

Effect of morphine added to multimodal cocktail on infiltration analgesia in total knee arthroplasty

A meta-analysis of randomized controlled trials

Yinxia Zhang, MD^a, Fadu Mi, MM^{b,*}, Haiyan Zhao, MD^c, Duowen Xie, MM^d, Xiaoyuan Shi, MM^e

Abstract

Background: The local injection of multimodal cocktail is currently commonly used in the treatment of postoperative pain after total knee arthroplasty (TKA). It is still inconclusive whether the morphine added to the intraoperative injection mixture could make some difference. This meta-analysis aimed to evaluate the efficacy and safety of additional morphine injection on postoperative analgesia in TKA, and provide some useful information on morphine usage in clinical practice.

Methods: The randomized controlled trials (RCTs) in databases including PubMed, Web of Science, Embase, Cochrane Library, Chinese biomedical literature database (CBM), and Chinese National Knowledge Infrastructure (CNKI) databases were systematically searched. Of 623 records identified, 8 RCTs involving 1093 knees were eligible for data extraction and meta-analysis according to criteria included.

Results: Meta-analysis showed that the use of local morphine injection was not associated with significant pain relief within 48 hours postoperatively at rest and on motion ($P > .05$, all). The use of morphine reduced postoperative total systemic opioids consumption ($P < .05$). This study found no significant differences in other outcomes including knee flexion range of motion (ROM) ($P > .05$), extension ROM ($P > .05$), The Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores ($P > .05$), Post-operative nausea and vomiting occurrence ($P > .05$) regardless of the presence of morphine or not in the injections.

Conclusion: Additional morphine added to multimodal cocktail did not decrease the postoperative pain scores significantly based on our outcomes, but it reduced the systemic postoperative opioids consumption in total knee arthroplasty.

Abbreviations: 95% CI = 95% confidence interval, ACB = adductor canal block, CBM = Chinese biomedical literature database, CNKI = Chinese National Knowledge Infrastructure, FNB = femoral nerve block, MD = mean difference, NRS = numerical rating scale, NSAIDs = non-steroidal antiinflammatory drugs, OR = odds ratio, PNVO = post-operative nausea and vomiting, POD = post-operative day, RCTs = randomized controlled trials, ROM = range of motion, SMD = standard mean difference, TKA = total knee arthroplasty, VAS = visual analog scale, WOMAC = Western Ontario and McMaster Universities Arthritis Index.

Keywords: infiltration analgesia, morphine, multimodal cocktail, total knee arthroplasty

Editor: Leonardo Roever.

This work is supported by the fundamental research Funds for the Central University (Northwest Minzu University; no.31920170044).

The authors report no conflicts of interest.

Supplemental Digital Content is available for this article.

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How to cite this article: Zhang Y, Mi F, Zhao H, Xie D, Shi X. Effect of morphine added to multimodal cocktail on infiltration analgesia in total knee arthroplasty. *Medicine* 2019;98:41(e17503).

Received: 21 December 2018 / Received in final form: 17 May 2019 / Accepted: 12 September 2019

<http://dx.doi.org/10.1097/MD.00000000000017503>

1. Introduction

Postoperative pain is an undesirable experience that patients are different to avoid after total knee arthroplasty (TKA). Local infiltration analgesia with multimodal cocktail injection has been frequently used for ages to reduce postoperative pain and has been considered as an effective method even not inferior to nerve block in recent years.^[1-4] Periarticular or intra-articular injection of multimodal cocktail is a safe and cost-effectiveness measure, it could exert effect on inhibiting inflammation in the operated tissue and decreasing the pain.^[2,5,6,7] Although the analgesic effect of various drug combinations for local injection during TKA has been well documented, the gold standard for drug combination has not yet been well established. This injection mixture usually contains multiply composition, which on basis of local anesthetics and epinephrine, and combined with other drugs such as non-steroidal anti-inflammatory Drugs (NSAIDs), corticosteroids, opioids et al.^[1-6]

Opioids have a strong analgesic effect. It exerts action on μ -receptors that distributed wildly in cerebral cortex, thalamus, medulla oblongata, spinal cord, and primary sensory neurons in central nervous system.^[8] Accordingly, opioids not only play a role in pain management, but also are easy to cause many adverse events, such as headache, dizziness, nausea, vomiting, drug

dependence et al.^[7–10] Therefore, try to reduce systemic opioids consumption is regarded as a meaningful procedure that must be paid attention postoperatively.^[9,10] Whereas, there are some studies have ever reported that periarticular or intra-articular multimodal injection including morphine is effective for pain relief in TKA and they believe single dose of local morphine injection is relative safe.^[5,11,12] Consequently, additional morphine added into multimodal cocktail injection has been commonly used in TKA for years.^[5,6,13,14] However, some studies published recently demonstrated that addition of morphine injection is not effective for relieving postoperative pain and enhancing knee functional recovery.^[15,16] So, it is still inconclusive whether the intraoperative injection of morphine is really beneficial, and additionally causes more complications, such as headache, dizziness, nausea, vomiting, drug dependence et al as mentioned previously.^[7–10]

This meta-analysis was conducted to include all randomized controlled trials that compared morphine with no morphine in the injection mixture in TKA to judge the efficacy and safety of additional morphine injection on postoperative analgesia to provide a reference for surgeons.

