of heterogeneity ($I^2 < 50\%$, $P > .05$), a fixed effects model is adopted. Otherwise, a random-effect model is used. Continuous outcomes (VAS scores, opioid consumption, length of hospital stay) are expressed as the weighted mean differences (WMD) and a 95% confidence intervals (CIs). Dichotomous outcomes (nausea, vomiting, and pruritus) are expressed as the risk difference (RD) with 95% CI.

3. Results

3.1. Search result

A total of 207 relevant articles were identified according to the initial search. After reading the titles and abstracts, 205 studies

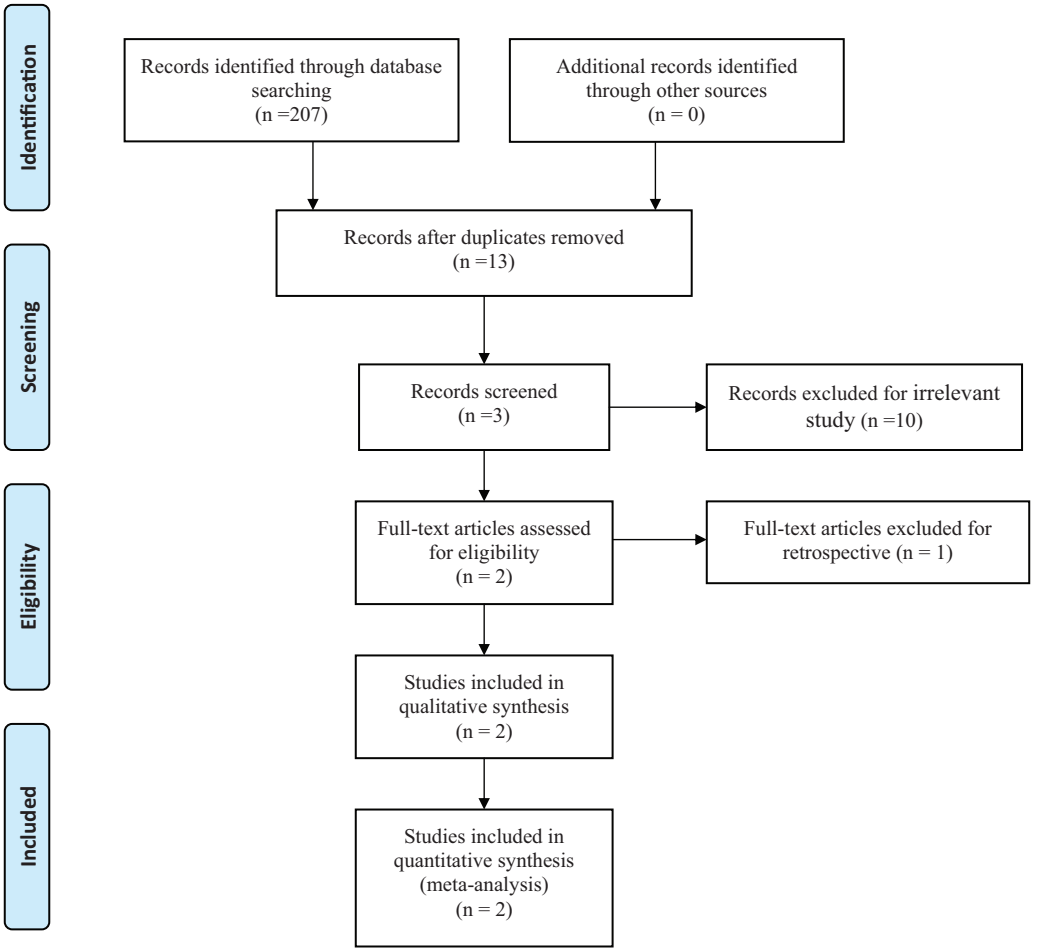


Figure 1. Search results and the selection procedure.

were excluded from the present meta-analysis. No additional articles were obtained after the reference review. Finally, 2 RCTs,[13,14] which published in 2017 were included in the present meta-analysis. These studies involved 120 participants in the experimental groups and 116 participants in the control groups. The search process was proceeded as presented in Figure 1.

