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ORIGINAL PAPER

Effects of morphine on peri-articular infiltration analgesia in total knee arthroplasty: a prospective, double-blind, randomized controlled trial

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Abstract

Purpose Peri-articular infiltration analgesia (PIA) is a widely used method to control post-operative pain in total knee arthroplasty (TKA) patients. However, there are limited data that support the use of morphine in PIA. This study aims to evaluate the efficacy of peri-articular morphine infiltration for pain management in TKA patients.

Methods Based on a double-blind, randomized approach, patients were allocated to the morphine or control group. Patients in the morphine group received a peri-articular infiltration of an analgesic cocktail consisting of ropivacaine, epinephrine, and morphine. Morphine was omitted from the cocktail in the control group. Primary outcomes were post-operative consumption of morphine hydrochloride used for rescue analgesia and post-operative pain as assessed by visual analog scale (VAS) score. Secondary outcomes were functional recovery as assessed by a range of knee motion, quadriceps strength, and daily ambulation distance. The duration of hospital stay was also recorded. Tertiary outcomes included the occurrence of post-operative adverse effects and the consumption of antiemetics.

Results Patients in the morphine group had significantly lower post-operative morphine consumption in the first 24 h and total morphine consumption. There was no significant difference between the two groups in post-operative VAS pain scores at rest or during motion. There was no significant difference between the two groups in the post-operative knee range of motion, quadriceps strength, daily ambulation distance, or duration of post-operative hospital stay. The two groups were similar in the incidence of adverse effects and the consumption of antiemetics.

Conclusion Adding morphine into the analgesic cocktail of PIA could reduce postoperative morphine consumption in TKA patients, but does not improve early pain relief or accelerate functional recovery or provide clinical benefits for TKA patients. In addition, the complications and safety of peri-articular morphine infiltration need to be further investigated in larger sample studies.

Keywords Total knee arthroplasty · Peri-articular infiltration · Analgesia · Morphine · Pain

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Introduction

Total knee arthroplasty (TKA) has been reported as one of the most successful pain-relieving surgical procedures for patients with end-stage knee degenerative diseases [1]. However, more than 60% of patients undergoing TKA suffer moderate to severe pain after surgery [2, 3]. Inadequate pain management after surgery can delay recovery, leading to an increased risk of immobility-related complications such as venous thromboembolism (VTE), hypostatic pneumonia, and arthrofibrosis [4]. Therefore, it is important to control post-operative pain and accelerate recovery of TKA patients.

Peri-articular infiltration analgesia (PIA) is widely used as a method of multimodal pain management in TKA [5–8]. It can provide satisfactory analgesic effects and can help maintain muscle strength without causing opioid-related complications. The administration of preemptive analgesics directly into the operative site can prevent central nervous system sensitization, thereby improving post-operative pain control [9, 10]. However, no gold standard protocol regarding the composition and amounts of drugs used in the analgesic cocktail is currently available [11].

Peri-articular infiltration analgesia usually consists of well-established local aesthetics with low-risk profile [12], and often combined with sympathetic nervous system modulators, such as epinephrine, in order to decrease their absorption, enhance and prolong their effectiveness [13]. In addition, the peri-articular cocktail injection including morphine is currently commonly used to treat post-operative pain after TKA [14–16]. That is based on the results of some arthroscopic studies and animal studies showing that peripherally administered opioids can produce powerful analgesia in stress and inflammatory conditions [17–20]. However, there are limited data that support the use of morphine in PIA for TKA patients and the efficacy and safety of morphine added to the cocktail for pain management is still controversial [11, 16, 21, 22]. At the same time, few studies have reported the effect of cocktail with or without morphine on reducing post-operative morphine consumption. In this prospective, double-blind, randomized controlled trial (RCT), we aimed to investigate the efficacy of morphine as a component of the analgesic cocktail used in PIA for TKA patients.

Materials and methods

This study was designed as a prospective, double-blind RCT and approved by the Clinical Trials and Biomedical Ethics Committee of our institution. Written informed consent was obtained from all patients.

