A prospective, double-blinded, placebo-controlled study assessing effectiveness of intraoperative periarticular cocktail injection for pain control and knee motion recovery after total knee replacement

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Abstract

Aim: The aim of the present study was to evaluate the benefits of a particular cocktail combination in patients undergoing TKR with respect to pain and knee motion recovery. **Methods:** A prospective, double-blinded, placebo-controlled trial included patients who underwent simultaneous bilateral TKR in the duration of 18 months in the institute. 200 consecutive patients who satisfied the inclusion criteria were selected for the study. All the patients had a full understanding of the 10-point visual analog pain scale (VAS). **Results:** When compared with the control knee, a statistically significant reduction in pain score was noted in the cocktail injected knee at 6, 12, 24 and 48 hours ($P < .001$ in all cases). However, the difference in the mean pain scores between both knees at the third ($P = .675$) and fourth ($P = .220$) days were not significant. Within the intervention group, there was a significant difference in the pain scores over different time points. A post hoc analysis showed no significant difference within various time points on the first day (6, 12, and 24 hours) after surgery. However, a statistically significant difference in the pain scores was noted at 48 hours ($P < .001$), 72 hours ($P < .010$) and 96 hours ($P < .001$), compared with the 24-hour score. Within the control group, there was a significant difference in pain scores over different time points. However, a post hoc analysis showed that there was no significant difference within various time points on the first day (6, 12, and 24 hours) after surgery, and statistically significant improvement was found only after 72 hours ($P < .001$) and 96 hours ($P < .001$), compared with the 24-hour value. **Conclusion:** The use of intraoperative periarticular cocktail injection significantly reduces early postoperative pain and provides better early knee motion.

Keywords: Total knee replacement, periarticular, cocktail injection, knee flexion, visual analog scale

Introduction

In patients with advanced knee arthritis, total knee replacement (TKR) has been found to be the most successful surgical procedure. Total knee replacement (TKR) is gold standard surgical treatment for advanced or end stage osteoarthritis of knee, but the promising postoperative pain management is still controversial.[1-3] However, early postoperative pain control is pivotal in reducing the hospital stay, increasing patient satisfaction, and for better rehabilitation. It also reduces the potential for postoperative complications such as pneumonia or deep vein thrombosis.[4] Approximately 60% of the patients experience severe pain following TKR and approximately 30% patient's experience moderate pain.[5] This is due to severe soft tissue dissection and trauma involved; TKR is one of the most painful surgical procedures known. Failure in postoperative pain management inhibits early rehabilitation of the knee joint. This can cause quadriceps muscle spasm, capsular contractures and muscular atrophy, which cause further pain.[1]

Control of pain is achievable through multiple ways, and each has its own risks and benefits. Epidural anesthesia is a common modality for providing effective pain relief during the postoperative period, but it hinders early mobilization which increases the chances of Deep Vein Thrombosis (DVT) and pneumonia [4] and leads to complications such as hypotension, postoperative headache and spinal infection, nausea, vomiting. Regional nerve blocks pose the risk of injuring neurovascular structures, hematoma formation, and infection. [6] Systemic opioids such morphine or fentanyl can cause nausea, vomiting, drowsiness, respiratory depression, urinary retention, and constipation. [7]

An innovative approach to pain management is to aim at controlling local pain pathways and receptors within the knee. This has been possible through local intraarticular or periarticular injection of analgesic combinations which has good efficacy, is cost-effective, and is easy to administer without causing motor blockade. Also, it does not require any special technical skill for administration.[8] Nowadays, cocktail injection is popular with surgeons which is injected into the tissues surrounding knee joint, such as the muscles, tendons, suprapatellar bursa, and subpatellar bursa. Various studies about cocktail intraoperative injection reported good results in pain management by controlling local pain pathway and knee receptors. It has the advantage of minimizing the pain, minimum side effect and not causing motor blockade. [8,9] Various drug combinations are being used in various centers such as bupivacaine, ropivacaine, ketorolac, morphine sulfate, epimorphine, methylprednisolone, epinephrine, cefuroxime and normal saline [10,11]. Hence the aim of the study was to compare the pain management scores between both the knees of patient who underwent bilateral TKR in one sitting. Intraoperative periarticular cocktail injection was given in right knee (intervention) and normal saline in left knee (control). In our cocktail we used bupivacaine, methylprednisolone, cefuroxime and normal saline. Postoperatively pain scores of both the knee were compared.

