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Clinical Effects of Topical Application of Compound Betamethasone in Total Knee Arthroplasty

Xiaobo Sun[1], Linjiao Wang[2], Kai Qin[1], Guoyang Bai[1], Qunli Dou[3,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Nanjing University of Chinese Medicine, Nanjing 210023, Jiangsu, China
[3]Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China
Correspondence Author, douqunli@126.com

Abstract: ***Total knee replacement is the most effective treatment for end-stage knee osteoarthritis, and then postoperative pain becomes a major impediment to rapid patient recovery. Perioperative local infiltration analgesia has become an important part of multimodal analgesic management, but the combination of analgesic drugs among them is formulated with different standards. Many scholars have reported that glucocorticoids have favorable analgesic and anti-inflammatory effects in recent years. Compound betamethasone has been used as a potent, long-acting glucocorticoid in TKA. The purpose of this article is to review the efficacy of the localized application of compound betamethasone in total knee arthroplasty and to provide a reference for the clinical application of compound betamethasone.***

Keywords: Total Knee arthroplasty, Compound betamethasone, Pain, Joint mobility, Safety.

1. Introduction

Total knee arthroplasty (TKA) is considered to be the most effective treatment for end-stage osteoarthritis of the knee [1, 2], relieving patients' knee pain, improving knee function, and enhancing quality of life [3]. However, surgical trauma can release inflammatory mediators from peripheral cells, stimulate injury receptors, exacerbate postoperative knee pain, cause periprosthetic swelling, and delay the recovery of knee function.

Pain management is an important part of the concept of accelerated recovery after surgery (ERAS) [4], which contributes to early recovery and improved patient satisfaction after surgery [5]. Multimodal analgesia can be more effective in relieving postoperative pain with fewer side effects than a single analgesic regimen. Multimodal analgesia is a regimen that effectively combines different analgesics and analgesic methods, which is important in controlling perioperative pain and reducing postoperative opioid use and related adverse effects [6,7]. Among them, local infiltration analgesia (LIA) has become an important part of perioperative multimodal analgesic management in TKA patients.

LIA is also known as “cocktail analgesia”, which is administered by periarticular and intraarticular injections during surgery to achieve analgesia [8]. LIA can directly reach the pain site, relieve pain at the source, and maintain muscle strength, all of which are favorable to postoperative functional exercise and recovery and reduce the use of postoperative opioids [9]. In total knee replacement, the combination of local infiltration analgesics contains glucocorticoids, epinephrine, and opioids [10]. Glucocorticoids are a key component because of their local anti-inflammatory effects and ability to reduce the local stress response to surgery [11].

Glucocorticoids may reduce inflammation around the knee joint by inhibiting prostaglandin synthesis, thereby reducing pain and improving joint function [12, 13]. Therefore, glucocorticoids are widely used in the perioperative period of orthopedic surgery to reduce postoperative pain and inflammatory markers and prevent nausea and vomiting [14]. Compound betamethasone is gradually being widely used as a long-acting glucocorticoid in TKA local infiltration analgesia [15-21]. The composition of compound betamethasone contains betamethasone sodium phosphate and betamethasone dipropionate, which have potential anti-inflammatory and pain control effects. Since betamethasone dipropionate is slightly soluble and acts as a slow absorber and reservoir, it prolongs the body's absorption of betamethasone, resulting in long-lasting relief of inflammation and pain [16].

Some studies have reported that the postoperative analgesic effect of compound betamethasone in joint replacement surgery is good. The clinical effects of compound betamethasone in total knee replacement LIA at home and abroad in recent years are summarized to provide a reference for the clinical application of compound betamethasone.

2. Results

Analgesic effects Postoperative pain in TKA patients is mainly caused by inflammation, and surgical trauma leads to the release of potassium ions, 5-hydroxytryptamine, and histamine from local cells, resulting in the development of local inflammation [22]. Glucocorticoids can reduce the excitability of local nociceptors by inhibiting pro-inflammatory cytokines and inducing anti-inflammatory cytokines, and decreasing the levels of cyclooxygenase-2 (COX-2) and prostaglandins [23]. In addition, it reduces the spontaneous discharge of injured nerves, thereby reducing pain [24].

