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Intravenous versus oral acetaminophen as an adjunct on pain and recovery after total knee arthroplasty

A systematic review and meta-analysis

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Abstract

Background: Total knee arthroplasty (TKA) is gradually emerging as the treatment of choice for end-stage osteoarthritis. In the past, intravenous (IV) versus oral acetaminophen (APAP) treatment is still a controversial subject in TKA. Therefore, we write this systematic review and meta-analysis to evaluate the efficacy of IV versus oral APAP on pain and recovery after TKA.

Methods: Embase, Pubmed, and Cochrane Library were comprehensively searched. Randomized controlled trials, cohort studies were included in our meta-analysis. Five studies that compared IV APAP groups with oral APAP groups were included in our meta-analysis. The research was reported according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines to ensure the reliability and verity of results.

Results: Pooled results indicated that no significant difference between the IV APAP groups and oral APAP groups in term of VAS score at 24 hours ($P = .67$), 48 hours ($P = 0.08$), and total morphine consumption at 24 hours ($P = .07$), but there was a significant difference in terms of length of hospital stay (LOS) ($P = .0004$).

Conclusion: IV APAP was not found to be superior to oral APAP in patients undergoing TKA in terms of VAS scores at 24 hours, 48 hours, and total morphine consumption at 24 hours. However, it can significantly reduce the LOS. We still need a large of high-quality research to verify the relationship between the oral and the IV APAP to give the conclusion.

Abbreviations: LOS = length of stay, PRISMA = the preferred reporting items for systematic reviews and meta-analysis, RCT = randomized controlled trial, TKA = total knee arthroplasty, VAS = visual analogue scale.

Keywords: acetaminophen, LOS, meta-analysis, total knee arthroplasty, VAS score

1. Introduction

Total knee arthroplasty (TKA) is a successful surgical procedure as the treatment of choice for end-stage osteoarthritis which can improve quality of life and functional for patients.[1,2] However, severe pain is an important clinical challenge after total knee

replacement, due to the soft tissue injury and a large amount of bone destruction involved.[3] At present, different regional analgesia techniques, which include peripheral nerve block, epidural anesthesia, and local infiltration analgesia,[4–6] cannot provide sufficient analgesia, so that additional opioids were taken to control the pain. However, the use of opioids could lead to some side effects such as headaches, urinary retention and so on that the clinical application of the drug is limited. Therefore, pain management remains a controversial topic after total knee replacement.[7]

Recently, acetaminophen (APAP) is widely applied for pain management which is a kind of nonsteroidal anti-inflammatory drugs.[8] Although several studies showed that the use of intravenous (IV) APAP could reduce pain significantly,[9,10] the cost of IV APAP is far more expensive than that of oral APAP tablets and the reimbursement is typically lower that make it less attractive to budget-conscious healthcare providers.[11] Previous studies have indicated that administration of equivalent doses of oral and IV APAP has identical plasma drugs levels after 2 hours. The only difference is that IV APAP reaches its peak concentration in plasma faster and higher, but no evidence showed that this phenomenon could bring better clinical outcomes in surgical patients.[12]

