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Brooke A. Bonnette

Philadelphia College of Osteopathic Medicine, brookebo@pcom.edu

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Is Local Infiltration Analgesia (LIA) a Safe and Effective Method for Post-Operative Pain Management after a Unilateral Total Knee Arthroplasty (TKA)?

Brooke A. Bonnette, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

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In

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Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
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ABSTRACT

OBJECTIVE: The objective of this systematic review is to determine whether or not local infiltration analgesia (LIA) is a safe and effective method for post-operative pain management after a unilateral total knee arthroplasty (TKA).

STUDY DESIGN: Review of three English language primary studies published in 2010 and 2011.

DATA SOURCES: Three randomized controlled trials comparing local infiltration analgesia to three separate controls: epidural analgesia, placebo infiltration and femoral nerve block found using PubMed.

OUTCOMES MEASURED: Clinical outcome was measured by total morphine use postoperatively and average knee pain intensity at rest and upon movement postoperatively. Total morphine use in milligrams used postoperatively was determined by amount used via IV PCA pump; each study differed upon postoperative follow-up periods. Average knee pain intensity at rest and upon movement was measured by subjective average VAS/NRS scores (0-100 mm visual analog scale; 0 = no pain, 100 = worst pain imaginable). Studies varied among postoperative time periods when VAS score was recorded from each patient. Data was analyzed with Mann-Whitney U-test.

RESULTS: In the study by Affas et al, LIA was found to have similar analgesic effects measured by average pain intensity and average total morphine use during first post-operative 24 hours, as the control femoral nerve block technique, but not to the point of statistical significance. In the study by Essving et al, the LIA group had a median morphine consumption during the first 48 hours postoperatively statistically significantly less than the placebo group. LIA also proved to have statistically significantly lower median VAS pain scores than the placebo group postoperatively. In the study by Andersen et al, morphine consumption and average VAS scores at rest and during mobilization were statistically significantly lower in group A (LIA) versus the control group (epidural analgesia).

CONCLUSIONS: The results of two of the RCTs show local infiltration analgesia to be an effective method for post-operative pain management after a unilateral TKA (Essving and Andersen).^{6,7} One RCT does not reach statistical significance (Affas).⁵ Safety of LIA was demonstrated with minimal ADR's in all RCTs.^{5,6,7}

KEY WORDS: Local infiltration analgesia, Total Knee Arthroplasty

INTRODUCTION

Total knee arthroplasty (TKA), also known as a total knee replacement, is a common orthopedic procedure performed to treat pathologic conditions of the knee for pain relief and restoration of knee mobility and function.¹ This paper encompasses three randomized controlled trials comparing the efficacy of local infiltration analgesia (LIA) as a post-operative pain management technique with femoral nerve block, placebo injections and epidural infusions. The consideration of pain relief management post-operatively for patients undergoing a total knee arthroplasty is an important topic to discuss in regards to the increasingly common nature of TKA among our aging population and the rise in physician assistant employment in the field of orthopedics. According to the Agency for Healthcare Research and Quality, more than 600,000 knee replacements are performed each year in the United States.² Not only are total knee arthroplasties extremely commonplace nowadays, the price for the surgery on a single knee is practically unaffordable without health insurance. The average cost in the United States for a unilateral total knee arthroplasty (TKA) ranges from \$45,000- \$70,000 with no health insurance.³ Usually, total knee arthroplasty is the last resort in management of patients with medical conditions that typically lead to deterioration of the essential hinge joint. The primary pathologic conditions that commonly predispose patients to necessitating TKA include osteoarthritis (idiopathic and post-traumatic), rheumatoid arthritis, psoriatic arthritis, avascular necrosis, tumors or congenital deformities.¹ Common indications for TKA primarily include pain relief (significant and disabling pain that reduces patients' quality of life), correction of significant deformity, older patients with modest activity levels and younger patients who have limitation of function due to systemic arthritis.⁴ The decision to undergo the a TKA is ultimately made between the patient and the orthopedic surgeon performing the procedure.

