

# Analgesia for Total Knee Arthroplasty: A Randomized Controlled Study Comparing Local Infusion Analgesia, Femoral Nerve Block and Intrathecal Morphine

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## ABSTRACT

**Introduction:** The aim of this study was to compare the effectiveness of continuous intra-articular local infiltration analgesia, femoral nerve block and intrathecal morphine for the management of post-operative pain and early function following total knee arthroplasty.

**Methods:** A single center, three-armed parallel group, double blinded, randomized controlled pilot trial was undertaken. Patients were randomized to receive either local infiltration analgesia, femoral nerve block or intrathecal morphine for post-operative analgesia following total knee arthroplasty. The efficacy of analgesia was determined by recording post-operative pain visual analogue scores, opiate requirements and side effects, and functional scores at 24 hours, 48 hours, and 6 weeks post-operatively.

**Results:** 45 patients were recruited to the study. 4 were excluded due to voluntary withdrawal and incomplete follow-up. The final analysis included 13 patients randomized to the local infiltration analgesia group, 14 patients to the femoral nerve block group and 14 patients to the intrathecal morphine group. There were no significant differences in post-operative pain scores, opiate requirements and associated side effects, or functional scores at any point during the study period.

**Conclusion:** This study did not identify any significant differences between continuous intra-articular local infiltration analgesia, femoral nerve block and intrathecal morphine for delivering post-operative analgesia following total knee arthroplasty.

**KEYWORDS:** Knee; Arthroplasty; Analgesia; Local; Regional; Intrathecal

**ABBREVIATIONS:** TKA: Total Knee Arthroplasty; LIA: Local Infusion Analgesia; FNB: Femoral Nerve Block; IM: Intrathecal Morphine; IV: Intravenous; TUG: Timed Up and Go (test); OKS: Oxford Knee Score; KSS: Knee Society Score; PRN: Pro Re Nata; PCA: Patient Controlled Analgesia; APS: Acute Pain Service; BMI: Body Mass Index

## INTRODUCTION

An estimated 60% of patients report severe pain following total knee arthroplasty (TKA) [1]. Inadequate post-operative analgesia may be associated with poorer patient treatment satisfaction, longer hospital stays and increased costs [2,3]. High dose oral opiates carry risks of side effects such as nausea and vomiting, pruritus, reduced

gut motility, sedation and respiratory depression. Therefore, a variety of techniques have been developed to deliver more effective post-operative analgesia such as local infiltration analgesia, peripheral nerve blockade, and intrathecal morphine. However, the relative analgesic efficacy of these techniques and their impact on post-operative opiate consumption and early mobility is unclear.

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Local infiltration analgesia via an infusion catheter has been shown to be more effective than single bolus administration, is easy to perform and delivers analgesia directly to the source of pain [4]. However, there may be an increased risk of deep infection [5,6]. Femoral nerve blockade delivers analgesia away from the surgical site which, whilst not posing a risk of prosthetic joint infection, may not provide analgesia to the posterior joint. It may also reduce post-operative quadriceps power and ability for early mobilization, increasing the risk of falls [7]. Furthermore, it is technically more demanding, requires additional equipment, and is time consuming. In contrast intrathecal morphine may be delivered at the same time as spinal anesthesia and therefore the additional time required is negligible. One disadvantage, however, is the potential risk of opiate toxicity.

The aim of this study was to compare the efficacy of continuous intraarticular local anesthetic infusion, femoral nerve block and intrathecal morphine, for providing post-operative analgesia,

reducing additional opiate consumption and associated side effects, and effect on early mobilization.

## METHODS

Three methods for delivering post-operative analgesia following total knee arthroplasty were compared in a single center, double blinded, randomized, place-controlled trial. An initial power calculation with 80% power and 5% significance indicated that a sample size of 59 patients in each group would be required. However due to limited funding a final cohort of 45 patients were recruited. Patients were randomized to receive either continuous intraarticular local infiltration analgesia (LIA), femoral nerve block (FNB) or intrathecal morphine (IM) using a randomization code generated with Excel software. All surgical procedures were performed at the Repatriation General Hospital, Adelaide, South Australia. The patient inclusion and exclusion criteria are given in Table 1.