However, whether the administration of IV APAP is effective and safe in reducing pain score and opioid consumption in patients undergoing TKA remains controversial.[13] So, before preoperative oral APAP can be incorporated into routine pain
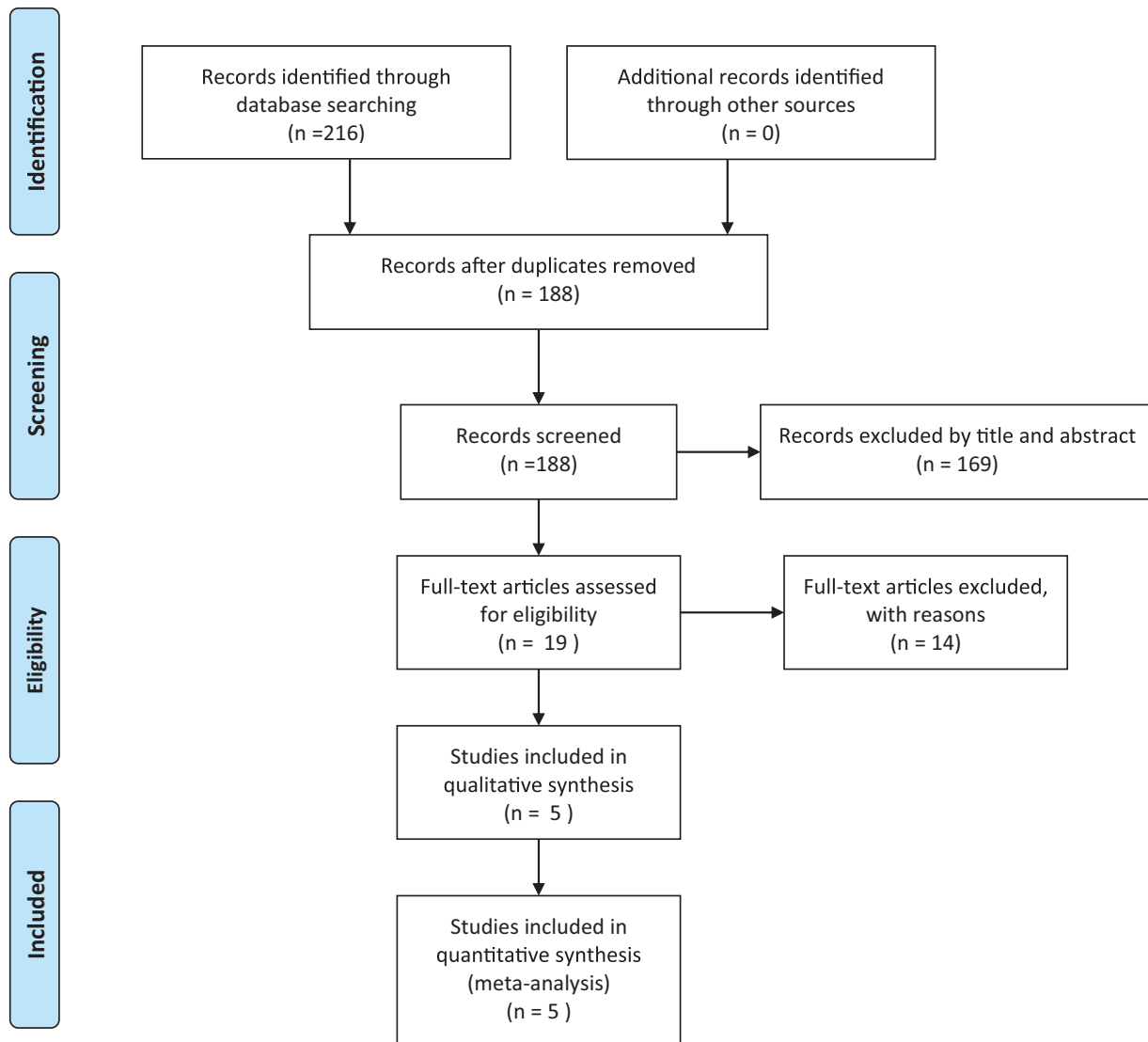
Figure 1. Search results and the selection procedure.

management plans, there must be evidence of comparable efficacy with the use of oral versus IV APAP in the management of postoperative pain. Therefore, we performed the present systemic review and meta-analysis to evaluate the efficiency and safety of IV versus oral APAP administration in TKA.

2. Methods

Our meta-analysis was reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) checklist. The study was approved by the ethics committee of the Tianjin Hospital of Tianjin.

2.1. Search strategy

Potential relevant studies including randomized controlled trials (RCTs), cohort studies were searched from PubMed, Embase, and Cochrane Library up to March 2019. A structured search was performed using the following search string: "acetaminophen" OR "acetamidophenol" AND ("TKA" OR "TKR" OR "total knee

arthroplasty" OR "total knee replacement" OR "Arthroplasty, Replacement, knee" [Mesh]"). No restrictions were imposed on language. The retrieval process is performed in Fig. 1.

2.2. Inclusion criteria

Studies were considered eligible for meta-analysis if they met the PICOS (population, intervention, comparator, outcome, study design) principle. Population: patients were scheduled for TKA. Intervention: APAP using IV administration for postoperative pain management after TKA. Comparisons: oral APAP for pain management. Outcomes were visual analogue scale (VAS) at 24 hours, 48 hours (0=no pain, 10=worst pain), total morphine consumption at 24 hours, length of hospital stay (LOS). Study design: RCTs and retrospective studies.