2. Materials and methods

This is a systemic review and meta-analysis, it is not associated with Clinical Trials and Biomedical Ethics Committee permits. This submission was approved by institutional review board of our institution. This meta-analysis conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.^[17]

2.1. Search strategy

We identified randomized controlled trials from 1974 to March 2, 2018 by searching databases including PubMed, Web of Science, Embase, Cochrane Library, Chinese biomedical literature database (CBM), and Chinese National Knowledge Infrastructure (CNKI) using the following terms: (total knee arthroplasty or total knee replacement) AND (morphine OR Opioids) AND (periarticular injection OR intra-articular injections). In addition, all additional trials that satisfied the inclusion criteria are also included by manual search. Furthermore, we contacted the authors for the raw data and complete the search strategy whenever necessary. Eligible studies were selected based on criteria aforementioned by 2 reviewers. Any disagreement between them was resolved by consensus.

2.2. Data extraction

We extracted the following data from the included articles.

1. Basic information: first author, publishing date, location of study, numbers of patients in each group, demographic data of participants including age and gender.
2. Techniques: study design, administration approach, dosages, combined drug regimens, and anesthesia method.
3. Primary outcome including visual analog scale (VAS) scores or numerical rating scale (NRS) at rest and on motion which were evaluated within the first post-operative 48 hours.
4. Second outcome containing total opioid consumption post-operation.

5. Third outcome recording the knee ROM and The Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores.
6. Forth outcome including the complications- nausea and vomiting. The data extraction was made by 2 reviewers.

Likewise, any disagreement between them was resolved by consensus.

2.3. Inclusion criteria

Inclusion criteria:

1. studies reported patients undergoing total knee arthroplasty surgery;
2. additional morphine was added to multimodal cocktail in local infiltration analgesia;
3. only periarticular injection OR intra-articular injections approach was required;
4. the control group did not use morphine but other cocktail composition was same;
5. the studies design were RCTs.

Exclusion criteria:

1. not TKA surgery, such as unicompartmental knee arthroplasty and knee arthroscopy operation;
2. the control group did not use morphine, but other composition was also not used;
3. local infiltration analgesia combined nerve block;
4. morphine was used via intrathecal or subcutaneous administration;
5. the studies design were not RCTs. The drug dosages, whether combined drug was used, anesthesia method was not limited.

2.4. Study quality

Two reviewers independently assessed study quality using modified Jadad scale.^[18] The modified Jadad scale evaluated the clinical studies in terms of randomization (2 points); concealment of allocation (2 points); double blinding (2 points); and total withdrawals and dropouts (1 point). Clinical studies achieving a score of >4 points were considered of high quality.

2.5. Statistical analysis

Review Manager Software (Revman 5.3, Cochrane Collaboration, Oxford, United Kingdom) was used for the meta-analysis. The continuous variable outcomes (VAS pain scores within the first post-operative 48 hours, the knee ROM, WOMAC score) for meta-analysis were presented as mean difference (MD) and with 95% confidence interval (95% CI). While as total opioid usage post-operatively including different kinds of remedial analgesics were used, the standard mean difference (SMD) and with 95% CI model was performed. Meanwhile, the dichotomous outcomes (nausea and vomiting occurrence) presented as odds ratio (OR) with 95% CI. Heterogeneity among the studies was evaluated using the I^2 statistic and Chi-Squared test. An $I^2 > 50\%$ was considered to indicate significantly statistical heterogeneity and the random-effect was used, while when $I^2 < 50\%$ was considered to indicate low heterogeneity and fixed-effect model can be used.^[17] Publication bias was visually examined using funnel plots. Values of $P < .05$ were considered statistically significant. The sensitivity analysis was performed to explore the impact of an individual study by the exclusion of 1 study each time. Publication bias was visually examined using funnel plots.