The aim of the present study was to evaluate the benefits of a particular cocktail combination in patients undergoing TKR with respect to pain and knee motion recovery.

Materials and Methods

A prospective, double-blinded, placebo-controlled trial included patients who underwent simultaneous bilateral TKR in the duration of 18 months in the institute. 200 consecutive patients who satisfied the inclusion criteria were selected for the study. All the patients had a full understanding of the 10-point visual analog pain scale (VAS).

Inclusion criteria

- Patients for whom spinal anesthesia was the mode of anesthesia were included only.

Exclusion criteria

- Patients with a history of allergy to the medications used in this study.
- Abnormal renal or liver function, uncontrolled diabetes.
- Those who could not receive spinal anesthesia.

All included patients signed an informed consent form, and the methods of this trial were approved by the institutional ethics committee of the institute.

Methodology

For all the patients, intraoperative periarticular cocktail injection was given to the right knee and the left knee was the control that received a same volume of normal saline (110 mL). The patients were blinded about which knee received the cocktail injection. All the patients received spinal anesthesia with a combination of 0.5% bupivacaine and 0.5 mL (25 mg) fentanyl. The antibiotic prophylaxis given was 1.5 g of injection cefuroxime 30 to 40 minutes before incision. All the operations and the cocktail injections were performed by a single surgeon using a medial parapatellar arthrotomy approach. A periarticular cocktail injection consisting of 90 mL of normal saline, 17.5 mL of 5% bupivacaine, 2 mL of inj. ketorolac (30 mg), and 0.5 mL of adrenaline (total volume: 110 mL) was given to the right knee of all the patients involved in the study. The infiltration was performed using a 21-gauge needle and syringe. The aforementioned cocktail injection was formulated by the orthopaedic surgeon based on his or her clinical experience and past clinical studies.

The cocktail was injected at the following 7 anatomical zones[12] as:

Zone 1: Medial retinaculum.
Zone 2: Medial collateral ligament and medial meniscus capsular attachment.
Zone 3: Posterior capsule.
Zone 4: Lateral collateral ligament and lateral meniscus capsular attachment.
Zone 5: Lateral retinaculum.
Zone 6: Patellar tendon and fat pad.
Zone 7: Cut ends of quadriceps muscle and tendon.

Injection at zones 2, 3 and 4 were administered after making the tibial and femoral cuts and ligament balancing. At zones 1, 5, 6 and 7, the injection was administered

after implant placement. Cemented cruciate-sacrificing implants were used for all the cases. After component placement and cement setting, tourniquet was released, and hemostasis was achieved before the wound was closed. No drains were used. During the postoperative period, systemic analgesics used were intravenous injection of diclofenac (75 mg) and inj. tramadol (100 mg) along with inj. ondansetron (4 mg) every 12 hours for the first 2 days followed by tablet naproxen 500 mg and tablet tramadol hydrochloride (37.5 mg) with paracetamol (325 mg) for the next 10 days. Buprenorphine patch (10 mg) or oral pregabalin (75 mg) were used in patients for whom the aforementioned medications were insufficient in controlling pain or could not be tolerated. Apart from mechanical deep vein thrombosis (DVT) prophylaxis such as DVT stockings, inj. fondaparinux 2.5 mg on the first day followed by oral aspirin 150 mg daily for 6 weeks were given. Patients were mobilized using a walker after 3 to 4 hours of surgery on the same day, and range of motion (ROM) and isometric exercises were started. All the patients were observed till discharge and are being followed up regularly. Postoperatively pain in both the knee was recorded using VAS at 6, 12, 24 and 48 hours and then once daily till 4th day.

