Morphine and dexamethasone-incorporated cocktail regimen for postoperative pain in patients undergoing primary total knee arthroplasty: a randomized controlled trial

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Abstract

Background
This study was conducted to evaluate the pain-reducing efficacy and safety of morphine and dexamethasone-incorporated cocktail regimen in patients undergoing total knee arthroplasty (TKA).

Methods
This study enrolled 213 patients and randomly assigned them to one of three groups. Group I patients were injected with morphine, dexamethasone, bupivacaine, flurbiprofen axetil, and normal saline. Patients in group II were injected with dexamethasone, bupivacaine, flurbiprofen axetil, and normal saline. Patients in control group were administered bupivacaine, flurbiprofen axetil, and normal saline. To compare the pain-controlling efficiency, the visual analog scale (VAS) score, active and passive range of movement (ROM), rescue analgesia use, and 1-min walking distances were recorded and evaluated. Indicators of inflammation include serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) levels, and white blood cells count (WBC) were tested and compared. The following side effects were monitored: headache, dizziness, nausea, vomiting, wound leakage and wound infection.

Results
Group I patients had the lowest VAS and the highest active and passive ROM. In Group I, the VAS reduced from day one to four, but the ROM increased. Group II patients had a smaller reduction in VAS and a smaller increase in ROM, compared with the patients in control group. Patients in group I required the least rescue analgesia use in the first 48 hours postoperative and demonstrated the best walking abilities on postoperative day 2 and day 4. Indicators of inflammation were similar in all enrolled individuals. Following side effects were not recorded: headache, dizziness, nausea, and vomiting. Wound leakage was observed in four patients in group I (two patients) and group II (two patients). No wound infection symptoms were detected.

Conclusions
Morphine and dexamethasone-incorporated cocktail regimen efficiently reduced postoperative pain in patients undergoing primary TKA.

Trial registration:
Randomized controlled trial ISRCTN25027558, registered retrospectively on 27/02/2022. (https://www.isrctn.com/ISRCTN25027558)
Background

Total knee arthroplasty (TKA) is considered one of the most successful surgeries with satisfying outcomes, including restored joint movement and significantly reduced pain over time [1]. However, patients undergoing TKA typically experience severe postoperative pain, which slows recovery and increases the hospital stay and cost [2]. Without adequate pain management, severe postoperative pain places adverse outcomes on the cardiovascular system, immune system and central nervous system and contributes to a higher risk of infection [3–6].

Local infiltration analgesia is a simple, practical, safe, and effective pain management strategy after knee and hip surgery [7]. Intraoperative periarticular injection of the multimodal cocktail has long been used to alleviate pain, and its analgesic effect has been considered comparable to the nerve block technique [8]. Nowadays, cocktail injections are commonly injected into muscles, tendons, and bursa around the knee joint [8]. The injection mixture consists of multiple compositions, including opioids, anesthetics, corticosteroids, and nonsteroidal anti-inflammatory drugs [9]. However, there has been no gold-standard regimen of the cocktail ingredient, and the proper dosage and composition of the injection cocktail have not been agreed upon. This is primarily due to the potential complications associated with using opioids and corticosteroids. Opioids operate on m-receptors distributed throughout the cerebral cortex, thalamus, medulla oblongata, spinal cord, and primary sensory neurons in the central nervous system [10]. Therefore, opioids typically demonstrate a strong analgesic effect. Over the past decades, corticosteroids have emerged as a steroidal medicine to reduce systematic inflammation caused by rheumatoid arthritis, systemic lupus erythematosus, and asthma. Corticosteroids have been widely used to reduce inflammation by suppressing the release of numerous inflammatory factors and inhibiting white blood cell infiltration and phagocytosis, thereby reducing pain and eliminating red blood cells [11]. However, note that inflammation is a defense response of the body, and the inflammation response is an important process of tissue repair. Therefore, improper use of this category of drugs can result in the spread of infection and delayed wound healing.

In this study, we developed three periarticular cocktail regimens and compared their postoperative pain-reducing efficiency for patients with TKA. The candidate ingredients were morphine (5 mg) and/or dexamethasone (5 mg), whereas the basic components were bupivacaine (10 mg) and flurbiprofen axetil (10 mg). To compare the pain-controlling efficiency, the visual analog scale (VAS) score and range of movement (ROM) were recorded and evaluated. Simultaneously, the potential side effects accompanied with the use of morphine and dexamethasone were monitored to determine the tolerability of the regimens.