3.2. Study characteristics

The sample size ranges from 116 to 120 and average age ranges from 66 to 70. In these articles, the experimental groups receive intravenous acetaminophen in the setting of postoperative pain and the control groups receive oral formulation. The characteristics of the included articles are shown in Table 3. Statistically similar baseline characteristics are observed among articles.

3.3. Risk of bias

The *Cochrane Handbook for Systematic Review of Interventions* is used to evaluate risk of bias of the RCTs. O'Neal et al[14] reported the technique to generate the random sequence and none of them indicated that allocation concealment was performed by closed envelopes. Only O'Neal performed blinding for partic-

Table 3

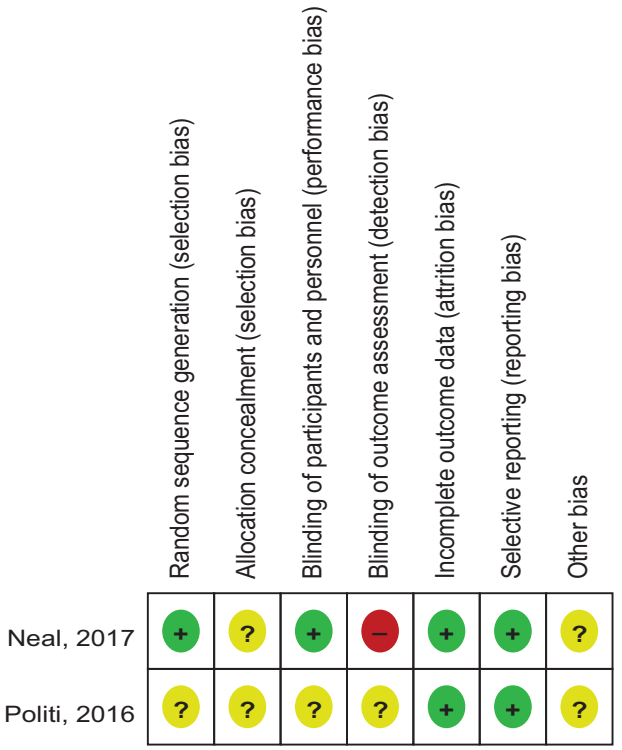
Trials characteristics.

Studies	Study design	Country	Sample size (IV/Oral)	Mean age (IV/Oral)	Female patient (IV/Oral)	Surgical method	Anesthesia method	IV group	Oral group	Concomitant pain management	Follow-up, mo
Politi, 2017	RCT	USA	63/57	66/69	45/40	THA and THA	General anesthesia	IV 1 g of acetaminophen preoperatively and then postoperatively every 6 hours for 24 hours	Oral 1 g of acetaminophen pre-operatively and then post-operatively every 6 for 24 hours	Patient-controlled analgesia pump	2
Neal, 2017	RCT	USA	57/59	68/70	36/45	TKA	spinal anesthesia	1 g IV acetaminophen	1 g oral acetaminophen	Intravenous morphine equivalents	1

C = control, IV = intravenous, RCT = randomized controlled trial, THA = total hip arthroplasty, TKA = total knee arthroplasty.

Table 4

Methodological quality of the randomized controlled trials.