Patient recruitment and randomization

This study recruited osteoarthritis patients undergoing primary unilateral TKA at our institution between January and February 2020. Patients between the ages of 40 and 85 years with an American Society of Anesthesiologists (ASA) functional status of I–III were included. We excluded patients with a diagnosis of non-osteoarthritis (including rheumatic arthritis, traumatic arthritis, and septic arthritis), a knee flexion deformity of $\geq 30°$, a varus-valgus deformity of $\geq 30°$, or known allergies to the drugs being used in this study. We also excluded those with a history of knee surgery (arthroscopy and open surgery), knee infection, excessive opioid consumption, psychiatric illness, cognitive impairment, narcotic dependency, recognized neuromuscular disorders, or thrombolytic events (myocardial infarction, cerebrovascular accident, deep vein thrombosis, and pulmonary embolus). Patients who were unable to communicate verbally or were unwilling to give informed consent were also excluded.

All patients were classified into two groups using a computer-generated list of random numbers (Excel, Microsoft Corporation, Redmond, USA). The random numbers were then sealed in opaque envelopes by an investigator (VV), who asked patients to select an envelope on the morning of their surgery. Based on the number in the chosen envelope, the investigator (VV) assigned the patients to a specific treatment group. Patients in the morphine group received an analgesic cocktail consisting of ropivacaine, epinephrine, and morphine. For the control group, morphine was omitted. Prior to the surgery, the investigator (VV) ensured that the anaesthesiologist (WW), who prepared the corresponding analgesic cocktail. The outcome assessor (XX) and surgeon (YY) were both blinded to the treatment group. Statistical analysis was performed by another researcher (ZZ), who was also blinded to group allocation. At the end of this randomized controlled trial (at discharge), the patients were told which group they belonged to.

Peri-operative analgesia and management

The following patient characteristics were recorded at admission: age, gender, BMI, pre-operative VAS pain score during daily activities, knee range of motion, quadriceps strength, and ASA functional status. On the day before the surgical procedure, Celecoxib (200 mg) was administered twice as a preemptive analgesic.

All the surgery was performed under general anaesthesia. Patients were given anesthetics intravenously (midazolam 2 mg, propofol 2 mg/kg, sufentanil 0.3 μg/kg, cis-atracurium 0.2 mg/kg) after six minutes of pure oxygen inhalation. Then, patients were intubated and given inhaled anaesthetics (sevoflurane, 1–1.5MAC). In the operating room, patients were continuously monitored as recommended by the

guidelines of the ASA. One of our experienced surgeons has performed all the surgical procedures by making a midline skin incision with a medial parapatellar approach after general anaesthesia with no application of pneumatic tourniquets. Cemented prostheses (DePuy Synthes, New Brunswick, New Jersey, USA) were used in all the procedures.

The cocktail administered to the morphine group consisted of 0.2% ropivacaine, 2.0 μg/mL epinephrine, and 0.1 mg/mL morphine hydrochloride, while the control group was given 0.2% ropivacaine and 2.0 μg/mL epinephrine. Apart from the composition of the analgesic cocktail, all methods used in PIA were the same for both groups. Prior to the placement of the prosthesis, 20 mL of the PIA cocktail was injected into the posterior aspect of the capsule, and another 20 mL of the PIA cocktail was used as an infiltration analgesic for the medial and lateral collateral ligaments. After implantation of the prosthesis, the quadricep and retinacular tissues were infiltrated with 20 mL of the PIA cocktail, while the fat and subcutaneous tissues were infiltrated with another 40 mL of the PIA cocktail. Drainage tubes were not routinely placed before the wound was sutured.

After awakening from general anesthesia, patients were sent to the bedward and an ice compress was applied around the incision. Simultaneously, they received passive and active physiotherapy. Celecoxib (200 mg) was administered twice daily to control post-operative pain. If the patient was unable to tolerate the pain, a further 10 mg of morphine hydrochloride as rescue analgesia was injected subcutaneously. Enoxaparin (0.2 mL) was administered 12 hours after surgery, followed by additional doses (0.4 mL every 24 hours) until discharge to prevent venous thromboembolism (VTE). Rivaroxaban (10 mg) was also administered once a day for two weeks after discharge from the hospital to continue to prevent VTE. At six hours after surgery, the patients began knee flexion and extension exercises. During their post-operative hospitalization period, they were required to walk with a walking aid.