Methods

Trial design
This was a prospective randomized controlled trial that adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomized clinical trials. After all inclusion and exclusion criteria were checked and written informed consent was obtained, participants were randomly allocated (1:1:1 ratio) by using opaque, sealed envelopes that included each group's number. Patients received their randomly allocated cocktail during the total knee replacement. Surgeons had role in the generated the random allocation sequence, enrolled participants, and assigned participants to interventions.

**Sample size**

Sample size of the current study was calculated based on previous studies [12-14]. The average VAS scores and standard deviation were applied. With an adopted significance level (α) of 0.05, and power of test (β) of 0.8000, based on one-way analysis of variance, the sample size of per group was calculated by Power Analysis and Sample Size Software (v.21.0.3; NCSS, Kaysville, LLC). As a result, 59 participants would be required for each group. Assuming a dropout rate of 15%, the final sample size per group will be 70 participants, and 210 participants would be required for the study.

**Patient enrollment**

From September 2018 to October 2020, 250 patients of ages 50–70 who were scheduled for elective primary TKA were assessed for eligibility (Figure 1) in the First Affiliated Hospital of Dalian Medical University. This study included all patients who had been diagnosed with knee osteoarthritis. Patients were excluded if they were diagnosed with rheumatoid arthritis or if they had a history of knee replacement surgery, hepatic or renal dysfunction, or ischemic heart disease. Ultimately, 213 patients were enrolled, and 37 were excluded. The enrolled patients were randomly assigned to the three groups. Table 1 depicts the demographic statistics, preoperative pain evaluation data, and ROM assessment.

**Administration of intraoperative periarticular injection**

Table 2 shows the cocktail regimens. Patients in group I were injected with morphine (5 mg), dexamethasone (5 mg), bupivacaine (10 mg), flurbiprofen axetil (10 mg), and normal saline (20 mL). For patients assigned to group II, dexamethasone (5 mg), bupivacaine (10 mg), flurbiprofen axetil (10 mg), and normal saline (20 mL) were injected into the joint space. Patients in control group were administered bupivacaine (10 mg), flurbiprofen axetil (10 mg), and normal saline (20 mL). The total volume of analgesic injection was 20 mL, which was the same for all patients.

**Surgical procedure and additional procedures**

All surgical procedures were conducted in our hospital by the same surgical team using the same approach. Total knee replacements were performed using the GENESIS II system (Smith & Nephew, London, United Kingdom). All surgical procedures were conducted using the same knee medial parapatellar approach under general anesthesia. Following the completion of osteotomy, cocktails were injected into the capsule of the knee joint.
Additional procedures including patella resurfacing, medial collateral ligament release, lateral retinaculum release, and vascular ligation were recorded and compared. All the three groups presented similar results and no difference was detected.

**Outcome evaluation**

Primary outcomes:

In the first four days after TKA surgery, the outcomes primarily include dynamic observation VAS score, active ROM, and passive ROM measured in the first 4 days after TKA surgery.

Secondary outcomes:

a. Rescue analgesia: Tramadol injection (2mL: 100mg) was used as rescue analgesia whenever patients experience a VAS score ≥ 4. The mean number of rescue analgesia used was recorded postoperatively.

b. Postoperative 1-min walking ability: Walk tests measure the distance walked over a definite time period. The 1-min walk tests were measured on postoperative day 2 and day 4, compared to the results recorded on day 1 before surgery.

c. Laboratory indexes: Indicators of inflammation include serum C-reactive protein (CRP, by nephelometric method), erythrocyte sedimentation rate (ESR, by Wintrobe’s method) levels, and white blood cells count (WBC) were tested and compared in the first four days postoperatively.

d. Other outcomes: Potential side effects (headache, dizziness, nausea, and vomiting), complications (wound leakage and superficial infection) and other adverse events (cardiac infarction, stroke, and acute renal failure) were carefully monitored by physical examination, questioning and hematology testing during hospitalization.