**Table 1:** Study inclusion and exclusion criteria.

<b>Inclusion Criteria</b>
Elective primary unilateral total knee arthroplasty
Age 40-75 years
BMI <40
Ability to self-mobilize
Patient understands the conditions of the study and is willing and able to give written informed consent to participate in the study, including prescribed follow-ups
<b>Exclusion Criteria</b>
Previous involvement in the study
Neuropathic pain or opioid tolerance (defined as use of > 30mg oral morphine/day or equivalent fentanyl or buprenorphine patch)
Contraindication to spinal anesthesia (refusal, coagulopathy, sepsis, local infection, spinal defects, previous laminectomy)
Contraindication to femoral nerve block (refusal, local infection, femoral neuropathy)
Contraindication to NSAIDs (moderate to severe renal impairment, active peptic ulcer disease, asthma triggered by NSAIDs/aspirin, allergy)
Patient has an emotional or neurological condition that would prevent their willingness to participate in the study including mental illness, intellectual disability, and drug or alcohol abuse.
Sensory and/or motor disorders in the operated limb, history of stroke with major neurological deficit.
Patient is immunosuppressed or receiving high doses of corticosteroids.

Patients were identified for surgical eligibility from the waiting list for TKA and recruited and consented by a single research assistant. Anesthetic eligibility was confirmed by an Anesthetist during a pre-admission assessment one or two weeks before surgery.

All patients received 150mg pregabalin orally 1 hour pre-operatively. The preparation of morphine, ropivacaine and placebo blinded products was undertaken by the hospital clinical trials pharmacy on the day before surgery. For spinal anesthesia the addition of morphine (200mcg morphine hydrochloride) or placebo (normal saline) to 2.5ml 0.5% bupivacaine was undertaken in the theatres immediately prior to intrathecal administration. Intrathecal anesthesia was delivered using a 25G Whitacre needle followed by an IV propofol infusion for sedation intra-operatively. Bolus femoral nerve injections were performed under ultrasound guidance and after administration of spinal anesthesia, using

either 20ml 0.2% ropivacaine or placebo (20ml normal saline). All patients underwent standard total knee arthroplasty using a tourniquet and via medial parapatellar approach. 200ml of either 0.2% ropivacaine or placebo (normal saline) was delivered to the posterior capsule, medial, and lateral wound edges in roughly equal quantities at the end of the procedure. Immediately prior to closing an intra-articular wound infiltration catheter was inserted and connected to syringe driver to deliver 5ml 0.2% ropivacaine or placebo normal saline per hour for 24 hours, after which time the catheter was removed. Post-operatively all patients received 40mg IV parecoxib and 1g IV paracetamol. The patient group allocation and placebo materials were blinded to both the anesthetist and surgeon during the operation.

All patients were reviewed pre- and post-operatively (24 hours, 48 hours, 6 weeks) by a physio-therapist who collected data with regards to pain scores at rest and on walking, maximal knee flexion,

distance covered in 2 minutes walking, and a 'timed up and go test' (TUG) defined as the time taken to stand from a seated position, walk a distance of 3 meters and return to the chair. Oxford Knee Scores (OKS) and Knee Society Score (KSS) were also recorded pre-operatively and at 6 weeks. All patients received routine post-operative oral analgesia of ibuprofen 400mg QDS and pregabalin 75mg BD. Additional analgesia was provided on a PRN basis of oxycodone 5mg-15mg hourly or fentanyl patient-controlled analgesia (PCA) as per the hospital protocol. The Acute Pain Service (APS) recorded and adjusted the use of oxycodone and fentanyl PCA at both 24 hours and 48 hours or prescribed additional tramadol in accordance with patient pain scores. Fentanyl PCA and tramadol use was converted to the equivalent oxycodone dose for post-operative opiate requirement comparisons between the groups. The presence of pruritus, nausea, vomiting, antiemetic use, hypotension requiring treatment, sedation or respiratory depression (RR<8, saturation <93%), requirement for urinary catheters, presence of a neurological block/deficit and blood transfusions was also recorded. Finally, the total length of hospital stay was recorded for each patient.