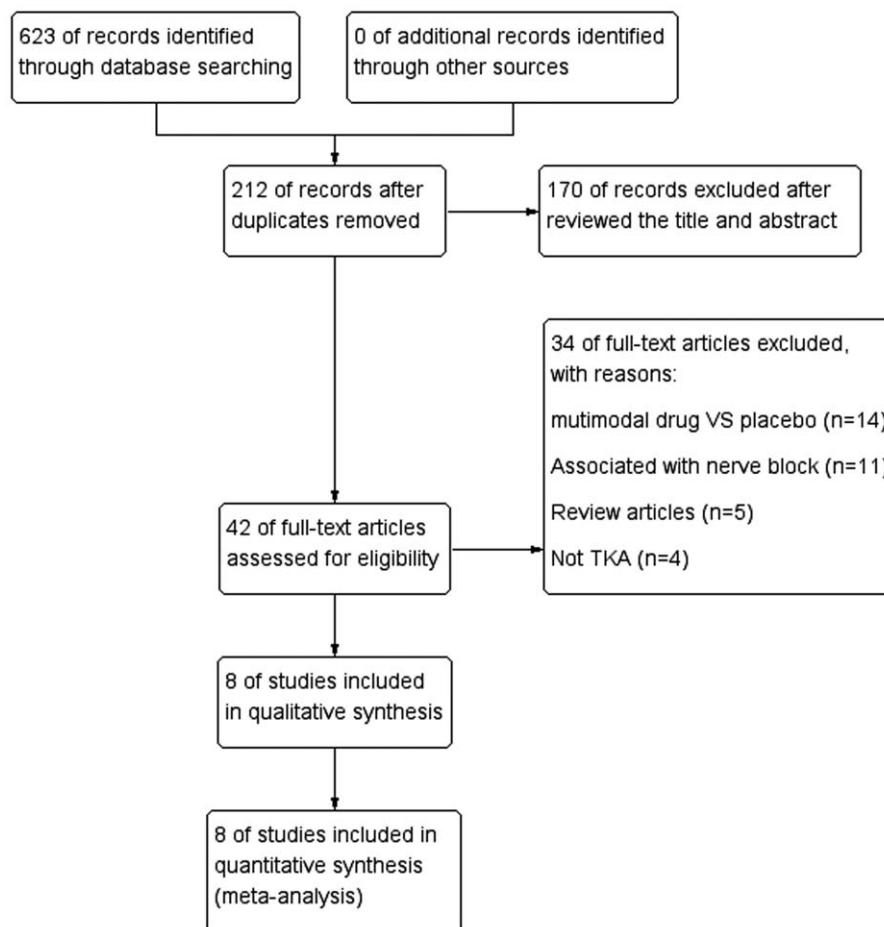


Figure 1. Flow chart of study selection.

3. Results

3.1. Search results and study characteristics.

As shown in Figure 1, a total of 623 potentially relevant articles were identified from the databases. Of them, 212 were screened. After a title and abstract screen, 170 were excluded. A total of 42 full-text articles were assessed for eligibility, but 34 were excluded for different reasons (not compared morphine with

no morphine specifically; reported nerve block, review article and not TKA). At last, 8 articles were found to fulfill the inclusion criteria were passed for synthetic evaluation for this meta-analysis.^[11,12,15,16,19–22] A summary of selected studies is shown in Table 1, a total of 1093 knees were included in this meta-analysis with 13 comparisons of morphine with no morphine. The basic techniques of the included studies are shown in Table 2. The assessed modified Jadad scale of the 8 studies is with a

Table 1

Basic information of the included studies.

Author	Year	Location	Morphine group Cases	Age	Sex (M/F)	Control group Cases	Age	Sex (M/F)
Iwakiri-1 ^[15]	2017	Japan	53	71.8±7.5	9/44	53	71.8±7.5	9/44
Iwakiri-2 ^[16]	2017	Japan	51	73.9±8.3	10/41	51	73.6±7.2	9/42
Tammachote ^[19]	2017	Thailand	30	67±10	6/24	31	67±8	2/29
Kim ^[20] (C1)*	2015	Korea	43	68.0±9.1	2/41	43	69.8±6.4	2/41
(C2)*	2015	Korea	43	70.6±5.5	4/39	42	68.0±9.1	3/39
Garcia ^[21]	2010	Brazil	25	66.2±7.4	10/15	25	64.4±9.9	8/17
Han ^[22]	2007	Korea	30	69.1±5	3/27	30	68±4.5	6/24
Ritter ^[11] (C1)*	1999	USA	109	69.5	41/68	97	72.9	25/72
(C2)*	1999	USA	117	72.3	41/76	114	71.7	36/78
Mauerhan ^[12] (C1)*	1997	USA	26	64.6±6.0	12/14	27	65.7±6.3	11/16
(C2)	1997	USA	28	66.1±7.1	11/17	25	66.8±6.3	11/13

* The study reported 2 comparisons.

C1 = comparison one, C2 = comparison two, F = female, M = male, NR = not reported.

Table 2
Study design and techniques for analgesia.

Author	Study design	Administration approach	Morphinedosage	Cocktail mixture in study group	Cocktail mixture in control group	Anesthesia
Iwakiri-1	RCT	periarticular injection	10 mg	ropivacaine+epinephrine +morphine+ ketoprofen +methylprednisolone	ropivacaine+epinephrine+ketoprofen + methylprednisolone	general anesthesia
Iwakiri-2	RCT	periarticular injection	10 mg	ropivacaine+epinephrine+ morphine+ ketoprofen +methylprednisolone	ropivacaine+epinephrine + ketoprofen +methylprednisolone	general anesthesia
Tammachote	RCT	periarticular injection	5 mg	levobupivacaine +ketorolac+morphine	levobupivacaine +ketorolac	spinal anesthesia
Kim (C1)* (C2)*	RCT	periarticular injection	5 mg	ropivacaine+morphine ropivacaine+ ketorolac+ morphine	Ropivacaine ropivacaine+ ketorolac	spinal anesthesia
Garcia	RCT	intra-articular injection	10 mg	morphine+ normal saline	normal saline	general anesthesia
Han	RCT	periarticular injection	5 mg	ropivacaine+epinephrine+morphine	ropivacaine+epinephrine	spinal anaesthesia
Ritter (C1)* (C2)*	RCT	intra-articular injection	10 mg	morphine+ normal saline bupivacaine+morphine	normal saline bupivacaine	general anaesthesia
Mauerhan (C1)* (C2)	RCT	intra-articular injection	5 mg	morphine+ normal saline bupivacaine+morphine	normal saline bupivacaine	general anaesthesia general anaesthesia

* The study reported multiply comparisons.
C1=comparison one; C2=comparison two; NR=not reported; RCT=randomized controlled trial.