**Statistical analysis**

The SPSS software (v.19.0; IBM, Chicago, IL) was applied to analyze statistical differences using one-way analysis of variance and Tukey’s post-hoc test to determine the significance of group differences in continuous variables. The Pearson Chi-squared test or Fisher exact test was applied to analyze qualitative comparative parameters. When \( P < 0.05 \), a significant difference was defined.

**Results**

213 patients were enrolled for final analysis. 71 patients were randomly assigned to groups I, II and control (Fig. 1.). General demographics and baseline VAS scores and ROM were not different between the groups (Table 1.). And additional procedures and the average operation time of the three groups were compared and no differences were observed (Table 3.). After TKA, the VAS scores, active ROM, and passive ROM of each group can be found in Tables 4 and 5.
Patients in group I had the lowest VAS and the highest active and passive ROM in knee extension on postoperative day 1 and in knee flexion from day 1 to day 4, as shown in Table 4 and Table 5. The VAS reduced from day one to day four, but the ROM increased. The patients in group II had a smaller reduction in VAS and a smaller increase in ROM compared with the patients in control group.

Patients in group I required less rescue analgesia in the first 48 hours postoperative, as shown in Table 6. Besides, in group I, longer 1-min walking distances on postoperative day 2 and day 4 were observed (Table 7). Similarly, patients in group II had a smaller reduction in rescue analgesia use and a smaller increase in walking distance compared with the patients in control group.

Serum C-reactive protein (mg/L) and erythrocyte sedimentation rate (mm/h) levels, and white blood cells count (n/µL) were similar in all enrolled individuals (Table 8). The following side effects were not recorded: headache, dizziness, nausea, and vomiting. Wound leakage was observed in four patients in group I (two patients) and group II (two patients). No wound infection symptoms were detected. No adverse events, such as cardiac infarction, stroke, or acute renal failure, were recorded. Patients in all three groups presented similar hospital admissions and costs (Table 9).

**Discussion**

TKA is one of the most common surgeries performed by orthopedic surgeons. However, patients suffer from severe postoperative pain after TKA [3–6], limiting postoperative recovery. A periarticular cocktail injection is widely used following TKA to alleviate pain [15, 16], although there is no agreement on the ingredients. This study aimed to compare three cocktail regimens for postoperative analgesia and examine the potential side effects of additional morphine and dexamethasone.

Patients in group I had the lowest VAS scores in the first four days after TKA, confirming that the regimen effectively reduced the damaging stimulus and release of inflammatory mediators, prevented pain sensitization and alienation, and achieved balanced analgesia. It was consistent with the results of Garcia et al. but inconsistent with the results of Iwakiri et al. and Wang et al. [14, 17, 18]; Interestingly, VAS on the first day after operation in the three groups was lower compared with some similar studies [19]. We believe that it could be due to the use of rescue analgesia and the requirement for patients to perform active knee movement and receive continuous passive movement only within the tolerable range. Although other conditions that affect the pain in the first days after TKA, such as inflammation at the surgical site, pain interpretation difference and the type of surgical technique or applied device, led to possible biased, the significant inter-group differences obtained from the randomized controlled trial were reliable enough. In addition, group I observed less use of rescue analgesia, which was consistent with most previous studies [19], reflecting the excellent analgesic effect of the regimen.

We tend to consider this reduction in pain was caused by the main components in the regimen functioning synergistically on diverse targets. As a long-acting amide local anesthetic, bupivacaine blocks nerve excitation and conduction, especially for unmyelinated nerve fibers in the periosteum, by primarily inhibiting the sodium ion channel of the nerve cell membrane [20, 21]. Flurbiprofen axetil is a
nonsteroidal analgesic that could be promptly hydrolyzed by carboxylesterase to produce flurbiprofen [22–24], which inhibits prostaglandin synthesis and alleviates pain [25, 26]. Morphine is a complete opioid receptor agonist. It can mimic endogenous opioid active substances by binding to opioid receptors in several brain regions, including the limbic system, to exert a reduction in persistent mild pain and a strong sedative effect, which improves the tolerance to pain significantly [27–31]. Thus, morphine is ideal for TKA postoperative pain management [32, 33]. Steroids have anti-inflammatory effects and may reduce these effects by inhibiting the cyclooxygenase pathway, stabilizing neuronal cell membranes, and reducing bradykinin levels in the tissue [34]. Dexamethasone inhibits the release of neuropeptides from nerve endings after tissue injury, such as calcitonin gene-related peptide and substance P, which were both aggravating pain [35, 36].