The results were compared between groups using ANOVA for continuous variables with post-hoc Tukey HSD tests as appropriate. Discrete data was analyzed using chi-squared tests. A *p*-value of less than 0.05 (two-tailed) was considered significant. All analyses were conducted using Excel (2010, Version 14.0.7214.5000).

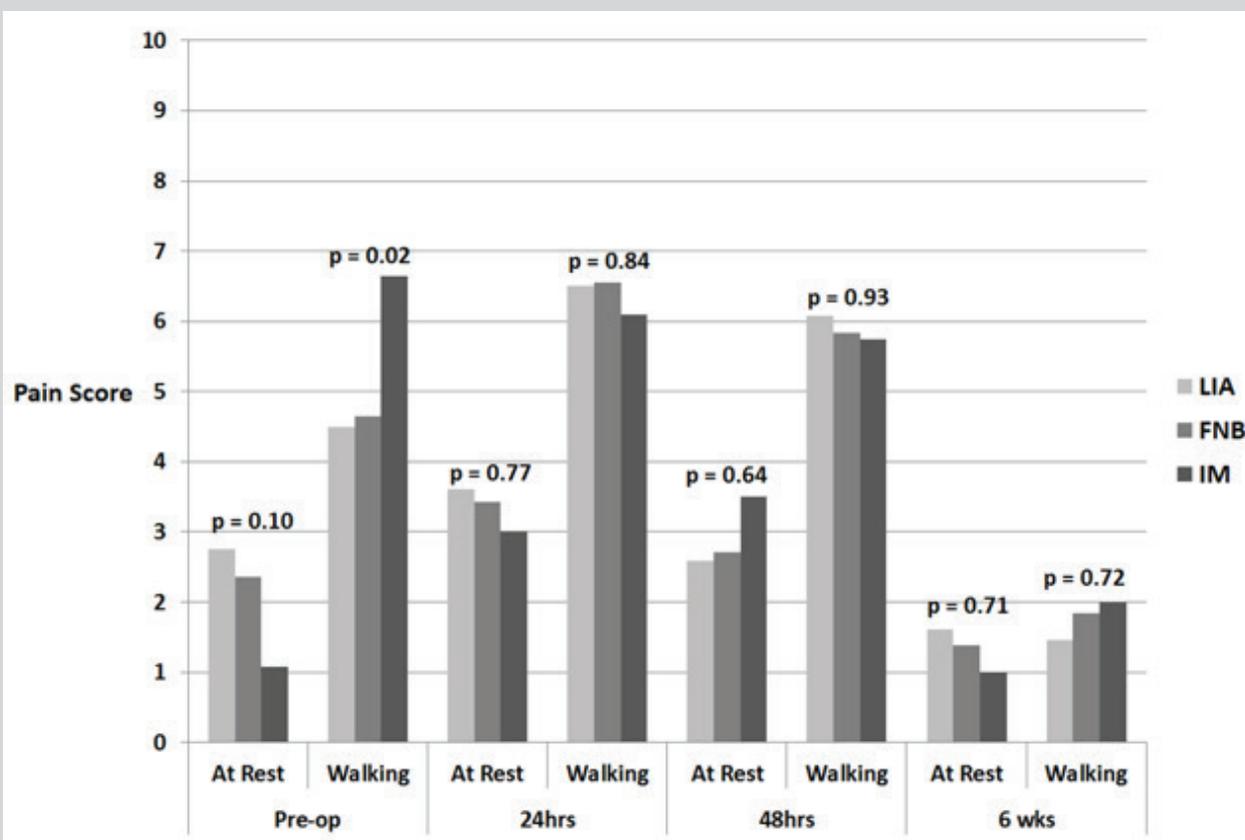
## RESULTS

A total of 45 patients were recruited and randomized to one of the 3 treatment modalities. Four patients were not included in the