Table 3
Modified Jadad score for study quality.

Study	Randomization	Concealment of allocation	Double blinding	Withdrawals and dropouts	Total
Iwakiri-1	**	*	**	*	6
Iwakiri-2	**	**	*	*	7
Tammachote	*	*	**	*	5
Kim	*	**	*	*	5
Garcia	*	*	*	*	4
Han	**	**	**	*	7
Ritter	**	**	*	*	6
Mauerhan	**	**	*	*	6

Each asterisk represents 1 point. Modified Jadad score is used to evaluate the quality of articles and studies achieving a score of ≥ 4 points were considered to be of high quality.

minimum of 4 points and maximum of 7 points, the average score was 5.8 points (Table 3), which suggests high quality trials are included in this study. Funnel plots (Figs. S5–S17) analysis showed no evident publication bias towards positive studies in general, further confirmed by Egger regression asymmetry test ($P > .05$).

3.2. Pain score at rest

Six comparisons with 653 knees showed pain score within 2 hours post-operatively, the outcome was similar whether or not morphine was used (MD = -0.50; 95%CI, -1.32 to 0.31,

$P = .23$, Fig. 2). There were 6 comparisons involving 435 knees indicated that local morphine did not showed improvement of pain control (MD = -0.08; 95%CI, -0.54 to 0.37, $P = .72$, Fig. 3) at 4 hours postoperatively. Meanwhile, there were no significant difference at 8 hours (MD = -0.47; 95%CI, -0.98 to 0.04, $P = .07$, Fig. 4) and 12 hours (MD = -0.15; 95%CI, -0.40 to 0.11, $P = .27$, Fig. 5) after operation whether morphine injection or not. At 24 hours postoperatively, 11 comparisons containing 1093 knees showed that morphine injection did not achieve better pain scores (MD = -0.0; 95%CI, -0.02 to 0.22, $P = .11$, Fig. 6). Meanwhile, we also can not find any better pain scores at 36 hours (MD = 0.02; 95%CI, -0.34 to 0.38, $P = .92$,

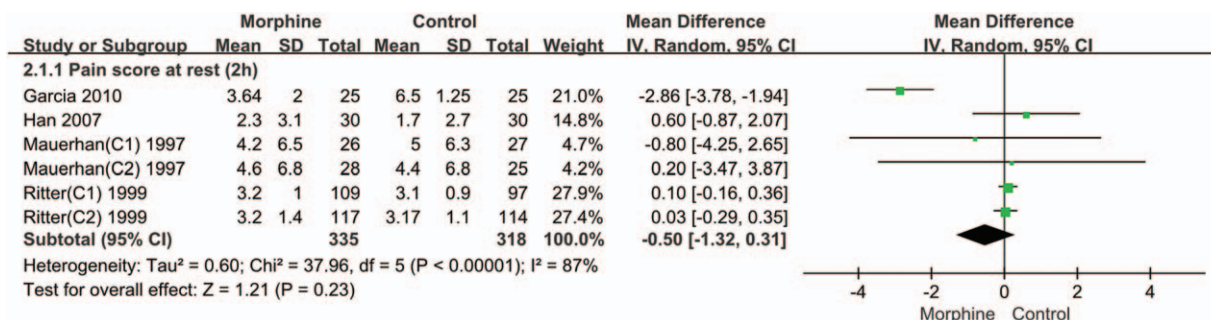


Figure 2. Forest plot showing pain scores within 2 hours postoperatively at rest.

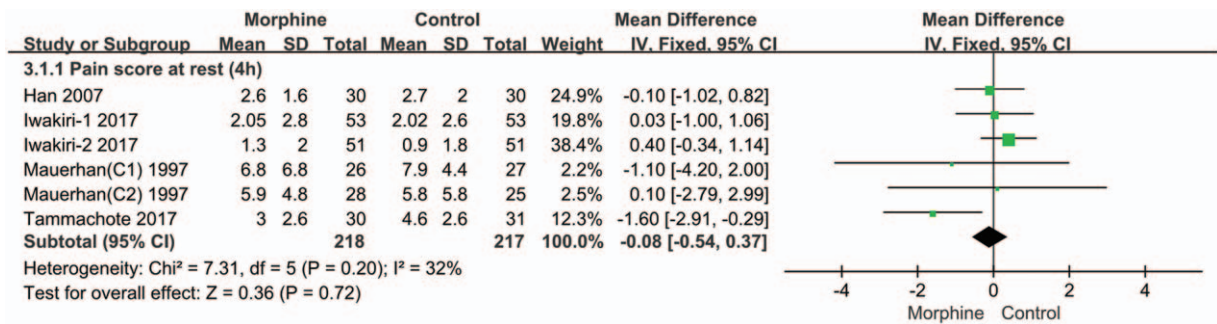


Figure 3. Forest plot showing pain scores at 4 hours postoperatively at rest.