2.3. Literature selection

All relevant studies which were collected were imported into Endnote X7, and then duplicate literature was excluded. Next,

Table 1

Description of included studies.

Description of included studies

| Studies | Liposomal bupivacaine group/control group | | | | | | | |
	Cases	Mean age, y	Female sex (%)	Type	Anesthesia	Surgical approach	Intervention group	Control group	follow-up
Barrington et al (2018)[15]	56,475/134,216	66/67	61.4/63.3	Retrospective study	Unclear	TKA	1000 mg of intravenous Acetaminophen	1000 mg of oral acetaminophen	Unclear
O'Neal et al (2017)[14]	57/58	68/67	44/55	RCT	Spinal anesthesia	TKA	1000 mg of intravenous acetaminophen	1000 mg of oral acetaminophen	1 mo
Suarez et al (2018)[16]	52/52	66.6/67.3	28/26	RCT	Spinal anesthesia	TKA	4000 mg of intravenous acetaminophen	4000 mg of oral acetaminophen	6 wk
Hickman et al (2018)[12]	170/168	67/67	57.1/61.4	RCT	General or spinal anesthesia	TKA	1000 mg of intravenous acetaminophen	2500 mg of oral acetaminophen	8 wk
Yu et al (2019)[13]	318/527	66/65	70/73	Retrospective study	Spinal anesthesia	TKA	1000 mg of intravenous acetaminophen	1000 mg of oral acetaminophen	Unclear

RCT = randomized controlled trial, TKA = total knee arthroplasty.

two researchers independently excluded studies by reading titles and abstracts. At last, the irrelevant studies were removed that did not satisfy the PICOS. A senior reviewer is consulted in case of disagreement regarding which literature to include.

2.4. Data extraction

A standard data extraction form was conducted independently to extract the applicable data from the included literature by 2 reviewers. The basic data extracted from studies contain author, publishing year, age, sample size, sex, study design, intervention procedure, the dosage of IV or oral APAP and follow-up. The primary outcome included VAS score which consisted of 11 pain levels (0 = no pain, 10 = extreme pain) at 24 hours, 48 hours, and the total opioid consumption at 24 hours. The secondary index was the LOS. For the missing data, we contacted the corresponding author of studies to ensure that the information integrated.

2.5. Quality assessment

According to the Cochrane Handbook for Systematic Reviews of Interventions version, the risk of bias was assessed for RCTs by 2 reviewers which consisted of the following items: sequence generation, allocation concealment, blinding of participants, blinding of outcome assessor, incomplete outcome data, reporting bias, and other bias. For non-RCTs, we used the Methodological Index for Non-Randomized Studies (MINORS) scale to evaluate the risk of bias. A total of 12 items were assessed and each items ranging from 0 to 2 (0 = low quality and 2 = high quality). Any discrepancy of the evaluations between the 2 reviewers was resolved by a third reviewer.

2.6. Data analysis and statistical methods

Review Manager Software for Windows (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was applied to conduct this meta-analysis. The effect size of continuous outcomes was usually represented by the mean differences (MDs) or standard mean difference (SMD) with 95% confidence intervals (CIs), dichotomous outcomes were expressed as relative risks (RRs) with 95% CIs. The statistical heterogeneity was conducted by the Q and χ^2 test in accordance

with the value of P and I^2. If $I^2 > 50\%$, $P < .1$, statistical was considered to be heterogeneous, we used a random-effects model to analyze the data. Otherwise, the fixed-effects model was performed to conduct the meta-analysis.

3. Results

3.1. Search results

A total of 216 relevant studies were collected through databases (Pubmed, Embase, Cochrane Library) based on the search strategies. We used Endnote Software (Version X7, Thompson Reuters, CA) to remove 28 duplicate studies. One hundred sixty-nine relevant studies were excluded by reading the title and abstract. And then, 14 studies were removed by reading the full text. Finally, 5 studies[12–16] were included in this meta-analysis according to the inclusion criteria. The PRISMA flow diagram is listed in Figure 1.