final analysis due to voluntary withdrawal and incomplete follow-up, resulting in 13 patients randomized to the continuous intra-articular local infiltration analgesia (LIA) group, 14 patients to the femoral nerve block group (FNB) and 14 patients to the intrathecal morphine group (IM). The baseline demographics and operative treatment data is shown in Table 2. There were no significant differences between the groups in terms of age, gender, body mass index (BMI), operative side, operative time, or tourniquet time. No patients required post-operative blood transfusions.

**Table 2:** Baseline demographics.

	LIA	FNB	IM	P-Value
Number of patients	13	14	14	
Age	69	66	68	0.4
Gender (% Female)	54%	43%	50%	0.84
Body Mass Index (BMI)	31	31	31	1
Operative Side (% Right)	69%	43%	71%	0.23
Operative time	97min	92min	99min	0.83
Tourniquet time	73min	77min	67min	0.4



**Figure 1:** Mean pain scores for LIA, FNB and IM, at rest and walking, pre-operatively and at 24 hours, 48 hours and 6 weeks post-operatively.

Pre-operative pain scores on walking were significantly greater in the IM group compared with the LIA group (ANOVA  $p=0.02$ , Tukey HSD  $p=0.04$ ). However, there was no other difference in pain scores during follow-up between the groups, either at rest or with walking (Figure 1). In addition, there was no significant difference

in post-operative opiate requirements in the first 24 hours or 48 hours between the groups. There was also no significant difference in the requirement for a PCA in the first 48 hours, or opiate side effects (Table 3).

**Table 3:** Opiate consumption and side effects.

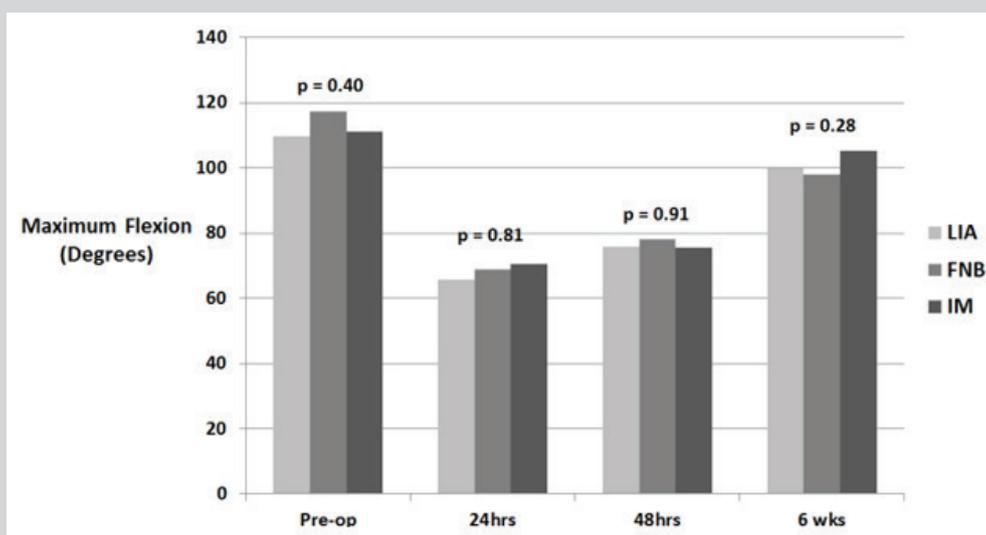
	LIA	FNB	IM	P-Value
24hrs post-operative opiate consumption - equivalent oxycodone dose (mg)	49	68	53	0.73
48hrs post-operative opiate consumption - equivalent oxycodone dose (mg)	85	68	48	0.26
48hrs PCA requirement	8%	43%	21%	0.1
Nausea, vomiting or antiemetic use	31%	36%	57%	0.18
Pruritus	23%	43%	7%	0.08
Hypotension requiring treatment	0%	0%	7%	0.37
Sedation and respiratory depression	0%	0%	0%	1
Urinary catheter	31%	43%	57%	0.38
Neurological block / deficit	15%	7%	7%	0.71