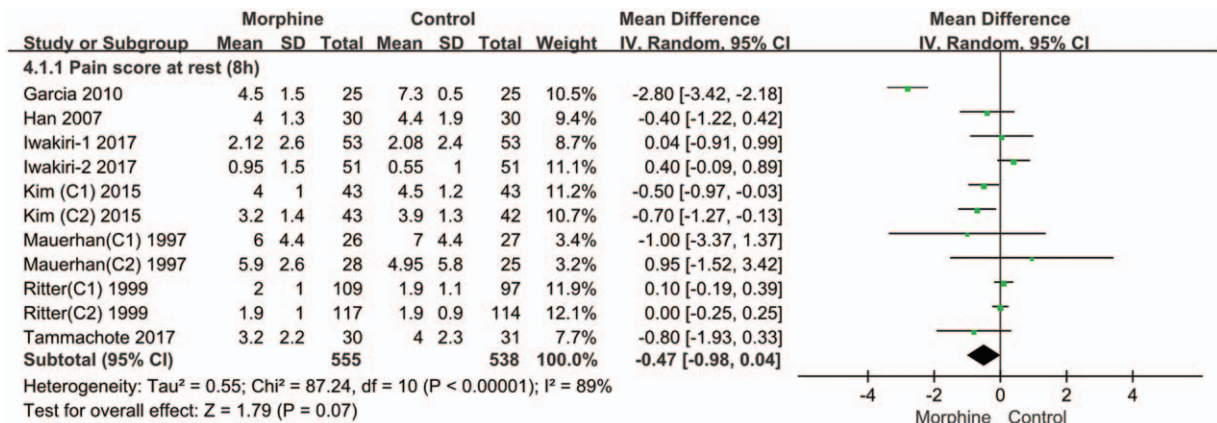


Figure 4. Forest plot showing pain scores at 8 hours postoperatively at rest.

Fig. 7) and 48 hours (MD=0.01; 95%CI, -0.21 to 0.23, P=.94, Fig. 8) after operation in morphine injection group compared with the control group.

3.3. Pain score on motion

There 3 comparisons with 329 knees, 2 studies involving 121 knees, and 2 studies containing 121 knees reported the pain score on motion at 24 hours (MD=-0.02; 95%CI, -0.41 to 0.38, P=.93), 36 hours (MD=0.23; 95%CI, -0.27 to 0.73, P=.36),

and 48 hours (MD=0.24; 95%CI, -0.19 to 0.66, P=.27), respectively after operation, and the pooled outcomes showed there were no significant difference between morphine injection group and control group (Table 4, Fig. S1 in supplementary materials, <http://links.lww.com/MD/D276>).

3.4. Opioid consumption

Nine comparisons with 885 knees assessed total systemic opioid consumption post-operatively. The combined data showed

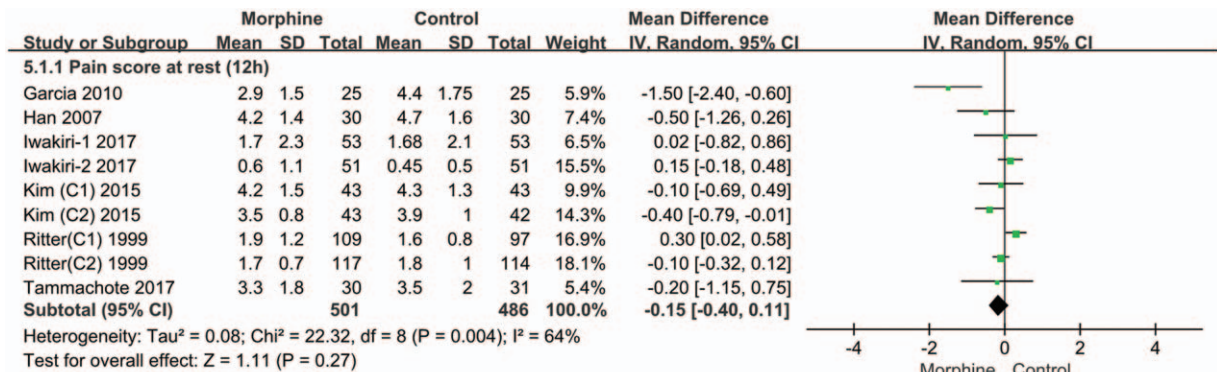


Figure 5. Forest plot showing pain scores at 12 hours postoperative at rest.