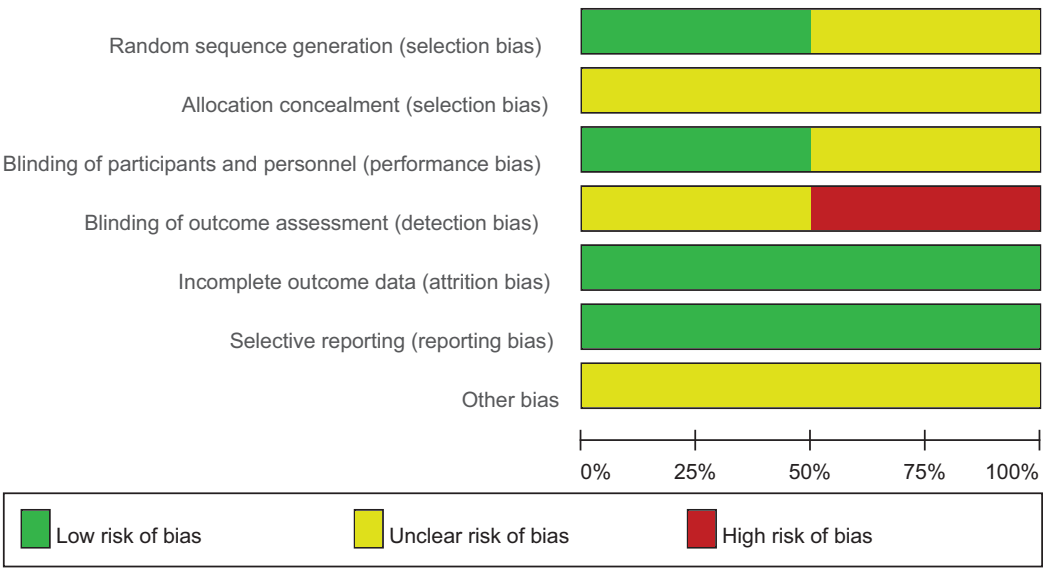
ipants and study personnel; however, no article applied blinding for the assessors. Low risk of bias due to incomplete outcome data and selective outcome reporting are observed. The quality assessment of the included RCTs is presented in Table 4. Judgments regarding each risk of bias item are presented as percentages across all the included articles in Table 5.

3.4. Outcomes for meta-analysis

3.4.1. Pain scores. Two studies[13,14] reported the pain scores at 12 hours after arthroplasties. The pooled results of the studies showed that there was no significant difference between the groups regarding to the pain scores at 12 hours (WMD = −0.407, 95% CI: −0.944–0.131, P = .138; Fig. 2). There was no

Table 5

Risk of bias.