With regard to pre-operative function, there was no significant difference between patients' base-line range of movement (Figure 2): flexion  $p=0.4$ , extension  $p=0.32$ , 2-minute walk test ( $p=0.84$ ), TUG test ( $p=0.84$ ) baseline OKS ( $p=0.83$ ) or baseline KSS scores (Figure 3): symptoms  $p=0.26$ , satisfaction  $p=0.97$ , expectation  $p=0.26$ , function  $p=0.61$ ) between the groups.

There was no significant difference in any of the follow-up time

periods for degree of knee flexion (Figure 2), 2-minute walk tests (24 hours  $p=0.87$ , 48 hours  $p=0.27$ , 6 weeks  $p=0.09$ ) or TUG tests (24 hours  $p=0.77$ , 48 hours  $p=0.70$ , 6 weeks  $p=0.44$ ).

In addition, there was no significant difference in post-operative OKS ( $p=0.45$ ) or KSS scores between the groups (Figure 3). The mean length of stay was 5 days with no significant difference between the groups ( $p=0.45$ ).



**Figure 2:** Maximum knee flexion pre-operatively and at 24 hours, 48 hours and 6 weeks post-operatively.

## DISCUSSION

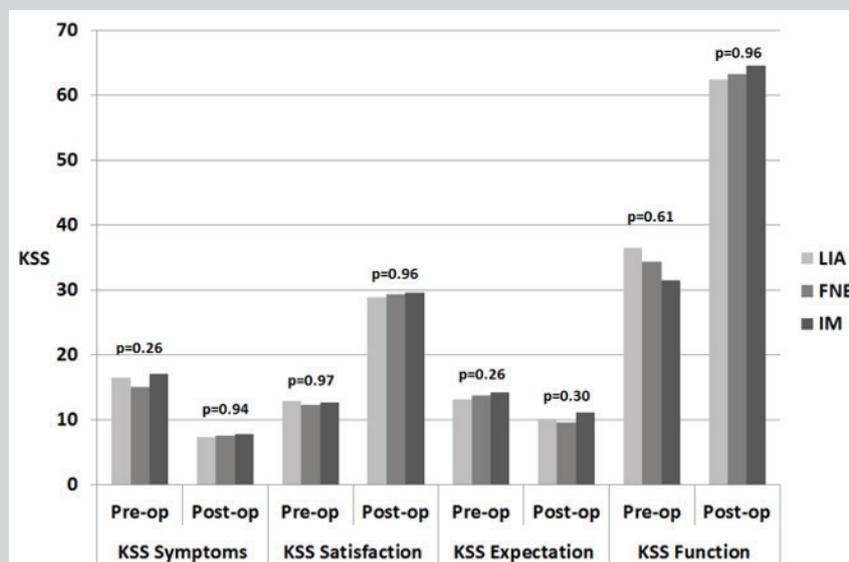
The results of this study do not demonstrate any significant differences between local infiltration analgesia, femoral nerve block or intrathecal morphine for providing post-operative analgesia or reducing additional opiate consumption and side effects. In

addition, there were no differences in post-operative rehabilitation.

The results of other studies investigating the analgesia effects of these techniques have produced conflicting results. Comparing LIA with placebo, Williams et al did not demonstrate any significant benefit of a continuous intra-articular bupivacaine

infusion compared with placebo for reducing pain scores, opiate consumption, opioid side effects, length of stay or knee function [8]. In contrast, Ali et al identified lower pain scores in the first post-operative day with a continuous ropivacaine infusion *versus* placebo [5]. However, there was no difference in additional opiate consumption, knee function or length of stay. A meta-analysis

by Zhang et al. [9] analyzing seven studies comparing LIA with placebo also concluded that LIA appeared to offer better post-operative analgesia. However, there are concerns that LIA may be associated with an increased risk of deep infection, possibly relating to colonization of the infusion catheter.