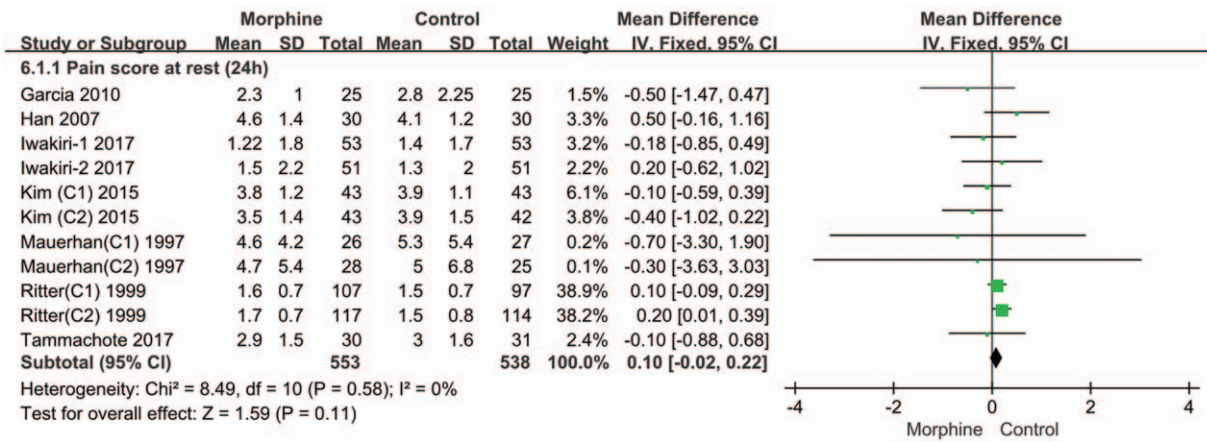


Figure 6. Forest plot showing pain scores during at 24hours postoperatively at rest.

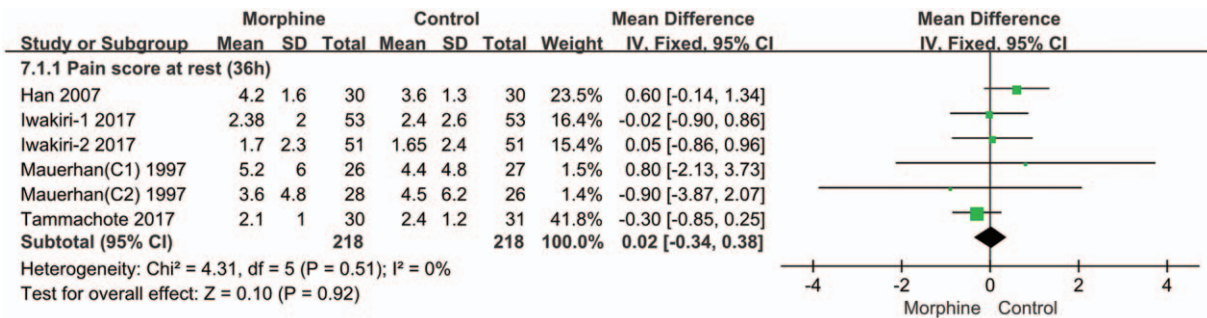


Figure 7. Forest plot showing pain scores during at 36hours postoperatively at rest.

morphine group obtained significant less opioid consumption (SMD = -0.29; 95%CI, -0.42 to -0.16, P < .01, Fig. 9).

3.5. Knee ROM

Morphine injection group did not increase knee flexion range of motion (ROM) at post-operative day 1 (POD1) (MD = -0.36; 95%CI, -7.46 to 6.73, P = .92) and post-operative day 2 (POD2) (MD = 0.30; 95%CI, -6.56 to 7.15, P = .43) compared with the control group during hospital stays. After leaving hospital, the knee flexion ROM revealed no significant difference between the 2 groups at 1 month (MD = -0.36; 95%CI, -7.46 to 6.73,

P = .93) and 3 months (MD = -0.36; 95%CI, -7.46 to 6.73, P = .43) post-operatively. Besides, knee extension ROM at 1 month (MD = 0.10; 95%CI, -0.66 to 0.85, P = .80) and 3 (MD = 0.20; 95%CI, -0.39 to 0.79, P = .50) months after operation also between the 2 groups showed no significant difference (Table 4, Figs. S2, S3 in supplementary materials, <http://links.lww.com/MD/D276>).

3.6. WOMAC score

There were 3 comparisons with 269 knees at 3 months (MD = 0.83; 95%CI, -2.04 to 3.70, P = .57) and 1 comparison with 106

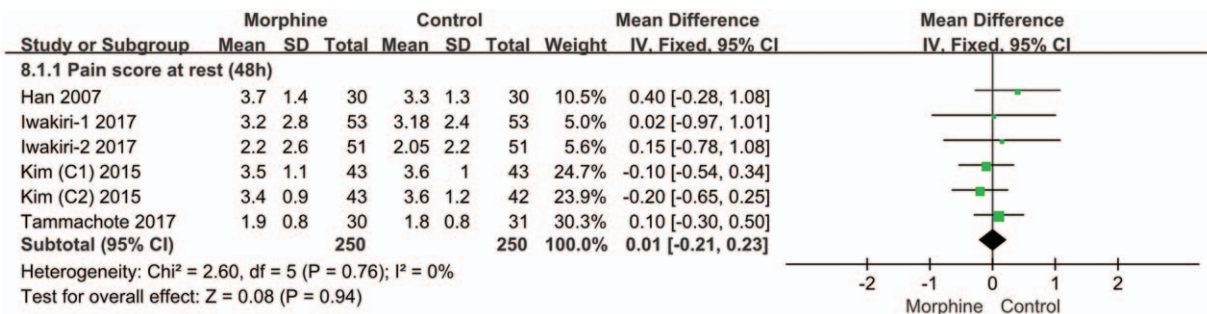


Figure 8. Forest plot showing pain scores during at 48hours postoperatively at rest.

Table 4
Results of meta-analysis.