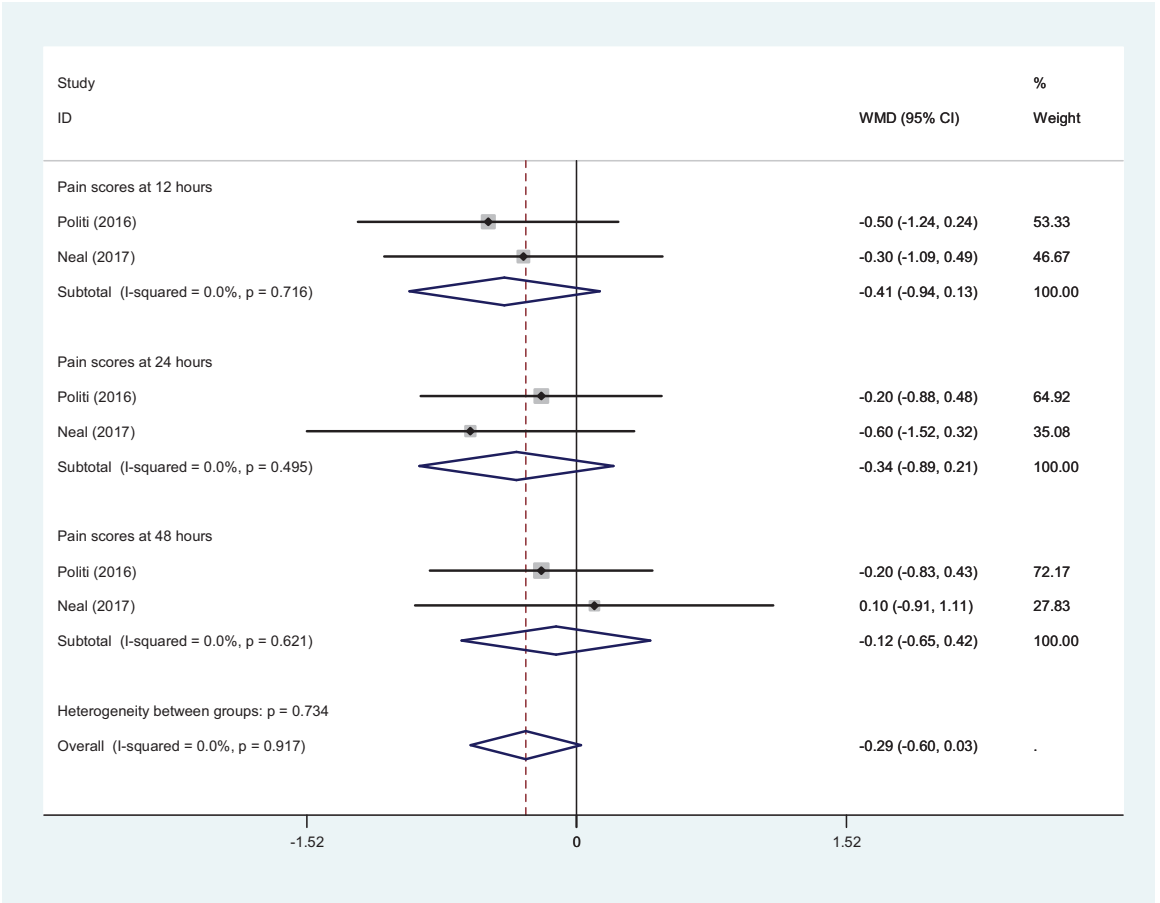


Figure 2. Forest plot diagram showing pain scores after arthroplasties.

significant heterogeneity among the studies ($\chi^2=0.13$, df = 1, I2 = 0%, $P=.716$) and a fixed-effects model was used. Two studies[13,14] with 236 participants showed the outcome of pain scores at 24 hours after arthroplasties. There was no significant heterogeneity between studies ($\chi^2=0.47$, df = 1, $I^2=0\%$, $P=.495$). The pooled results of the studies showed that there was no significant difference between the groups regarding to the pain scores at 24 hours (WMD = −0.340, 95% CI: −0.888–0.208, $P=.223$; Fig. 2). Two studies[13,14] with 236 patients provided the outcome of pain scores at 48 hours after arthroplasties. A fixed-effects model was used because no significant heterogeneity was found among the studies ($\chi^2=0.24$, df = 2, $I^2=0\%$, $P=.621$). There was no significant difference in pain scores at 48 hours between groups (WMD = −0.286, 95% CI: −0.598–0.025, $P=.669$; Fig. 2).

3.4.2. Opioid consumption. Opioid consumption at 12 hours was reported in 2 articles.[13,14] There was no significant heterogeneity among the articles ($\chi^2=1.36$, df = 1, $I^2=26.7\%$, $P=.243$) and a fixed-effects model was adopted. There was no significant difference in opioid consumption at 12 hours between groups (WMD = −0.593, 95% CI: −3.798–2.612, $P=.717$; Fig. 3). Two articles[13,14] with 236 participants showed the outcome of opioid consumption at 24 hours after arthroplasties. The pooled results of the articles demonstrated that no significant difference was detected (WMD = 1.983, 95% CI: −0.975–4.941, $P=.189$; Fig. 3). There was no significant heterogeneity among the studies ($\chi^2=2.64$, df = 1, $I^2=62.1\%$, $P=.104$) and a fixed-effects model was used. Two studies[13,14] reported the opioid consumption at 48 hours after arthroplasties. The pooled results of the studies showed that there was no significant difference between the groups regarding to the opioid consumption at 48 hours (WMD = −0.159, 95% CI: −2.238–1.920, $P=.881$; Fig. 3). There was no significant heterogeneity among the studies ($\chi^2=0.18$, df = 1, $I^2=0.0\%$, $P=.671$) and a fixed-effects model was used.

3.4.3. Length of hospital stay. Two studies[13,14] showed the length of hospital stay between groups. A fixed-effects model was used ($\chi^2=0.00$, df = 1, $I^2=0.0\%$, $P=1.00$). No significant difference in the length of hospital stay was found between the groups (WMD = −0.100 95% CI: −0.224–0.024, $P=.113$; Fig. 4).