**Figure 3:** KSS scores pre-operatively and 6 weeks post-operatively.

Comparing LIA with FNB, Mei et al. [10] demonstrated lower pain scores with FNB upon movement but otherwise no significant differences in pain scores at rest, or opioid consumption at 24 hours were identified. In contrast, Yun et al demonstrated better pain scores at 6 hours post-operatively with LIA when compared with FNB, although this effect was not sustained at 24 hours [11]. Antoni et al. [12]; Stathellis et al. [13] both demonstrated better post-operative analgesia with LIA when compared with FNB, with quicker rehabilitation and shorter hospital stay. Zinkus et al. [14] did not demonstrate any difference in analgesic effects between LIA and FNB. However, they identified reduced opiate consumption and improved knee function with LIA at 1 week and 1 month post-operatively. Interestingly, a study by Reinhardt et al. [15] comparing LIA with a combination of FNB and IM, concluded that LIA was less effective for providing post-operative analgesia but improved rehabilitation probably due to retained quadriceps strength. Chang et al. [16]; Kunopart et al. [17] have also demonstrated that combining IM with FNB improves post-operative analgesia and reduces additional opiate consumption, highlighting the benefit of utilizing a multi-modal approach.

Several studies have also compared FNB with IM. Olive et al demonstrated an inferior analgesic effect and poorer mobility with IM compared with FNB, with more patients reporting pruritus [18]. In contrast studies by Sundarathiti et al. [19]; Tarkkila et al. [20]; Frassanito et al. [21] identified better pain control with IM over FNB, although opiate side effects were again more prevalent in the IM group. In a study by Sites et al there was no difference in analgesic effect or additional opiate consumption between IM and FNB [22]. However, the increased risk of opiate side effects with IM resulted in poor patient treatment satisfaction.

A greater risk of opiate side effects with IM have also been shown in studies comparing IM with LIA. Tammachote et al. [23]

did not demonstrate any significant difference in analgesia effect between LIA and IM but more patients in the IM group complained of nausea, vomiting and pruritus. Similarly, a meta-analysis by Jia et al identified that LIA appeared to provide superior analgesia with fewer side effects [24]. Essving et al. [25] also compared LIA with IM and identified that LIA provided better analgesia, reduced additional opiate consumption and facilitated quicker recovery with shorter length of stay and better patient satisfaction compared with IM. However, they did not notice any difference in opiate side effects.

This study has several limitations. Firstly, due to the limited funding available and recruitment, this study may be underpowered. Nonetheless we believe the methodology of this study to be robust, with placebo controls and blinding as strengths to reduce the risk of bias. It is also important to recognize that significant variation exists in clinical practice regarding the types of local anesthetics used, their dosage, additional drug combinations, delivery sites and techniques. In this study a low dose femoral nerve block was selected to minimize the effect on motor function and post-operative mobilization. However other techniques, such as adductor canal blocks are also becoming popular due to their minimal motor blockade. As a result, it is not possible to investigate every possible approach. Furthermore, a multi-modal approach to delivering post-operative analgesia may be more important and effective than relying on any one individual technique, by capitalizing on multiple mechanisms of action and enabling the use of lower doses to reduce potential side effects.

## CONCLUSION

This study did not identify any significant differences between local infiltration analgesia, femoral nerve block and intrathecal morphine for delivering post-operative analgesia following total knee arthroplasty. We therefore recommend that the technique of

analgesia employed be based on surgeon preference and tailored to individual patients in light of their suitability for spinal anesthesia, estimated tolerance to rehabilitation regimens, infection risk and past susceptibility to opiate side effects.

**TRIAL REGISTRATION NUMBER:** ID ACTRN12613000983707. The study was registered with the Australian New Zealand Clinical Trials Registry.

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