Outcomes and follow-up

The primary outcomes addressed in this study were the supplementary use of morphine hydrochloride and post-operative pain at rest and during motion (knee flexion of 45°) measured using a visual analog scale (VAS) score [23]. The scale ranged from 0 to 10, where 0 indicates no pain and 10 indicates severe pain. Pain at rest was measured at two hours, six hours, 12 hours, 24 hours, 48 hours, and discharge after surgery, and pain during motion was measured at six hours, 12 hours, 24 hours, 48 hours, and discharge after surgery.

The secondary outcomes were the functional recovery of the knee measured by range of motion, quadriceps strength, and daily ambulation distance. The quadriceps strength was assessed by the outcome assessor when patients flexed their hip and knee after surgery. The evaluation criteria are as follows: 0 point—no muscle contraction; 1 point—muscle contraction, no joint movement; 2 points—joint movement, no gravity resistance; 3 points—gravity resistance, no forced resistance; 4 points—gravity and partial resistance; 5 points—normal joints function. The duration of hospital stay was also recorded. The discharge criteria of patients included adequate pain control on oral pain medication, knee flexion ≥ 100°, transfer independently with the walking aid, and absence of complications in the wound and other serious complications during hospitalization.

Tertiary outcomes were the occurrence of adverse effects, including nausea, vomiting, wound ooze, delayed wound healing (defined as mild wound dehiscence or inflammation, hematoma, effusion around the wound), postoperative infection, VTE, nerve damage, cardiovascular diseases, and falls after surgery. Postoperative vomiting was treated with 10 mg metoclopramide dihydrochloride intramuscular injection. The consumption of metoclopramide dihydrochloride was compared between the two groups.

Statistical analysis

A pre-study power analysis suggested that in order to achieve a 30% difference in post-operative total morphine consumption used for rescue analgesia, each group should consist of at least 44 patients with a two-sided alpha level of 0.05 and a power of 90%. Considering the risk of dropouts, 50 patients were included in each of the two groups. Data were presented as means and standard deviations, unless otherwise indicated. Since the demographic characteristics of the patients in both groups were normally distributed, inter-group differences in continuous data (e.g., age and BMI) were assessed for significance using Student's t test, while differences in categorical data (e.g., gender and target side of the body) were assessed using Pearson's chi-squared test. Data on postoperative outcomes were not normally distributed. Therefore, differences in continuous data (e.g., morphine consumption, pain score, knee range of motion) were assessed using the Mann-Whitney U test, and differences in categorical data (e.g., occurrence of adverse effects) were assessed using Pearson's chi-squared test or Fisher's exact probabilities test. Simultaneously, the repeated measures ANOVA of the general linear model was used for the correction of repeated measured outcomes (VAS pain scores and postoperative functional recovery). All statistical analyses were performed using SPSS 25.0 (IBM, Chicago, IL, USA). Differences were considered statistically significant when $p < 0.05$.

Results

A total of 177 osteoarthritis patients were assessed for eligibility, of whom 32 did not meet the eligibility criteria and

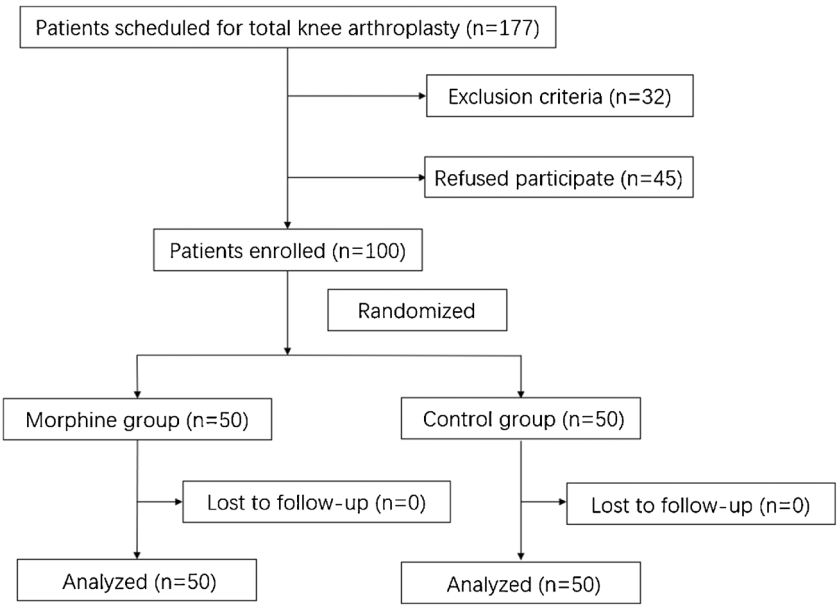

Fig. 1 Flow diagram of patients' selection and exclusion

another 45 were unwilling to give consent. Therefore, we collected data from 100 eligible patients. During post-operative outcome assessments, no patients were excluded from the analysis. In the end, there were 50 patients in each group (Fig. 1).