3.2. Study characteristics

The baseline characteristics of the 5 studies[12–16] are collected in Table 1. All of them evaluated the efficiency and safety of IV versus oral APAP for reducing postoperative Pain in TKA. Among them, 3 studies[12,14,16] were RCTs, and 2 studies[13,15] were non-RCTs. Four studies[12–14,16] reported VAS score at 24 hours and 2 studies[13,16] showed VAS score at 48 hours. Four articles[12–14,16] evaluated on the 24 hours of total morphine consumption. Four studies[12,13,15,16] reported the LOS.

3.3. Quality assessment

The quality of RCTs can be concluded in Figure 2. One study[12] did not state the specific way of random allocation. The allocation concealment of the study[16] was not adequately illustrated. All rest were at low risk. The other bias was unclear. Two non-RCTs were evaluated by the MINORS and were of high quality. More information can be listed in Table 2.

3.4. Meta-analysis result

3.4.1. VAS Score at 24 hours. Data from 4 studies[12–14,16] including 1551 patients reported the VAS scores at 24 hours.
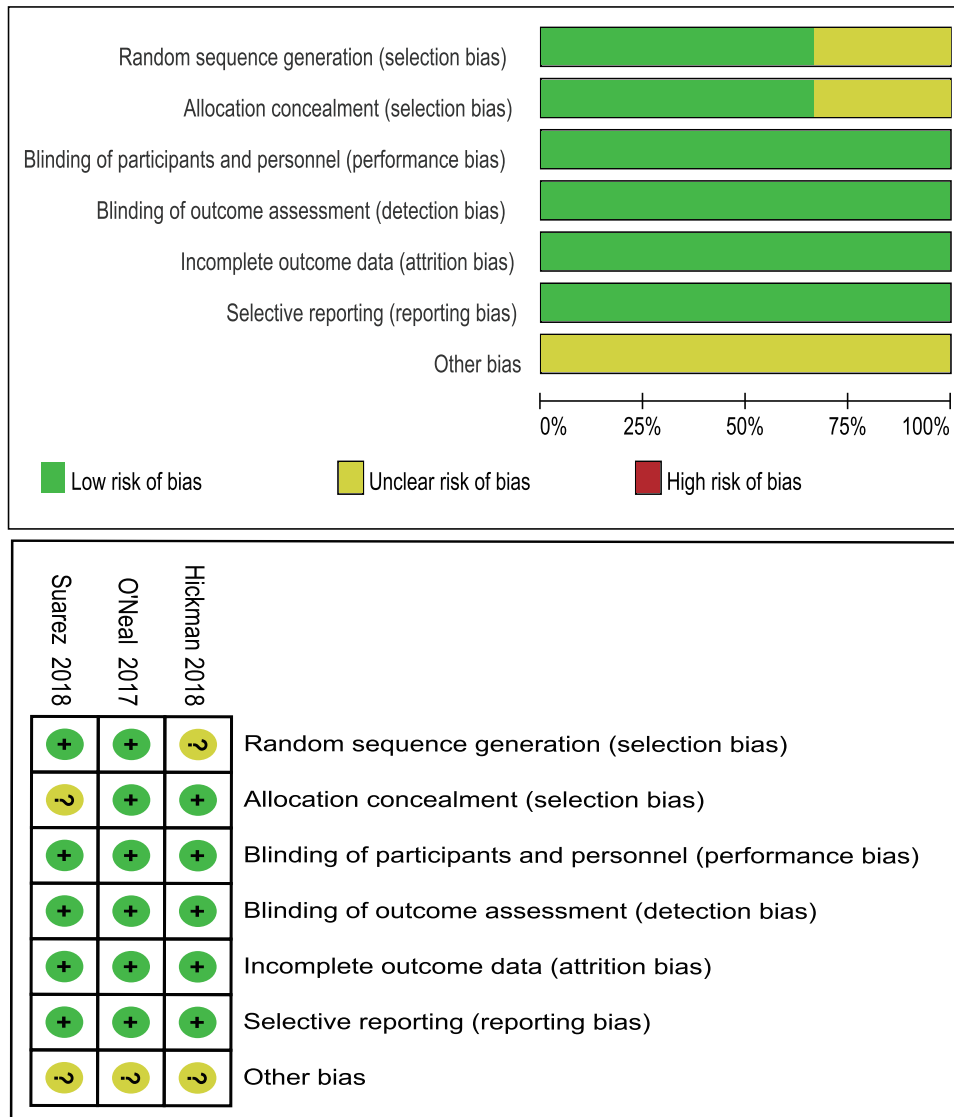
Figure 2. Risk of bias.