3.4.4. Postoperative complications. Two studies[13,14] provided the postoperative complications of nausea. A fixed-effects model was used ($\chi^2=0.20$, df = 1, $I^2=0\%$, $P=.656$). No significant difference regarding to the incidence of nausea was found between groups (RD = −0.028, 95% CI: −0.134–0.079, $P=.609$; Fig. 5). Two articles[13,14] showed the postoperative complications of vomiting after arthroplasties. A fixed-effects model was adopted due to the low significant heterogeneity among the studies ($\chi^2=0.43$, df = 1, $I^2=0\%$, $P=.511$). There was no significant difference in terms of the vomiting between groups (RD = −0.018, 95% CI: −0.119–0.083, $P=.681$; Fig. 5). Two articles[13,14] reported the postoperative complications of constipation. A fixed-effects model was applied ($\chi^2=0.15$, df = 1,

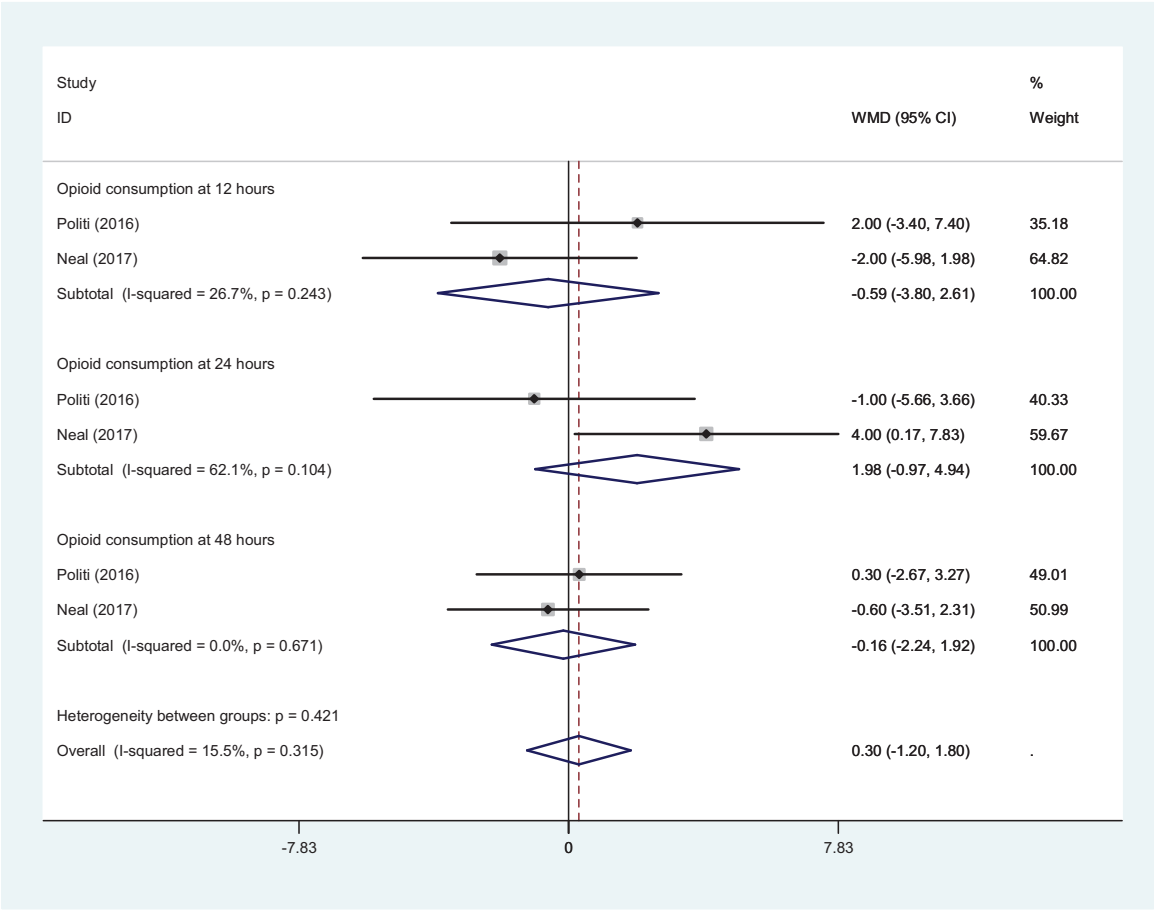


Figure 3. Forest plot diagram showing opioid consumption after arthroplasties.