Before surgery, the two groups showed no significant differences in demographic characteristics or clinical characteristics (Table 1). Patients in the morphine group showed significantly lower post-operative morphine consumption within the first 24 hours and lower total morphine consumption (Table 2). However, there was no significant difference between the two groups in post-operative VAS pain scores at rest or during motion (Figs. 2 and 3). In terms of functional recovery after surgery, the two groups showed no significant difference in the range of knee motion, quadriceps strength, and daily ambulation distance during hospitalization (Table 3). The results of repeated measures ANOVA also showed that there was no significant difference between the two groups in terms of repeated measured outcomes including VAS pain scores, range of knee motion, quadriceps strength, and daily ambulation distance (Table 4). There was also no significant difference between the two groups in the post-operative duration of hospital stay.

During post-operative hospitalization, the incidence of nausea and vomiting was similar (Table 5), and there was no significant difference in the consumption of metoclopramide

Table 1 Patient clinical and demographic characteristics

Characteristic	Control group ($n = 50$)	Morphine group ($n = 50$)	p value
Age (years)	63.1 ± 8.0	65.7 ± 9.3	0.138[a]
Gender (M/F)	17/33	13/37	0.383[b]
Weight (kg)	67.9 ± 9.3	66.6 ± 10.0	0.507[a]
Height (cm)	161.3 ± 8.1	160.6 ± 7.4	0.672[a]
Body mass index (kg/m^2)	26.0 ± 2.8	25.8 ± 3.4	0.685[a]
Surgery side (right/left)	33/17	30/20	0.534[b]
VAS pain score during daily activities (prior to surgery)	4.9 ± 1.0	4.7 ± 0.9	0.169[c]
Knee ROM (prior to surgery)	118.3 ± 15.6	121.4 ± 12.9	0.361[c]
Quadricep strength	4.9 ± 0.4	4.9 ± 0.3	0.540[c]
ASA status (I/II/III)	3/37/10	1/34/15	0.170[c]
Duration of operation (min)	69.1 ± 14.4	70.1 ± 12.9	0.448[c]

VAS, visual analogue scale; *ROM*, range of motion; *ASA*, American Society of Anesthesiologists

[a] Student's t test

[b] Pearson's chi-squared test

[c] Mann-Whitney U test

Table 2 Rescue analgesia

Outcome	Control group ($n = 50$)	Morphine group ($n = 50$)	p value*
Morphine consumption (mg)			
Post-operative day 1	14.6 ± 7.1	9.0 ± 6.1	< 0.001
Post-operative day 2	3.6 ± 4.8	3.2 ± 5.5	0.486
Post-operative day 3	0.6 ± 2.4	0.4 ± 2.0	0.648
Total	18.8 ± 7.7	12.6 ± 8.3	< 0.001

*Mann-Whitney U test

dihydrochloride. One patient in the morphine group developed foot drop due to sensorimotor blockade of the common peroneal nerve after surgery. However, this case recovered within one day after surgery. During hospitalization after surgery, there was no significant difference in the incidence of post-operative VTE or wound complications (wound ooze, and delayed wound healing). Neither group suffered cardiovascular disease, post-operative infection, or falls.

Discussion

In this study, we evaluated the efficacy of morphine used in PIA for pain management after TKA. Our results suggest that including morphine in the cocktail of local anaesthetics in PIA can reduce post-operative morphine consumption used for rescue analgesia, but it cannot improve post-operative pain relief or accelerate post-operative recovery. Although the analgesic cocktail including morphine seems not to increase the risk of post-operative complications.