Outcomes	Comparisons	No. of knees	MD or OR (95% CI)	Heterogeneity (I ²)
Pain score at rest				
PO 2 hours	6	653	-0.50 [-1.32, 0.31]	87%
PO 4 hours	6	435	-0.08 [-0.54, 0.37]	32%
PO 8 hours	11	1093	-0.47 [-0.98, 0.04]	89%
PO 12	9	987	-0.15 [-0.40, 0.11]	64%
PO 24 hours	11	1093	0.10 [-0.02, 0.22]	0%
PO 36 hours	6	436	0.02 [-0.34, 0.38]	0%
PO 48 hours	6	500	0.01 [-0.21, 0.23]	0%
Pain score on motion				
PO 24 hours	3	329	-0.02 [-0.41, 0.38]	0%
PO 36 hours	2	121	0.23 [-0.27, 0.73]	44%
PO 48 hours	2	121	0.24 [-0.19, 0.66]	0%
Opioid consumption	9	885	-0.29 [-0.42, -0.16]*	44%
ROM (Flexion,°)				
POD 1	3	331	-0.36 [-7.46, 6.73]	0%
POD 2	3	331	0.30 [-6.56, 7.15]	0%
PO 1 month	3	269	-1.22 [-4.26, 1.82]	0%
PO 3 months	2	167	-0.11 [-2.68, 2.46]	0%
ROM (extension, °)				
PO 1 month	3	269	0.10 [-0.66, 0.85]	0%
PO 3 months	2	167	0.20 [-0.39, 0.79]	0%
WOMAC score				
PO 3 months	3	269	0.83 [-2.04, 3.70]	0%
PO 12 months	1	106	-0.20 [-3.02, 2.62]	NA
Nausea and vomiting	6	444	1.72 [0.83, 3.56]	69%

* indicates standard mean difference was used for different measurement of the outcome.

MD=mean difference; 95% CI=95% confidence interval; NA=not applicable; OR=odds ratio; PO=postoperative; POD=post-operative day; ROM=range of motion; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

knees at 12 months (MD=-0.20; 95%CI, -3.02 to 2.62, P=.89) after operation reported WOMAC score, the outcomes were both without significant difference between the 2 groups (Table 4, Fig. S4 in supplementary materials, <http://links.lww.com/MD/D276>).

3.7. Complications

Post-operative nausea and vomiting (PNVO) were recorded in 6 comparisons involving 444 knees, and the outcomes suggested that morphine injection did not increase the PNVO occurrence (OR=1.72; 95%CI, 0.83 to 3.56, P=.14) (Fig. 10).

4. Discussion

In this meta-analysis of randomized controlled trials, we evaluated the efficacy of local injections of multimodal cocktail containing morphine in terms of pain relief and knee function recovery after TKA. According to the results, the additional of morphine injection was not associated with significant pain score decreasing within 48 hours postoperatively. However, we found that the use of morphine significantly reduced systemic rescue opioids consumption after operation. Moreover, this study found no significant differences in any other outcomes: knee ROM, WOMAC scores, Post-operative nausea, and vomiting occurrence, were similar outcomes regardless of the presence of morphine in the injections.

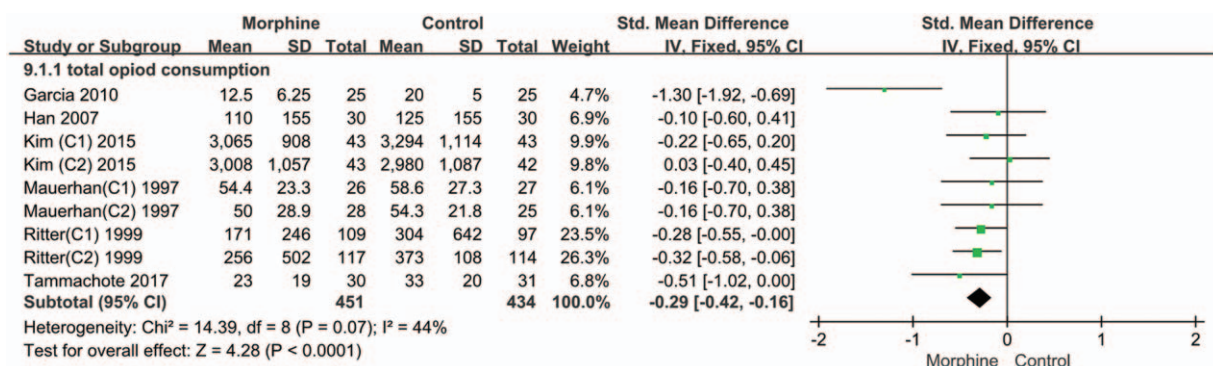


Figure 9. Forest plot showing postoperative total opioids consumption.