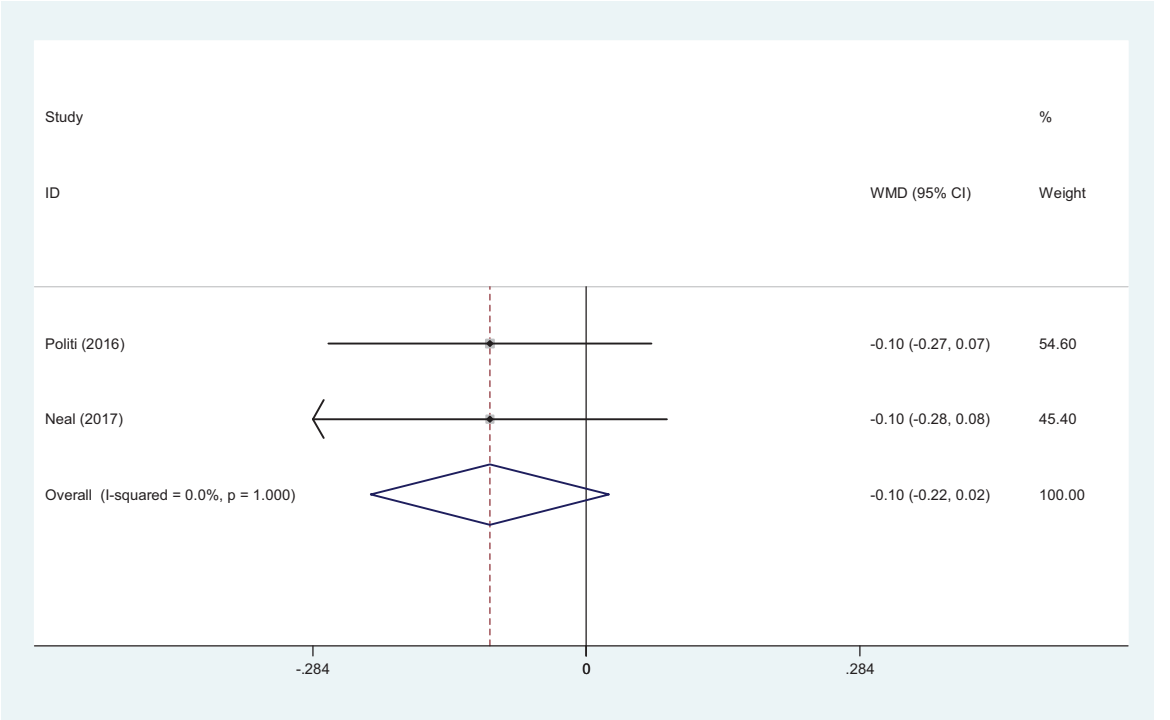


Figure 4. Forest plot diagram showing length of hospital stay. CI = confidence interval, WMD = weighted mean difference.