Peri-articular infiltration analgesia is widely used as a method of multimodal pain management in TKA [6–8]. It can provide satisfactory analgesic effects and help maintain muscle strength. Some studies have suggested that periarticular cocktail infiltration including morphine is commonly used to treat post-operative pain after TKA [16]. A randomized, double-blind, placebo-controlled trial included 5 mg of morphine as part of a multimodal cocktail with bupivacaine and betamethasone. This cocktail was found to reduce the need for oral opiates and to improve pain scores [22]. In addition, Busch et al. used 4 drugs, including epinephrine, nonsteroidal anti-inflammatory agents (NSAIDs), and opioids, for local anaesthesia [14], and Parvataneni et al. used a mixture of five drugs, including epinephrine, NSAIDs, opioids, morphine, and steroids, for local anaesthesia [15]. All these studies reported that their combinations of drugs were effective for analgesia after TKA. However, these benefits may come from other drugs such as local anaesthetics, NSAIDs, and steroids. It is not clear that morphine played a role. In a recent randomized controlled trial using peri-articular infiltration analgesia with or without morphine in TKA, they found that the addition of morphine to the multimodal cocktail injection is not effective for relieving post-operative pain, alleviating swelling, or improving ROM, even results in nausea and vomiting [16]. At the same time, their team also reported when using PIA with or without morphine in bilateral total knee arthroplasties, there was no advantage to adding morphine to PIA, in terms of post-operative pain relief [24]. At present, the efficacy of morphine added to the analgesic cocktail for peri-articular infiltration is still controversial and few studies have reported the effect of cocktail with or without morphine on reducing post-operative consumption of morphine used for rescue analgesia [21].

It is generally accepted that morphine exerts its analgesic effect by binding opioid receptors of the central nervous

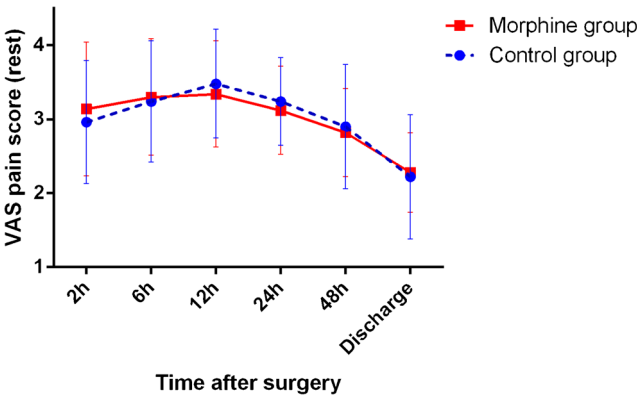

Fig. 2 The average post-operative VAS pain scores at rest of patients in both groups. The error bars indicate the standard deviation of the mean

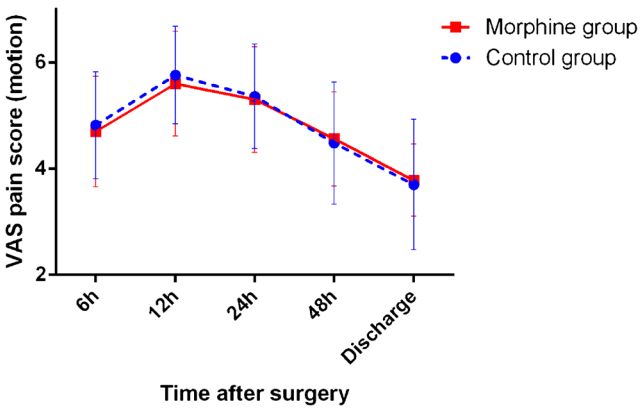

Fig. 3 The average post-operative VAS pain scores during motion of patients in both groups. The error bars indicate the standard deviation of the mean

Table 3 Post-operative functional recovery

Outcome	Control group ($n = 50$)	Morphine group ($n = 50$)	p value*
Degree of knee ROM (degrees)			
Post-operative day 1	83.6 ± 15.3	85.4 ± 14.8	0.762
Post-operative day 2	94.1 ± 10.9	95.5 ± 9.5	0.817
Post-operative day 3	107.6 ± 10.7	108.5 ± 9.4	0.933
Quadriceps strength			
Post-operative day 1	2.9 ± 0.6	2.8 ± 0.7	0.554
Post-operative day 2	3.6 ± 0.7	3.5 ± 0.7	0.328
Post-operative day 3	4.4 ± 0.5	4.3 ± 0.5	0.290
Daily mobilization (m)			
Post-operative day 1	11.0 ± 9.2	11.9 ± 9.0	0.560
Post-operative day 2	21.2 ± 10.3	22.5 ± 10.2	0.559
Post-operative day 3	33.9 ± 11.8	35.6 ± 10.7	0.410
Post-operative hospital stay (h)	78.2 ± 14.8	76.1 ± 11.0	0.714