In a study by Zhang [21] et al, pain VAS scores in group A (ropivacaine + epinephrine + compounded betamethasone) were lower than group B (ropivacaine + epinephrine) in the resting state at 6h, 12h, 24h and 3d, 5d postoperatively, significantly improving early postoperative pain. Luo [17] et al. observed that the addition of 10 mg morphine and 5 mg betamethasone to the LIA of ropivacaine had a significant analgesic effect that could be prolonged up to 72 hours postoperatively. In a study by Luo [16] et al, during the

perioperative period of TKA, group A was treated with ropivacaine and group B was treated with a combination of ropivacaine, betamethasone, and morphine; group B was significantly lower than group A in resting and active VAS pain scores during the 48 h postoperative period, and group B was also lower in opioid consumption, and the inflammatory markers of group B in the 48h postoperative period, C-reactive protein (CRP) and interleukin-6 (IL-6) were significantly lower than the control group A. It is worth mentioning that in this study, the investigators observed the patients' postoperative sleep quality, and the results showed that group B had a better sleep quality than group A. In Fu [15] et al. study, it was found that the addition of a cocktail (morphine + bupivacaine + betamethasone) in the test group significantly reduced the postoperative morphine dosage from 0-12h, 12-24h, and 24-36h, and reduced the total morphine dosage; postoperative rest pain VAS scores of the test group were significantly smaller than those of the control group (saline) for 6h, 10h, 24h, and 36h, and the postoperative active pain VAS score of the test group for 24h was significantly smaller than that of the control group.

In a Meta-analysis by Li [14] et al. based on the results of 11 RCTs, it was shown that the addition of glucocorticoids to a cocktail analgesic regimen provided better postoperative pain control, reduced inflammation, consumed less morphine, and facilitated early functional recovery within the first 48 hours after TKA; this is similar to the findings described above, which suggest that compound betamethasone can reduce TKA-induced inflammation, relieve postoperative pain, reduce opioid consumption, and favor the postoperative recovery of TKA patients.

However, opposite results were given in the study of Peng [18] et al. who, in looking at the efficacy and safety of a topical cocktail of applications in patients undergoing simultaneous bilateral total knee arthroplasty, showed that there was no variability in pain scores, range of motion, at rest or during exercise in the two operated knees on the third day after the surgery, or even in the three months of treatment, with or without betamethasone, and that this may be related to the design of the trial as simultaneous bilateral knee replacement.

Knee mobility and muscle strength restoration Range of motion (ROM) is an important index for judging patients' early postoperative functional recovery [25]. As the loosened soft tissues of the knee joint gradually heal in the early and middle stages of the postoperative period, a certain degree of contracture will be produced, and adequate exercise in the early postoperative period can lead to greater preservation of knee ROM in the middle and distant stages of the postoperative period [26]. Compound betamethasone can inhibit capillary dilatation and reduce tissue edema and tissue exudation in the early stage of inflammation, thus reducing inflammatory symptoms; in the late stage of inflammation, it can inhibit the proliferation of capillary walls and fibroblasts, and reduce scarring and tissue adhesion [27].

Fu [15] et al. clinically observed that in terms of the recovery time for patients to be able to perform straight leg raising and achieve 90° of knee flexion, the experimental group receiving local analgesia was significantly earlier than the control group; the average mobility of the experimental group was also better than that of the control group in the 15d postoperative period; the follow-up at 90 days postoperatively showed that there was no significant difference in ROM between the two groups, indicating that intra-articular injections of analgesic medication helped in early postoperative recovery. In a retrospective study by Zheng [20] et al, it was observed that the maximal extension angle, maximal flexion angle, and passive ROM of patients in the study group were significantly better than those of the control group on the 3rd postoperative day, which showed that the application of compound betamethasone in LIA could better improve the exercise effect of knee function in patients with TKA.

In a study by Zhang [21] et al, the addition of compound betamethasone enabled patients to achieve better active knee mobility in the early postoperative period. Luo [16] et al. clinically observed that the experimental group demonstrated significant advantages in early functional rehabilitation exercises after applying the compound betamethasone.

In a retrospective analysis by Wang [19] et al. it was analyzed that muscle strength at 6h and 12h was significantly lower than that at 24h and 36h in group A (Intrathecal morphine 3mg in epidural anesthesia catheter before extubation) and group B (Intrathecal morphine 3mg in epidural anesthesia catheter plus local injection cocktail in knee joint before extubation), whereas muscle strength at 6h postoperatively in group C (local injection of cocktail in the knee) was significantly lower than that at 12h, 24h, and 36h. Individuals in Group C had statistically significantly higher muscle strength at 6h and 12h postoperatively than individuals in Groups A and B. This result suggests that local analgesia can be used as an alternative to local analgesia. This result suggests that a local analgesic cocktail can promote early muscle strength recovery after TKA.