Postoperative range of active flexion was noted each day till the fourth postoperative day on both the knees separately by the physiotherapist, who was also blinded about the study.

Statistical Analysis

Data obtained is then tabulated and analyzed using SPSS-17 of Microsoft. Statics was reported as mean and standard deviation. Unpaired t test was used to test the statistical association between the intervention and control. We used repeated measures analysis of variance for analyzing the change in pain scores in the same knee during the follow-up. Post hoc test was conducted to assess the presence of any statistical significance between the 2 time points.

Results

Table 1: The mean pain scores (VAS)

Postoperative duration	Group	Mean	Standard deviation	Standard error mean	*P* value
6 h	Control	3.16	1.945	.190	<.001
	Intervention	1.85	1.420	.123	
12 h	Control	3.20	1.705	.154	<.001
	Intervention	1.40	1.316	.120	
24 h	Control	2.55	1.350	.130	<.001
	Intervention	1.70	.690	.070	
48 h	Control	2.24	1.060	.110	<.001
	Intervention	1.25	.844	.085	
3 d	Control	1.40	1.055	.109	.675
	Intervention	1.30	1.036	.101	
4 d	Control	1.20	1.015	.102	.220
	Intervention	0.99	.835	.085	

When compared with the control knee, a statistically significant reduction in pain score was noted in the cocktail injected knee at 6, 12, 24 and 48 hours (P < .001 in all cases). However, the difference in the mean pain scores between both knees at the third (P =.675) and fourth (P = .220) days were not significant.

Table 2: Mean pain scores (VAS) within intervention group

Group	Mean	Standard deviation	N	P value
Control				
6 h	3.16	1.945	200	<0.001
12 h	3.20	1.705	200	
24 h	2.55	1.350	200	
48 h	2.24	1.060	200	
3 d	1.40	1.055	200	
4 d	1.20	1.015	200	
Intervention				
6 h	1.85	1.420	200	<0.001
12 h	1.40	1.316	200	
24 h	1.70	0.690	200	
48 h	1.25	0.844	200	
3 d	1.30	1.036	200	
4 d	0.99	0.835	200	

Within the intervention group, there was a significant difference in the pain scores over different time points. A post hoc analysis showed no significant difference within various time points on the first day (6, 12 and 24 hours) after surgery. However, a statistically significant difference in the pain scores was noted at 48 hours (P < .001), 72 hours (P < .010), and 96 hours (P < .001), compared with the 24-hour score. Within the control group, there was a significant difference in pain scores over different time points. However, a post hoc analysis showed that there was no significant difference within various time points on the first day (6, 12 and 24 hours) after surgery, and statistically significant improvement was found only after 72 hours (P < .001) and 96 hours (P < .001), compared with the 24-hour value.

DISCUSSION

Total knee arthroplasty (TKA) is one of the most effective methods of treating end-stage osteoarthritis of the knee joint, relieving pain and improving joint function. Approximately 80-90% of patients reported having a better function of the knee after total knee arthroplasty [13], which improves the quality of life. The postoperative period is painful following TKA, unlike THA due to varied reasons. The pain hampers the postoperative rehabilitation which in turn leads to severe arthrofibrosis which in turn leads to reduced range of motion and decreased functional outcome. So, to get optimum pain relief different pain management modalities are available which include epidural analgesia, femoral nerve blocks, intravenous analgesia, and opioids. However, epidural analgesia can cause nausea, vomiting, urinary retention,

hypotension and spinal headache. A femoral nerve block may lead to falls or postoperative femoral nerve neuritis [14]. Multiple studies have been done to introduce the concept of multimodal analgesia intraoperatively in patients undergoing TKA [15], which includes cocktails containing opioids or non-opioids. Achieving the painless TKA is within reach using regional anesthesia and multimodal pain control measures that avoid unnecessary use of narcotics [16].