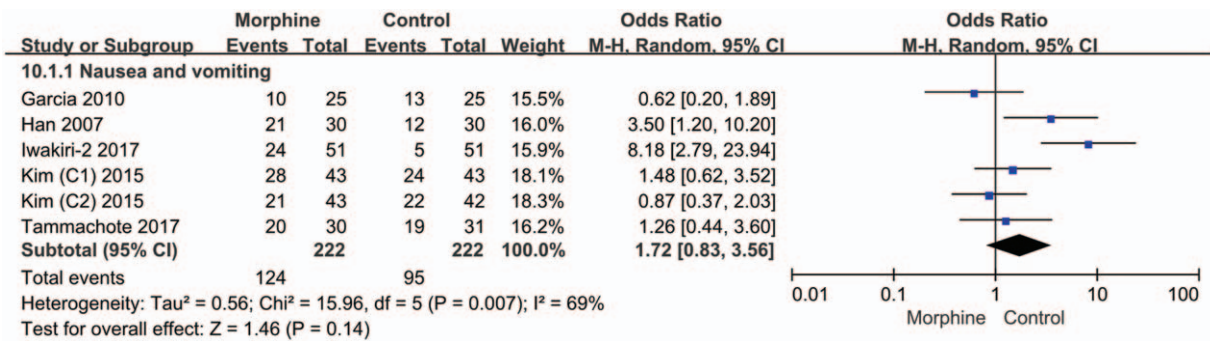


Figure 10. Forest plot showing the total occurrence of nausea and vomiting.

To relieve postoperative pain in TKA, tremendous of work has been done in this field. Although nerve block including femoral nerve block (FNB), adductor canal block (ACB), and sciatic nerve block has caught much attention,^[23–28] but the local infiltration analgesia with multimodal cocktail was still regarded as the golden standard for the postoperative pain relieve in joint arthroplasty.^[1–7] Some researchers even suggest that using periarticular or intra-articular infiltration analgesia without nerve block could obtain good postoperative pain relief results.^[2,29,30] Multiple studies have shown the pain relief efficacy of multimodal periarticular injection of analgesics for TKA recently.^[1–6] So, choosing optimum drug composition in local injection should be paid attention and is meaningful in postoperative pain relief. Anesthetic, such as ropivacaine and bupivacaine, combined with epinephrine are most commonly used in local infiltration analgesia.^[1–6,13–16] The use of NSAIDs and corticosteroids for the periarticular injection has been reported to reduce postoperative pain,^[15,16,20] but it is still inconclusive whether the use of morphine in such injections is beneficial. Although it is clear that intra-articular analgesic injection containing morphine has been proved to be effective on decreasing postoperative pain.^[5,6,13,14] But, it is confused about whether the intra-articular administration of morphine is necessary composition and is really beneficial.

According to our outcomes, the pain score at rest and on motion at all measurement time after TKA were not improved after morphine was injected, which indicated that morphine added to multimodal cocktail did not improve the pain scores. However, we found that local injection of morphine significantly reduced postoperative opioids consumption. This can be associated with the local injection of morphine in multimodal cocktail may play a role in relieving the severe pain and therefore decreasing the requirement of additional morphine consumption after surgery. According to the pain evaluation outcomes, the pain scores were not decreased in local morphine group, which was in contradictory with the decreasing the additional morphine consumption. Two reasons may lead to this contradictory. Firstly, the pain score were evaluated on schedule, for example at 2 hours, 4 hours, 8 hours, 12 hours, 24 hours, 36 hours, 48 hours postoperatively, which may be influenced by the postoperative morphine consumption that was administrated when patients can not suffer the pain. So, the pain score may decrease when it was measured after morphine administration. Secondly, the sample size in this meta-analysis is small, which lead to high heterogeneity and publication bias when evaluating the pain

scores, both of which may make the outcomes without statistical significance. However, it was also an encouraging outcome. Because it can reflect that the local morphine may have effect on reduce postoperative pain, and so decreasing systemic opioids consumption, which usually associated less adverse event and better patients' rehabilitation. Even though, when evaluating the knee functional recovery, there were also no improvement of knee ROM and WOMAC score, the morphine injection still make some difference. Finally, the nausea and vomiting evaluated in this study had no significant difference, and other complications were also not reported. It demonstrated that morphine injection in operation did not increase complication occurrence. This may be explained that the local morphine decreased the blood concentration and reduced the side effects of the drug on cerebral cortex. The local morphine is a relative safe procedure. Accordingly, although morphine local injection did not decrease the pain score, it helped to reduce postoperative opioids usage.

There are several limitations in our study. First, there were only 8 RCTs with 1093 knees were included in our study, which is still a relatively small sample and more studies with large sample were still needed in the future. As the sample size is small in this meta-analysis, the funnel plots that evaluate the publication bias did not make much significance. Second, the anesthesia methods in these trials were different, periarticular or intra-articular were both included in this meta-analysis, and the multimodal cocktail compositions were different among the studies, all of which may lead to bias and influence the postoperative pooling pain scores. Fourth, the different efficiency of pain relief and complication occurrence by using different dosage morphine was not assessed for limited cases included. So, we did not know whether morphine dosage could influence the outcomes. Thus, further research should be done.

5. Conclusion

Additional morphine added to multimodal cocktail did not contribute to decrease the postoperative pain scores significantly based on our outcomes, but it reduced the systemic opioids consumption in total knee arthroplasty.

Author contributions

Conceptualization: Faduo Mi, Haiyan Zhao.

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Writing – original draft: Yinxia Zhang, Fadu Mi, Duowen Xie.

Writing – review & editing: Yinxia Zhang, Fadu Mi, Xiaoyuan Shi.

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