The patients in group I also demonstrated the highest active and passive ROM in the first four days, which was inconsistent with existing studies [14,17–19]. Furthermore, the best 1-min walking abilities on postoperative day 2 and day 4 were observed in group I. Better postoperative motor function recovery partially due to the pain being reduced to the lowest level so the range of passive knee movement could achieve the highest level. The reduced pain and use of opioid analgesics (tramadol) postoperative also encouraged patients to conduct active exercise. Further, good ROM could be partially reasoned with the use of corticosteroids. More than directly suppressing inflammation, corticosteroids also increase vasoconstriction, reduce vascular permeability, antagonize the expansion of blood vessels by inflammatory mediators such as histamine, reduce local congestion, and inhibit the exudation of white blood cells and body fluids. Thus, corticosteroids were used locally to reduce exudation and edema, which was beneficial for achieving a higher ROM in the beginning.

For complications, only with regard to wound leakage, there is a difference in distribution among the three groups. However, due to the low incidences, in this small sample size study, it is not possible to assert that there is a statistically significant difference in these complications. No side effects were observed during the hospital stay mainly because morphine and dexamethasone were used in small amounts. Furthermore, dexamethasone decreased capillary permeability, allowing morphine to enter the bloodstream at a slow rate and reducing the likelihood of morphine-related side effects. The well-controlled pain and limb swelling are beneficial for early rehabilitation after TKA, which could aid in restoring the general condition and the immune system. Infection was not observed despite continuous monitoring of serum C-reactive protein and erythrocyte sedimentation rate and white blood cells count.

LIA of intra-articular corticosteroids is commonly performed to treat pain. Corticosteroids injected into the joint area can reduce inflammation from the synovial fluid and membrane. Generally speaking, most people will experience an evident decrease in pain immediately after the injection [37]. However, a study found that 14 days post LIA procedure, pain scores had significantly increased, and only 6% of people reported significant improvements in pain after 6 weeks [37]. Basically, LIA injections may work to relieve inflammation and pain but the benefits are only short-term. In addition, the potential risks of using LIA are becoming more recognized by physicians and should be considered carefully before LIA injections. For example, identification of a subchondral insufficiency fracture before LIA injection is clinically important,
as glucocorticoids (type of corticosteroid) may inhibit the healing processes of such a fracture. This is because the IACS injection can reduce pain, which may lead to increased load and weight-bearing activities thus increasing the risk of joint collapse [38].

This study had several limitations. First, the current study was a 4-day study on pain management after TKA, which was a relatively short period of evaluation. A longer follow-up may help evaluate the medium-term and long-term effect of different cocktail regimens. Second, due to the 4-day short-term follow-up, some more objective rating scales cannot be observed to fluctuate significantly in the short term, so rescue analgesia was chosen to be a secondary outcome to balance the possible biased of VAS score. Finally, for comparisons of secondary outcomes with low incidences including side effects, complications and other adverse events, this single-center study with a small sample size was limited. Future multicenter studies with a larger sample size could help find a clearer intergroup difference.

Conclusion

Conclusively, for patients undergoing primary unilateral TKA, morphine and dexamethasone-incorporated cocktail regimen considerably reduced postoperative pain and increased ROM, which was beneficial for early postoperative enhanced recovery. The combined cocktail had no side effects.

Abbreviations

TKA: Total knee arthroplasty; VAS: Visual analog scale; ROM: Range of movement;

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cells count.

Declarations

Acknowledgments

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Authors' contributions

JG collected the data and wrote the manuscript, YL conducted the study, SL analyzed the results, CX drew the figures and tables, and YG designed the study. All authors have read and approved the manuscript.

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Availability of data and materials
The data collected and/or analyzed in the current study are available from the corresponding author upon reasonable request.

**Ethics approval and consent to participate**

All procedures performed in this study were following the ethical standards of the first affiliated hospital of Dalian Medical University hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients enrolled in this study had signed a consent form to participate in this study.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare there is no conflict of interest.

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**References**


**Tables**

Tables 1-9 are available in the supplementary files section.

**Figures**
Figure 1. Flow chart of the whole study.

See above image for figure legend.

Supplementary Files

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