The component ketorolac not only acts as anti-inflammatory and analgesic but also possesses synergistic activity when given along with other oral nonsteroidal anti-inflammatory drugs, such as acetaminophen and gabapentin, thereby reducing the requirement of these systemic agents [8]. Significant pain relief was obtained when intraarticular ketorolac was given along with bupivacaine and epinephrine as a cocktail combination in previous studies [6, 11, 17]. According to Badner *et al*. [18], addition of an opioid like morphine in the cocktail mixture did not provide any significant additional advantage when compared to cocktail mixtures without opioids with respect to postoperative pain relief [19]. In accordance with their study, our study also excluded the use of opioids in the cocktail mixture. According to Christensen *et al*. [20], addition of steroids to multimodal periarticular cocktail injection only minimized the length of hospital stay in patients undergoing TKR. It did not improve pain relief or early postoperative ROM. They also posed an increased risk of postoperative infection.

When compared with the control knee, a statistically significant reduction in pain score was noted in the cocktail injected knee at 6, 12, 24, and 48 hours ($P < .001$ in all cases). However, the difference in the mean pain scores between both knees at the third ($P = .675$) and fourth ($P = .220$) days were not significant. Within the intervention group, there was a significant difference in the pain scores over different time points. A post hoc analysis showed no significant difference within various time points on the first day (6, 12 and 24 hours) after surgery. However, a statistically significant difference in the pain scores was noted at 48 hours ($P < .001$), 72 hours ($P < .010$) and 96 hours ($P < .001$), compared with the 24-hour score. Within the control group, there was a significant difference in pain scores over different time points. However, a post hoc analysis showed that there was no significant difference within various time points on the first day (6, 12 and 24 hours) after surgery and statistically significant improvement was found only after 72 hours ($P < .001$) and 96 hours ($P < .001$), compared with the 24-hour value. This is in comparison with the study by Fu *et al*. [5] which showed VAS score at rest was significantly lower at 6, 10, 24, and 36 hours postoperatively in the trial group compared with the control group, although the difference was insignificant at 24 hours postoperatively and at days 2, 7 and 15 between the 2 groups. VAS score during activity was also lower in the trial group at 24 and 36 hours postoperatively than that in the control group, although the difference was insignificant at days 2, 7 and 15 [10]. According to a comparative study by Rasmussen *et al*., use of 24- to 72-hour continuous intraarticular infusion of morphine plus ropivacaine showed a significant improvement in ROM and decreased the length of hospital stay [21].