Quality assessment for non-RCT	Barrington et al[15]	Yu et al[13]
A clearly stated aim	2	2
Inclusion of consecutive patients	2	2
Prospective of data collection	2	2
Endpoints appropriate to the aim of the study	2	2
Unbiased assessment of the study endpoint	1	1
A follow-up period appropriate to the aims of study	1	1
Less than 5% loss to follow-up	0	0
Prospective calculation of the sample size	2	2
An adequate control group	2	2
Contemporary groups	2	2
Baseline equivalence of groups	2	2
Adequate statistical analyses	2	2
Total score	**20**	**20**

RCT = randomized controlled trial.

Pooled results indicated that no significant difference between the IV APAP groups and oral APAP groups in VAS scores at 24 hours (SMD = 0.02, 95% CI: −0.08 to 0.13, P = .67; Fig. 3). A fixed-effects model was used due to no statistical heterogeneity through the meta-analysis (χ^2 = 2.95, df = 3, I^2 = 0%, P = .40).

3.4.2. VAS Score at 48 hours. The results of the VAS score at 48 hours was reported by 2 studies[13,16] including 949 patients. The IV APAP groups were not significantly superior to oral APAP groups (SMD = 0.12, 95% CI: −0.01 to 0.25, P = .08; Fig. 4). A fixed-effects model was chosen because no significant heterogeneity existed among the studies (χ^2 = 0.75, df = 1, I^2 = 0%, P = .39).

3.4.3. Total morphine consumption at 24 hours. The total morphine consumption at 24 hours after TKA was evaluated in 4 studies.[12–14,16] The results demonstrated that there was no significant difference in opioids consumption at 24 hours between the IV and the oral APAP groups (SMD = −0.10, 95% CI: −0.21 to 0.01, P = .07; Fig. 5). We chose a fixed-effects model because of no significant heterogeneity. (χ^2 = 1.83, df = 3, I^2 = 0%, P = .61).
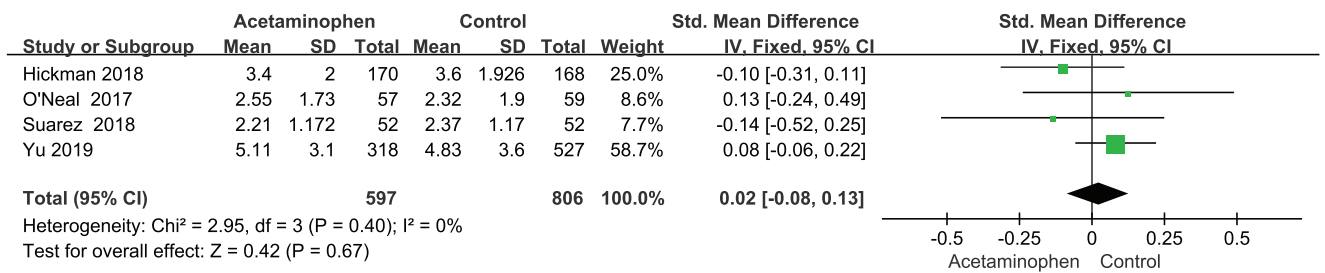
Study or Subgroup	Acetaminophen			Control			Weight	Std. Mean Difference IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Hickman 2018	3.4	2	170	3.6	1.926	168	25.0%	-0.10 [-0.31, 0.11]	
O'Neal 2017	2.55	1.73	57	2.32	1.9	59	8.6%	0.13 [-0.24, 0.49]	
Suarez 2018	2.21	1.172	52	2.37	1.17	52	7.7%	-0.14 [-0.52, 0.25]	
Yu 2019	5.11	3.1	318	4.83	3.6	527	58.7%	0.08 [-0.06, 0.22]	
Total (95% CI)			597			806	100.0%	0.02 [-0.08, 0.13]	
Heterogeneity: Chi² = 2.95, df = 3 (P = 0.40); I² = 0%									
Test for overall effect: Z = 0.42 (P = 0.67)									

Figure 3. VAS score at 24 hours after TKA. TKA = total knee arthroplasty, VAS = visual analogue scale.