This is consistent with the findings of most studies that the addition of glucocorticoids to the local analgesic cocktail reduces the duration of postoperative straight leg raising and improves postoperative joint motion [14, 28, 29]. In conclusion, the local infiltration analgesic regimen should be transported with compound betamethasone in the early postoperative period to restore muscle strength more quickly, which is clinically important for ROM exercise.

Safety In TKA the patients are generally older, with relatively weaker underlying physical conditions, and are also affected by intraoperative traumatic stress and early postoperative activity limitations, which can easily lead to a variety of postoperative complications, such as deep vein thrombosis of the lower extremities and wound infections. Although compounded betamethasone reduces inflammation, relieves pain, and contributes to wound healing and organic recovery, the use of topical glucocorticoids may be associated with adverse events such as delayed wound healing and lead to wound infection [30].

However, in previous studies, many scholars have found that perioperative periarticular injection of steroids or morphine in TKA does not result in serious adverse effects [16, 20, 21, 28, 31-33]. In a study by Zheng [20] et al, the incidence of postoperative fever and lower-extremity deep vein thrombosis in patients in the study group (ropivacaine + epinephrine +

morphine + compounded betamethasone) with compounded betamethasone was lower than that in the control group (ropivacaine + epinephrine + morphine), but there was no statistically significant difference, suggesting that perioperative compounded betamethasone application in LIA does not increase the risk of early postoperative complications. In a study by Luo [16] et al, there were no wound complications or other adverse reactions after the use of compound betamethasone in the cocktail in the test group; furthermore, no long-term complications were observed during the 2-year follow-up period. Zhang [21] et al also observed that the addition of compound betamethasone to topical analgesics did not increase the risk of complications such as wound infection. In a trial by Peng [18] et al. who studied simultaneous bilateral total knee arthroplasty with or without the addition of betamethasone to the cocktail, the results of the trial showed that the patients participating in the trial did not show any change in the associated complications between the two groups when they were returned for a 3-month postoperative visit. In a study by Wang [19] et al, the incidence of urinary retention, vomiting, and pruritus was significantly higher in patients in Groups A and B who received morphine administered through an epidural anesthesia catheter, suggesting that local analgesic cocktail injections are superior to morphine administered through an epidural anesthesia catheter. A study by Luo [17] et al also found that LIA with ropivacaine, morphine, and betamethasone did not increase the incidence of adverse events.

Li [14] et al. conducted a Meta-analysis of 11 RCTs of TKA patients receiving periarticular infiltration analgesia, which showed no statistically significant differences in the incidence of side effects and complications (e.g., wound infections, prosthetic joint infections, blood glucose levels, and deep vein thrombosis) between the glucocorticoid and non-glucocorticoid groups. Based on previous studies, there is no evidence of a significant increase in serious adverse events with the use of compounded betamethasone in TKA, which may be related to the different doses, duration, and routes of compounded betamethasone administration in TKA, among others.

3. Summary and Outlook

Effective pain management after TKA can reduce traumatic stress response, which is conducive to accelerating patient recovery, shortening hospitalization time, and improving postoperative satisfaction. Among the multimodal analgesia, local anesthetic analgesia has been proven to be an effective analgesic and easy-to-operate measure in TKA, however, the drug combinations among them are of different standards. Clinical trials have found that glucocorticoids exhibit powerful anti-inflammatory and analgesic effects among many drugs. In recent years, compound betamethasone has been gradually used in various fields of orthopedics, such as knee replacement and hip replacement, due to its potent and long-acting properties, which can prolong the duration of analgesia.

In conclusion, the use of compounded betamethasone in perioperative local infiltration analgesic regimens can relieve early postoperative pain, reduce opioid consumption, and is important for early rehabilitation and exercise. In terms of safety, the early application of betamethasone in the perioperative period of TKA has a high safety profile, but more experiments are needed to explore the long-term safety with follow-up. Therefore, compound betamethasone, as a drug in cocktail formulation, may be one of the future research directions for the local application of analgesia in the perioperative period of TKA.