ROM, range of motion

*Mann-Whitney *U* test

system. A study has reported that injection of a small dose of morphine into the knee articular cavity after arthroscopy produced a marked analgesic effect, but this effect could be reversed by an opioid-specific antagonist, naloxone, indicating the existence of morphine specific receptors in the articular cavity [18]. This finding provides evidence for the clinical use of opioids in local intra-articular analgesia. Our results indicate that including morphine in the analgesic cocktail containing can reduce post-operative morphine consumption within the first 24 hours and total morphine consumption. This may be due to the preemptive administration of morphine directly into the operative site that can act on morphine specific receptors in the articular cavity, preventing central sensitization and reducing the need for post-operative morphine. We know that surgical trauma causes central sensitization by increasing the excitability of spinal neurons, and it causes peripheral sensitization by reducing the threshold for afferent nociceptive neurons [14]. All these changes contribute to hypersensitivity to post-operative pain. Our results were consistent with the results of a previous randomized controlled trial [21]. They found that adding morphine to the PIA cocktail containing levobupivacaine hydrochloride and dexamethasone can reduce the number of times analgesics used for the first 12, 24, and 48 hours; and the numbers of times analgesics used for the first 12 hours reached a statistical difference.

Although the post-operative morphine consumption was reduced, it did not seem to reduce the subjective pain feeling of patients after surgery. We found that there was no significant difference in post-operative VAS pain scores at rest or during motion. As shown in Figs. 2 and 3, you cannot even see any trends that the VAS score was different. This may be because the reduction in morphine equivalents was relatively small in the morphine group, or the low opioid receptor density in the peripheral tissues limited the effectiveness of morphine in PIA [12]. Unsurprisingly, as with VAS pain scores, the morphine group showed no improvement in post-operative functional recovery, and the duration of hospital stay was also not shortened. Under the approach of enhanced recovery after surgery (ERAS), patients should begin their functional exercise as soon as possible after surgery to reduce the risk of post-operative infection, venous thrombotic events, and joint stiffness [25–27]. However, adding morphine to the cocktail did not seem to show any advantage in ERAS.

Some studies have suggested that adding morphine into the cocktail of infiltration could result in complications such as nausea and vomiting [16, 21]. While other studies reported that local administration allows sustained effect with a minimum of the typical opioid side effects (e.g., sedation, nausea, and vomiting) which occur through central opioid receptors [22]. In our study, we found that the incidence of nausea and vomiting between the two groups was similar, and there was no significant difference in the consumption of metoclopramide dihydrochloride. Patients in the morphine group did not suffer more opioid-related adverse effects such as post-operative nausea and vomiting as reported [16, 21]. This may be because

Table 4 Correction of repeated measurements

Outcome	p value*
VAS pain score (rest)	0.390
VAS pain score (motion)	0.666
Degree of knee ROM	0.850
Quadriceps strength	0.806
Daily mobilization	0.872

VAS, visual analog scale; *ROM*, range of motion

*Repeated measures ANOVA

Table 5 Postoperative adverse events (*n*, %)

Adverse events	Control group (*n* = 50)	Morphine group (*n* = 50)	*p* value
Nausea	16 (32.0)	19 (38.0)	0.529[a]
Vomiting and antiemetics consumption			
Vomiting	9 (18.0)	12 (24.0)	0.461[a]
Metoclopramide consumption (mg)	2.6 ± 6.3	2.8 ± 5.4	0.527[b]
Wound ooze	7 (14.0)	5 (10.0)	0.538[a]
Delayed wound healing	4 (8.0)	3 (6.0)	1.000[a]
Post-operative infection	0 (0.0)	0 (0.0)	
Venous thrombotic events	2 (4.0)	2 (4.0)	0.610[a]
Nerve damage	0 (0.0)	1 (2.0)	1.000[c]
Cardiovascular disease	0 (0.0)	0 (0.0)	
Falls after surgery	0 (0.0)	0 (0.0)	