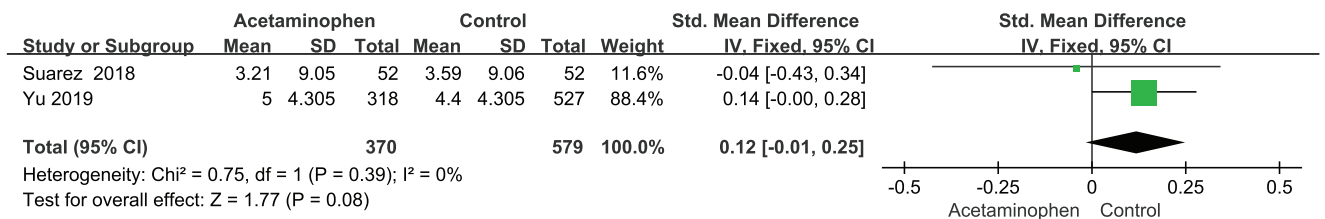| Study or Subgroup	Acetaminophen			Control			Weight	Std. Mean Difference IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Suarez 2018	3.21	9.05	52	3.59	9.06	52	11.6%	-0.04 [-0.43, 0.34]	
Yu 2019	5	4.305	318	4.4	4.305	527	88.4%	0.14 [-0.00, 0.28]	
Total (95% CI)			370			579	100.0%	0.12 [-0.01, 0.25]	
Heterogeneity: Chi² = 0.75, df = 1 (P = 0.39); I² = 0%									
Test for overall effect: Z = 1.77 (P = 0.08)									

Figure 4. VAS score at 48 hours after TKA. TKA = total knee arthroplasty, VAS = visual analogue scale.

3.4.4. LOS. The LOS was evaluated in four studies.[12,13,15,16] The LOS of IV APAP groups was significantly lower than that in control groups (SMD = −0.02, 95% CI: −0.03 to −0.01, P = .0004; Fig. 6). A fixed-effects model was applied because the low statistical heterogeneity existed among the studies (χ^2 = 3.23, df = 3, I^2 = 7%, P = .36).

4. Discussion

This systematic review and meta-analysis aimed to summarize the effect of IV versus oral APAP for pain management following TKA. Reasonable pain management can help restore function after TKA and reduce postoperative complications and treatment costs. The current evidence reported that IV [APAP] is an effective and safe analgesic for pain management after TKA. Some research data[17,18] demonstrated that IV APAP significantly reduced postoperative VAS score and total opioid consumption which compared with the control group after TKA. However, the problem that IV APAP costs more and has a lower reimbursement rate is difficult to solve. On the contrary, oral APAP has the advantage of lower prices and higher reimbursement rates. Meanwhile, although some studies[14] have shown that there was no significant difference in the efficacy of oral and IV APAP, the

efficacy of oral administration is still controversial.[13] Therefore, we conducted 5 studies for this systematic review and meta-analysis that contained 3 RCTs and 2 non-RCTs. Surprisingly, our pooled data demonstrated that IV APAP groups were not superior to oral APAP groups in terms of VAS score at 24 hours, 48 hours, total morphine consumption except LOS.