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Summary of studies of compound betamethasone in total knee replacement

Researches	year	Pilot program	Key findings
Zheng [20] et al.	2024	Control group: 200 mg ropivacaine, 0.5 mg 1:1 000 epinephrine, 5 mg morphine with saline to 80 ml. Study group: 200 mg ropivacaine, 0.5 mg 1:1 000 epinephrine, 5 mg morphine, 5 mg/2 mg compound betamethasone with saline to 80 ml.	The maximum knee extension angle was smaller in the study group than in the control group at 3d postoperatively, and the maximum knee flexion angle and passive ROM were larger than in the control group.
Luo [16] et al.	2024	Control group A: received LIA and 200 mg of ropivacaine diluted to 80 mL in saline. Experimental group B: received LIA and 200 mg of ropivacaine, 10 mg of morphine, and 1 mL of compounded betamethasone, saline diluted to 80 mL combined.	1. In resting and active VAS pain scores at 48h postoperatively, group B was significantly lower than group A. 2. At 48h postoperatively, opioid consumption was less in group B than in group A. CRP and IL-6 levels were significantly lower in group B than in group A. In terms of joint mobility, group B was superior to group A. 3. Sleep quality was better in Group B than in Group A.
Wang [19] et al.	2022	Group A: morphine 3mg was injected in the epidural anesthesia catheter before extraction. Group B: morphine 3mg injected into the epidural anesthesia catheter before extraction plus local injection of cocktail in the knee joint. Group C: local injection of cocktail in the knee joint. Cocktail: 100mg ropivacaine, 10mg morphine, and 30mL of 0.9% sodium chloride solution containing 2mL betamethasone (4mg).	1. The VAS scores of group C were significantly higher than those of groups A and B at 6 and 12 hours postoperatively. In addition, the muscle (quadriceps) strength scores of group C were significantly higher than those of groups A and B at 6 and 12 hours postoperatively. 2. The incidence of postoperative complications was significantly lower in Group C than in Groups A and B. The incidence of postoperative complications was significantly lower in Group C than in Groups A and B.
Luo [17] et al.	2022	Group A: local infiltration of 200mg ropivacaine, 10mg morphine, 5mg betamethasone diluted to 60mL with saline. Group B: Local infiltration of 200mg ropivacaine, 10mg morphine, 5mg betamethasone diluted to 60mL with saline + 20mL of 0.5% ropivacaine for ultrasound-guided endosteal myotube block.	1. Postoperative resting pain with good pain control in both groups. 2. There was no statistically significant difference between the two groups in terms of PONV, urinary retention, pruritus, and no other adverse events noted.
Peng [18] et al.	2021	Control group: ropivacaine 200mg/20mL, epinephrine 0.25mg (1: 1000), flurbiprofen axetil injection 50mg/5mL, tranexamic acid 2000mg/20 mL and morphine 10mg/1mL.	There was no change in pain scores, range of motion, clinical values, or associated complications at rest or during exercise in either knee on the third day after surgery or even during the three-month treatment period.
Zhang [21] et al.	2018	Intervention group: control group on top of +7mg/1mL betamethasone Group A: Intraoperative application of 0.9% sodium chloride solution 60mL + 0.75% ropivacaine 75 mg + epinephrine 0.1mL + compound	1. The pain VAS scores at 6h, 12h, 24h, and 3d, 5d postoperatively were lower in group A than in group B. The pain VAS scores at 2 days and 2 weeks postoperatively were better in

		bethanechol injection 1mL. Group B: Intraoperative application of 0.9% sodium chloride solution 60mL + 0.75% ropivacaine 75 mg + epinephrine 0.1mL.	group A than in group B. 2. Knee active mobility at 2 days and 2 weeks after surgery was better in group A than in group B.
Fu [15] et al.	2009	Test group: 5mg morphine, 30mg bupivacaine, and 1ml betamethasone diluted to 60mL in saline. Control group: 60 ml of saline.	1. The resting VAS scores of the test group were significantly lower than those of the control group at 6h, 10h, 24h, and 36h postoperatively; the VAS scores of the test group were also lower than those of the control group at 24h and 36h postoperatively during activity. 2. The morphine dosage and total dosage of the experimental group were significantly lower than those of the control group in the postoperative periods of 0-12h, 12-24h, and 24-36h. 3. The time to be able to perform straight leg raises and achieve 90 knee flexion was significantly shorter in the test group compared to the control group.