Metoclopramide consumption is presented as mean ± SD, while other data are presented as n (%)

[a] Pearson's chi-squared test

[b] Mann-Whitney *U* test

[c] Fisher's exact probabilities test

these patients received significantly lower post-operative morphine consumption, and the total morphine dose used intra-operatively and post-operatively may be similar between the two groups. The effects of intra-operative and post-operative morphine may interfere with each other. There was one patient in the morphine group developed foot drop due to sensorimotor blockade of the common peroneal nerve after surgery. We are not sure if it is caused by PIA including morphine or the surgical procedure, but we cannot ignore the possibility that PIA including morphine may cause sensorimotor blockade of the common peroneal nerve. The sample size of our study is still small and our study is not powered to detect side-effects; therefore, studies with a larger sample are still needed to determine the safety of morphine used in PIA.

At present, no gold standard protocol regarding the composition of drugs used in the analgesic cocktail is currently available. Local an aesthetics are the base ingredient in the cocktails and function by blocking voltage-gated sodium channels, while sympathetic nervous system modulators can provide adjunct effects to periarticular cocktails to increase the duration of action and effectiveness of medications [12]. Therefore, researchers have summarized that the well-established drug combination of cocktail used in PIA was local anaesthetics combined with sympathetic nervous system modulators [11, 12]. Most current studies on the composition of cocktails are based on the combination of the two drugs [8, 28–30]. Similarly, we chose not to incorporate additional drugs such as NSAIDs and corticosteroids which can block peripheral production of inflammatory mediators in order to isolate the analgesic effects of morphine. Whether adding NSAIDs or corticosteroids to the current cocktail would yield different results remains to be further explored.

Besides the composition of drugs, there is also no gold standard protocol regarding the dose of drugs used in the cocktail available. The recommended dose of drugs might differ among countries and regions. Previous studies reported that the commonly used dose range of ropivacaine and epinephrine for PIA is 150 mg to 300 mg and 0.1 mg to 0.3 mg respectively, and the total volume of the analgesic cocktail is often between 60 mL and 100 mL [8, 16, 24, 28–31]. In our study, we used a 100 mL cocktail consisting of 200 mg ropivacaine and 0.2 mg epinephrine, with or without 10 mg morphine hydrochloride according to the recommended dose. Because the total volume of the cocktail we used was larger, the concentration of drugs was relatively lower compared with that in previous studies. Different drug doses may cause different results, further studies would be a desirable future investigation.

Our study may help clarify the efficacy of peri-articular morphine infiltration for pain management in TKA patients. At the same time, our results should be interpreted with caution in light of several limitations. First, we included only patients with osteoarthritis, therefore the results cannot be interpreted for all patients with other primary diseases requiring TKA. Further studies are needed to verify the efficacy of peri-articular morphine infiltration for pain management in patients who were excluded from our study. Second, our study was limited to the hospitalization period, so we were not able to assess differences in outcomes and complications after discharge. The lack of any form of outcome measure beyond hospital discharge is another shortcoming of our study. Third, the sample size of our study is still small and our study is not powered to detect complications; therefore, studies with a larger sample are still needed to determine the safety of morphine used in PIA. The fourth limitation was that we did not use additional multimodal analgesia modalities such as regional anaesthesia and peripheral nerve blocks in our study, which might have played a role in the results. Additionally, since most patients in this study were female (70.0%), a larger sample size could

help us explore potential sex-specific differences in functional recovery and sensitivity to post-operative pain.

Conclusions

Adding morphine into the analgesic cocktail of PIA could reduce post-operative morphine consumption in TKA patients but does not improve early pain relief or accelerate functional recovery or provide clinical benefits for TKA patients. In addition, the complications and safety of peri-articular morphine infiltration need to be further investigated in larger sample studies. However, it should be noted that all conclusions are confined to this study.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical review committee statement This study was approved by the Clinical Trials and Biomedical Ethics Committee of West China Hospital, and written informed consents were obtained from all participants. The study had IRB approval, the clinical trial registration number was ChiCTR2000028919.

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