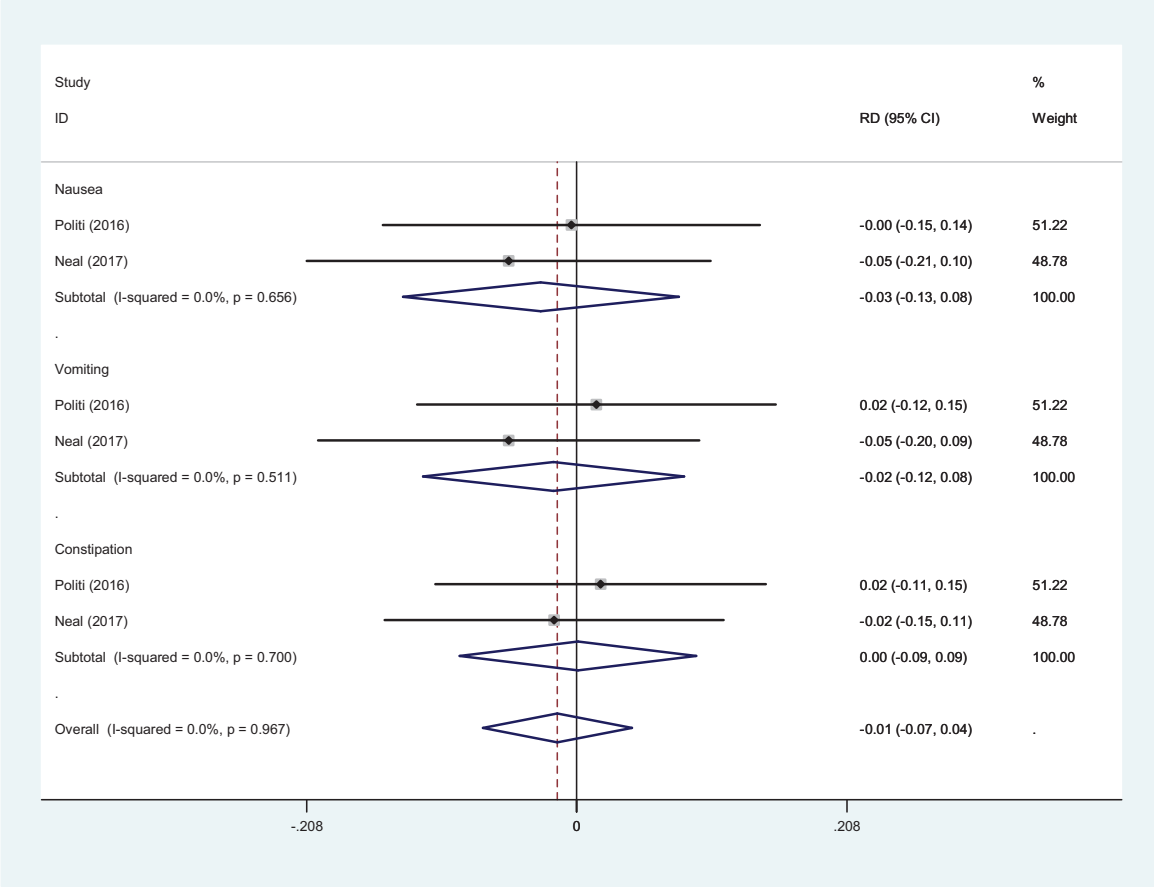


Figure 5. Forest plot diagram showing the incidence of postoperative complications. CI = confidence interval, RD = risk difference.

$I^2 = 0\%$, $P = .700$). No significant difference was identified between groups (RD = 0.001, 95% CI: −0.090–0.092, $P = .610$; Fig. 5).

3.4.5. Quality of the evidence and recommendation strengths. Quality of evidence for main outcomes in our study was assessed using the GRADE system. The evidence quality for each outcome was moderate, which means that further research is likely to significantly change confidence in the effect estimate but may change the estimate (Table 6).

4. Discussion

To the best of our knowledge, this is the first meta-analysis to compare the efficacy and safety of intravenous and oral acetaminophen as adjunct to multimodal analgesia regimens for pain control after TKA and THA. The most interesting finding of the present meta-analysis is that intravenous acetaminophen shows similar pain relief and opioid consumption after TKA and THA. In addition, no increased risk of postoperative complications is observed in both groups. The evidence quality for each outcome was moderate, which means that further research is likely to significantly change confidence in the effect estimate but may change the estimate.

With the aging population, the incidence of joint osteoarthritis is increasing. Arthroplasty is a popular surgical procedure to relieve pain and disability. However, it is usually associated with mild to severe postoperative pain. Consensus has been reached that effective pain control after major orthopedic surgery is

Table 6

The GRADE evidence quality for main outcome.