VAS scores at 24 hours and 48 hours are the most important outcome in our meta-analysis and pooled data reported that IV APAP group was as effective for postoperative pain management in TKA as oral APAP group. The results of our meta-analysis are consistent with other literature investigating a difference between the two methods of APAP administration. A RCT on individuals undergoing lower third molar extractions demonstrated that IV or oral APAP had no significant difference in VAS scores within 24 hours between the groups.[19] Although Yu et al[13] indicated that VAS scores at 24 hours and 48 hours were similar between oral and IV groups, the immediate postoperative pain rating in IV APAP group was significantly lower than that in the oral group. Our analysis suggested that this phenomenon might be associated with the use of IV APAP that results in earlier and higher peak drug concentrations in both plasma and cerebrospinal fluids. Likewise, a prospective, randomized, double-blind clinical trial evaluating the administration of IV versus oral
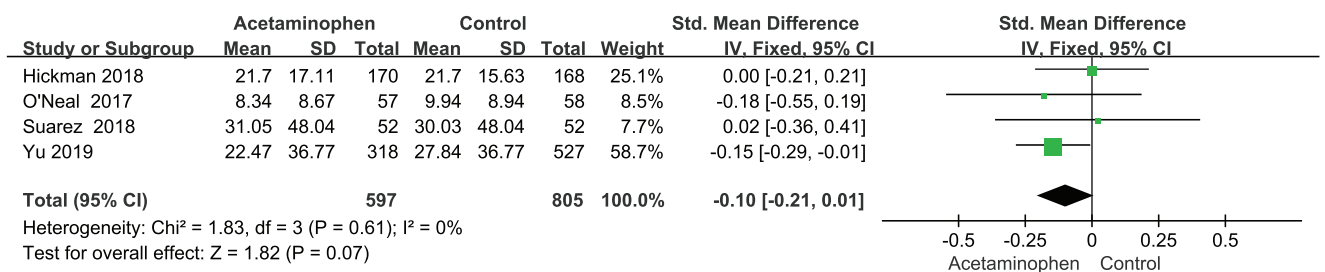
Study or Subgroup	Acetaminophen			Control			Weight	Std. Mean Difference IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Hickman 2018	21.7	17.11	170	21.7	15.63	168	25.1%	0.00 [-0.21, 0.21]	
O'Neal 2017	8.34	8.67	57	9.94	8.94	58	8.5%	-0.18 [-0.55, 0.19]	
Suarez 2018	31.05	48.04	52	30.03	48.04	52	7.7%	0.02 [-0.36, 0.41]	
Yu 2019	22.47	36.77	318	27.84	36.77	527	58.7%	-0.15 [-0.29, -0.01]	
Total (95% CI)			597			805	100.0%	-0.10 [-0.21, 0.01]	
Heterogeneity: Chi² = 1.83, df = 3 (P = 0.61); I² = 0%									
Test for overall effect: Z = 1.82 (P = 0.07)									

Figure 5. Opioid consumption at 24 hours after TKA. TKA = total knee arthroplasty.

Study or Subgroup	Acetaminophen			Control			Weight	Std. Mean Difference IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Barrington 2018	2.8	11.46	56475	3	11.46	134216	99.2%	-0.02 [-0.03, -0.01]	
Hickman 2018	2.44	0.79	170	2.42	0.74	168	0.2%	0.03 [-0.19, 0.24]	
Suarez 2018	1.87	0.31	52	1.79	0.31	52	0.1%	0.26 [-0.13, 0.64]	
Yu 2019	2.58	1.3	318	2.69	1.1	527	0.5%	-0.09 [-0.23, 0.05]	
Total (95% CI)			**57015**			**134963**	**100.0%**	**-0.02 [-0.03, -0.01]**	

Heterogeneity: Chi² = 3.23, df = 3 (P = 0.36); I² = 7%
Test for overall effect: Z = 3.51 (P = 0.0004)

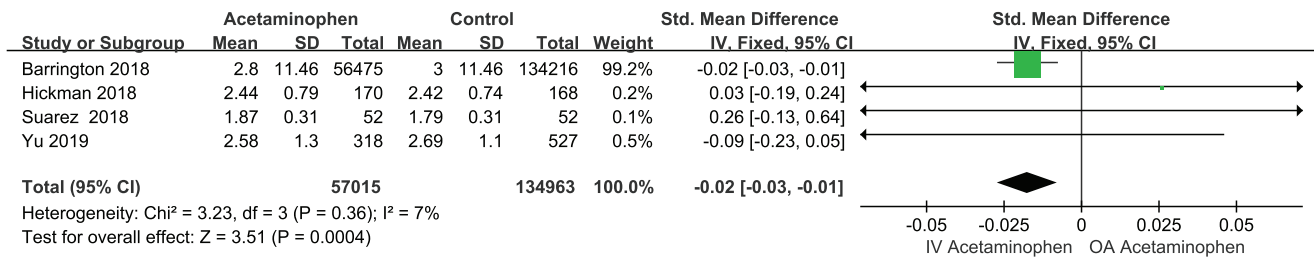-0.05 -0.025 0 0.025 0.05
IV Acetaminophen   OA Acetaminophen

Figure 6. Length of hospital stay after TKA. TKA = total knee arthroplasty.