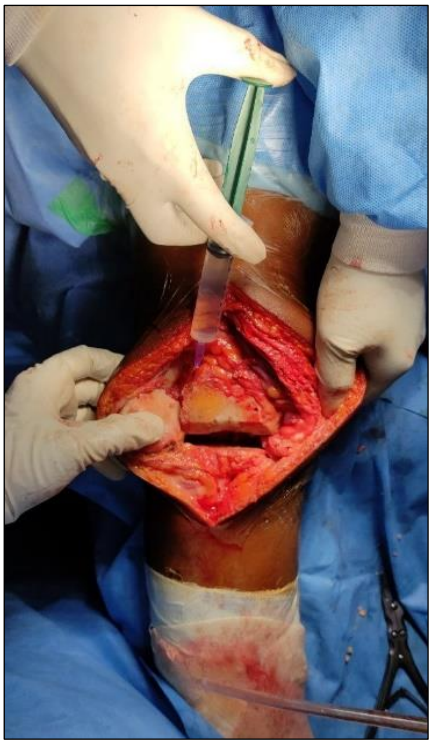

Fig 1: Injection of cocktail to lateral collateral ligament and lateral capsule

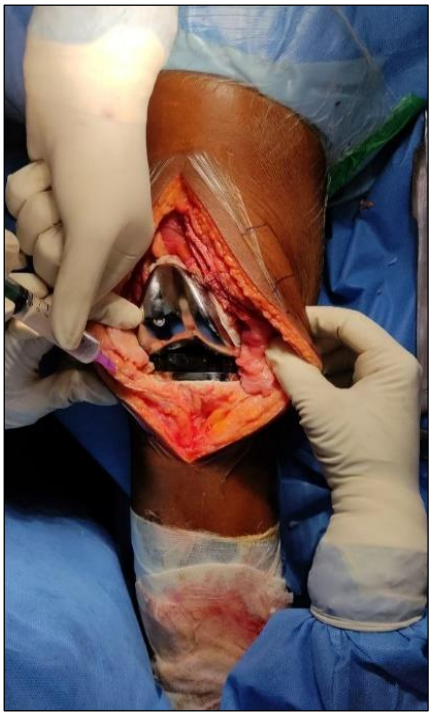

Fig 2: Injection of cocktail into patellar tendon

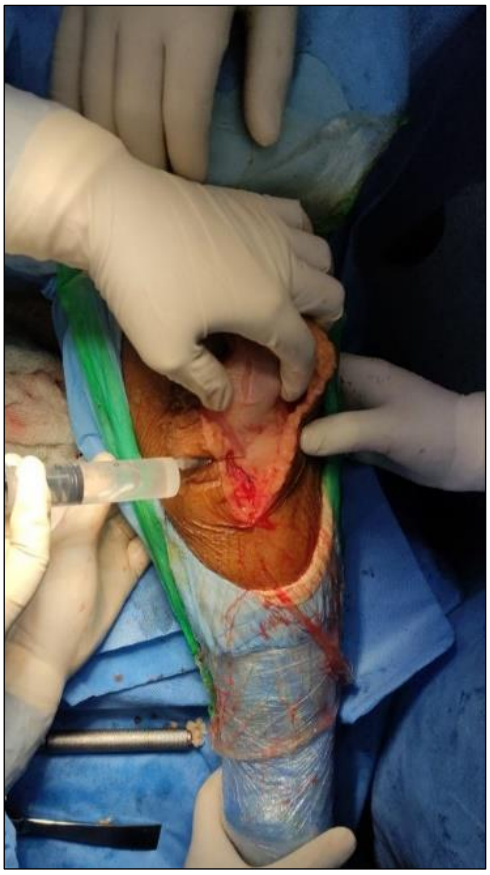

Fig 3

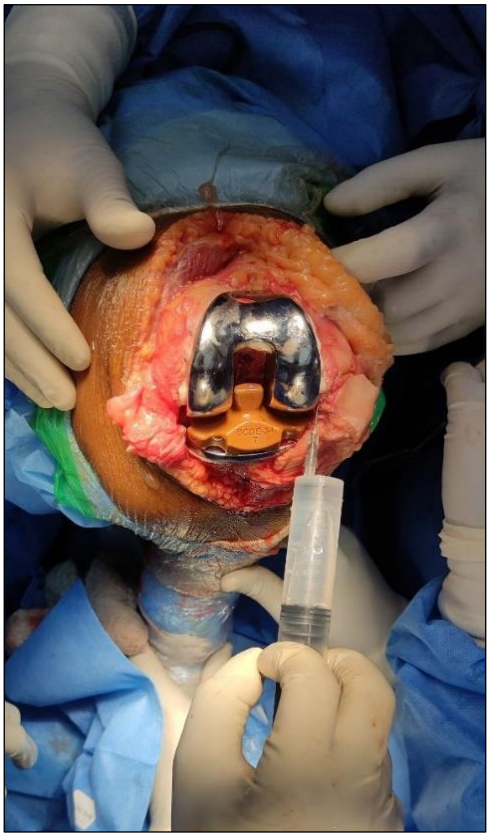

Fig 4: Injection into medial collateral ligament and medial capsule

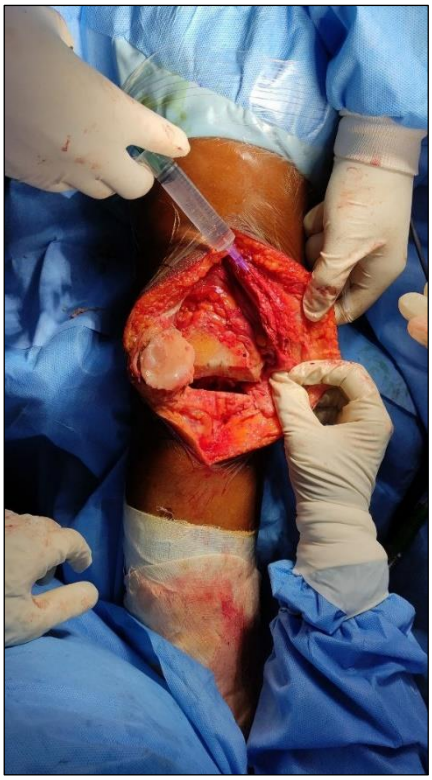

Fig 5: Injection into the quadriceps tendon

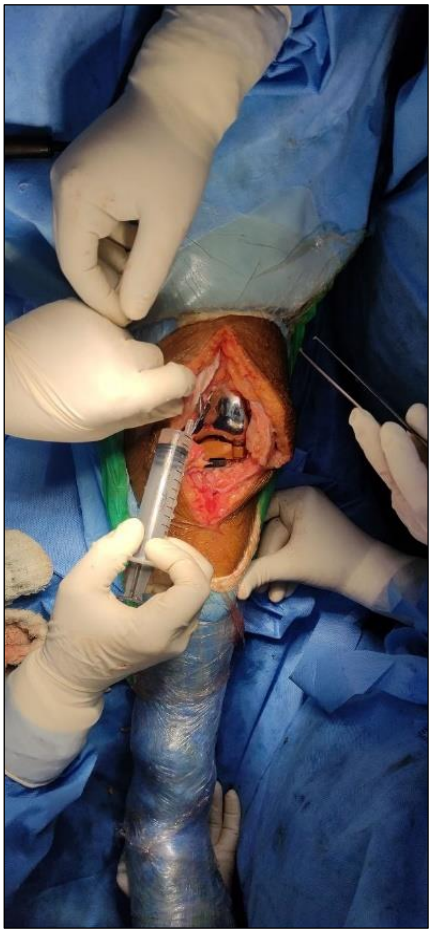

Fig 6: Injection into the quadriceps tendon

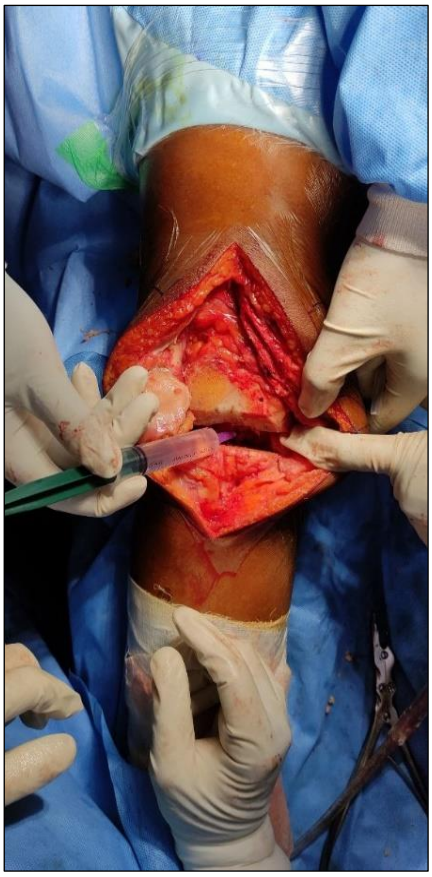

Fig 7: Injection into posterior capsule

Conclusion

The use of intraoperative periarticular cocktail injection significantly reduces early postoperative pain and provides better early knee motion. This study concluded that the combination of drugs that was used as a cocktail for periarticular injection safely provided excellent postoperative pain control and accelerated functional recovery in the patients undergoing total knee arthroplasty. It can be substituted for conventional pain control alternatives like femoral blocks and epidural analgesia with minimal adverse effects.

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