		Quality assessment							
Outcomes	No of studies	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Effect WMD (95% CI)	Quality	Importance
Pain scores at 12 h	2	Serious	No serious	No serious	No serious	No serious	WMD = −0.407, 95% CI: −0.944–0.131	Moderate	Critical
Pain scores at 24 h	2	Serious	No serious	No serious	No serious	No serious	WMD = −0.340, 95% CI: −0.888–0.208	Moderate	Critical
Pain scores at 48 h	2	Serious	No serious	No serious	No serious	No serious	WMD = −0.286, 95% CI: −0.598–0.025	Moderate	Critical
Opioid consumption at 12 h	2	Serious	No serious	No serious	No serious	No serious	WMD = −0.593, 95% CI: −3.798–2.612	Moderate	Critical
Opioid consumption at 24 h	2	Serious	No serious	No serious	No serious	No serious	WMD = 1.983, 95% CI: −0.975–4.941	Moderate	Critical
Opioid consumption at 48 h	2	Serious	No serious	No serious	No serious	No serious	WMD = −0.159, 95% CI: −2.238–1.920	Moderate	Critical

CI = confidence interval, WMD = weighted mean difference.

important for functional recovery.[15] Multimodal pain management after arthroplasties surgery has been shown to improve pain relief.[16,17] Recently, the administration of acetaminophen as adjunct to multimodal pain management have been shown to improve pain relief and facilitate early mobilization. However, the comparison of oral and intravenous acetaminophen for reducing pain after arthroplasties was still unknown. Therefore, we conduct a meta-analysis and indicate that intravenous acetaminophen does not show a significant benefit in pain control compared to oral form. However, there is a lack of standardization for preoperative and intraoperative care for patients in included studies. In addition, various dosage of intravenous and oral acetaminophen in treatment groups may also influence the results. More high-quality RCTs with large sample size are required for further research.

Opioids are frequently used for pain control after TKA or THA but there are concerns about side effects and dependency. Opioid-related side effects such as nausea, vomiting, constipation, bradycardia, and pruritus are well known.[18,19] Thus, multimodal pain management is applied to minimize the opioid consumption to promote recovery and quality of life. Acetaminophen is considered and tried for alternatives. Yang et al[20] reported that intravenous acetaminophen was associated with a decreased opioid utilization after TKA or THA. Thus, they concluded that intravenous acetaminophen show compatible results to opioids with less frequency of side effects. Oral medication is more convenient than intravenous medication but there exists concerns about pharmacokinetics. Previous study[21] has compared plasma pharmacokinetics of paracetamol after intravenous and oral administration (1 g IV vs 1 g oral). They indicated that IV obtains earlier and higher plasma concentration than oral medication. However, few articles have compared the efficacy of IV acetaminophen to the oral formulation and it remains controversial. Meta-analysis can enhance statistical power and enlarger sample size, which may provide more reliable evidence. Two RCTs with 236 participants described the outcome of opioid consumption. The pooled results revealed that oral acetaminophen has demonstrated similar outcome to its intravenous counterpart in patients undergoing arthroplasties. Thus oral route is more recommended. Further research is still required because only 2 RCTs are included in our study.

Analgesic effect is not the only concern when evaluating the analgesia of various methods. Gastrointestinal reactions are common adverse effects associated with additional opioid. Minimizing the opioid consumption can subsequently decrease such complications which contribute to recovery. The overall incidence of nausea is 25 of 120 in the intravenous groups compared with 27 of 116 in the oral groups ($P > .05$). Furthermore, no increased risk of other complications is observed in our study. However, high-quality RCTs with long-term follow-up are still required.

There are several limitations in this meta-analysis: (1) Only 2 RCTs are included and the sample size in each trial is small. (2) Functional recovery is an important outcome, which is not included in our study. (3) Different dose of acetaminophen in both groups is not discussed; therefore, more RCTs are needed for subgroups analysis. (4) The follow-up period is short which leads to the underestimation of complications. (5) Publication bias that existed in the meta-analysis also influences the results.

5. Conclusion

Intravenous acetaminophen to multimodal analgesia dose not demonstrate a significant benefit in reducing pain and opioid consumption compared oral formulation after TKA and THA. Higher-quality RCTs are required for further research.

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