APAP did not observe a decrease in pain in patients who received IV APAP.[14]

The total opioid consumption at 24 hours is identified as an important indicator of TKA to evaluate postoperative analgesic effectiveness. Although a variety of analgesic methods are applied to try to reduce postoperative pain management, they are not effective in most cases. Usually, additional opioid has been used as concomitant pain management, but opioid-related side effects, such as vomiting and dizziness, have been frequently mentioned in the literature,[20,21] and drug dependence is also an important question that should be considered. Now IV APAP has been applied to try to increase pain control. In a randomized, double-blind, placebo-controlled trial, Sinatra et al[9] reported that the total opioid consumption at 24 hours in IV APAP group was significantly less than that in the placebo group. However, few studies have directly compared IV versus oral APAP in opioid consumption. Some experts compared outcomes of oral and IV APAP use in patients that had orthopedic or plastic surgery and reported that no statistically significant differences in terms of VAS score at 24 h and opioid requirements in 2 groups.[12] O'Neal et al[14] compared opioid consumptions of IV, oral APAP, and placebo groups and demonstrated that there was no significant statistical difference between the 3 groups. A consideration offered by the authors was that the use of a multimodal analgesia regimen on all individuals might have decreased postoperative pain to a degree in which the effect of administering APAP may have been diminished. Our meta-analysis indicated that TKA patients consumed similar amounts of opioid drugs in both IV and oral APAP groups.

LOS is one of the most common complications as well as fast recovery index of TKA patients. The results of our meta-analysis were consistent with those who have demonstrated decreased LOS associated with the use of IV APAP. Hansen et al[22] reported on 51,835 patients who received IV APAP and 60,751 patients who received oral APAP after undergoing spine surgery. Compared with the oral group, they found that the IV APAP group was associated with a 0.68 day shorter LOS. However, length of stay was influenced by multivariate risk index including body mass index, age, and physiological conditions.[23] Although Barrington reported the IV group still had a shorter LOS than the oral group after adjusting for confounders (age, sex, race, risk of mortality, surgery year, admitting physician type, hospital type), it still needs a lot of high-quality research to validate it.

Our systematic review and meta-analysis still have some limitations. First, only 5 studies were included in our meta-analysis, the amount of sample is relatively small; if more studies had been contained, the statistical efficacy of our analysis would increase. Second, all studies lacked long-term follow-up. Long-term follow-up studies should be conducted in the future. Third,

only English publications were included in our meta-analysis; thus, publication bias is unavoidable. Fourth, as a result of TKA postoperative recovery criteria, functional recovery results are important parameters. Due to the lack of postoperative functional recovery data, we cannot conduct a meta-analysis about it. We applied the PRISMA guidelines and Cochrane Handbook to assess the quality of the results published in all included studies to ensure that the results of our meta-analysis were reliable and veritable. Despite the above limitations, this is the most recent RCT of meta-analysis to evaluate the first efficiency and the safety of IV versus oral APAP in TKA. There is also a need for a large number of RCTs to be verified.

5. Conclusions

IV APAP was not found to be superior to oral APAP in patients undergoing TKA in terms of VAS scores at 24 hours, 48 hours, and total morphine consumption at 24 hours. However, it can significantly reduce the LOS. We still need a large of high-quality research to verify the relationship between the oral and the IV APAP to give the conclusion.

Author contributions

Yanbin Teng, Yan Zhang, Baojie Li contributed to the conception of the study. The manuscript of the protocol was drafted by Yanbin Teng, Yan Zhang, which was revised by Baojie Li. The search strategy was developed by all authors and run by Yanbin Teng, who will also independently screen the potential studies, extract data of included studies, assess the risk of bias and finish data synthesis. Yan Zhang will arbitrate the disagreements and ensure that no errors occur during the study. All authors have approved the publication of the protocol.

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