In the realm of pain control and anesthesia, a total knee arthroplasty has a few options and approaches that can be taken in order for a patient to undergo the operation. Currently, patients undergo TKA with regional or general anesthesia. The decision to use regional or general anesthesia is decided among the patient and surgical team as well as taking the patient's medical condition into consideration for the best outcome.⁴ Epidural anesthesia and femoral nerve blocks have been the primary methods of analgesia for patient's undergoing TKA. Epidural anesthesia has been shown to prevent the development of fewer DVT's and the constant indwelling catheter provides better pain relief control post-operatively as compared to other analgesic methods.⁴ Continuous femoral nerve block with perineural ropivacaine 0.2% is shown to reduce pain, lower morphine use post-operatively and decrease time to discharge following TKA as opposed to placebo methods.⁴

The proposed method of treatment for TKA post-operative pain is effective, easy to administer and evidence supports its superiority to traditional pain control methods. Local infiltration analgesia (LIA) is an analgesic method administered intra- and periarticularly during the TKA operation (with ropivacaine, ketorolac and epinephrine).^{5,6,7} LIA is shown among the three RCT's to provide comparable or superior pain relief and decrease morphine consumption postoperatively in patients undergoing unilateral TKA in comparison to the traditional pain relieving methods.^{5,6,7}

OBJECTIVE

The objective of this systematic review is to determine whether or not local infiltration analgesia (LIA) is a safe and effective method for post-operative pain management after a unilateral total knee arthroplasty (TKA).

METHODS

In order to find adequate information for the research of this topic, a set of criteria was used for selection of contributory studies. The populations in the studies encompass male and female patients undergoing unilateral total knee arthroplasty, over age 18. The common intervention among all of the studies includes the objective intervention being studied, local infiltration analgesia (LIA). The comparison interventions in each of the three randomized controlled trials to local infiltration analgesia (LIA) includes femoral nerve block with ropivacaine directly after spinal anesthesia, no injections given intra-operatively and epidural infusion (4 mL/h) of 192 mL ropivacaine (2 mg/mL) combined with 6 intravenous administrations of 0.5 mL ketorolac (30 mg/mL) for 48 h postoperatively, respectively.

All three studies utilized for research are randomized controlled trials (RCT). Data sources for the systematic review were selected from PubMed and the Cochrane Library. Key words used to search for the articles included “total knee arthroplasty” and “local infiltration analgesia”. All articles were published in peer-reviewed journals and in English. Articles were selected on their clinical relevance and inclusion of my selected patient-oriented evidence that matters (POEMS), specific to my clinical question. Inclusion criteria for the studies are patients > 18 years of age scheduled for elective, unilateral total knee arthroplasty.^{5,6,7} Exclusion criteria encompasses hypersensitivity to study drugs, serious liver, heart or renal disease, epilepsy, mental disorder, language difficulty, dementia, QT interval on ECG > 450 msec before start, inflammatory joint disease, chronic pain, bleeding disorder, contraindications to spinal anesthesia and epidural analgesia, regular narcotic use, drug-treated diabetes, neuropathic pain or sensory disorders in the leg to be operated on, RA, pregnancy, severe obesity (BMI > 40),

treatment with tricyclic antidepressants, antiepileptic drugs and/or antacids.^{5,6,7} A summary of the statistics reported or used in the three randomized controlled studies include RRR, ARR, NNT and p-values.

Table 1: Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Affas ⁵ (2011)	RCT	40	67 ± 21-38 years	Patients with osteoarthritis or rheumatoid arthritis scheduled for primary unilateral elective total knee arthroplasty under spinal anesthesia, American Society of Anesthesiologists (ASA) classification I-III, and more than 18 years old	Allergy or intolerance to one of the study drugs, Renal insufficiency, Epilepsy, Language difficulty, Mental illness, Dementia, QT interval on ECG > 450 msec before start	0	Group LIA: received peri- and intra-articular infiltration with ropivacaine + ketorolac and epinephrine
Essvin ⁶ (2010)	RCT (double-blind)	48	70 ± 9 years	Patients scheduled for total knee arthroplasty (TKA) because of osteoarthritis age 20-85 years old, ASA I-III and normal preoperative mobility	Known allergy or intolerance to one of the study drugs, Serious liver, heart or renal disease, Inflammatory joint disease, Chronic pain, Bleeding disorder	1	<u>Group A:</u> 400 mg ropivacaine, 30 mg ketorolac, and 0.5 mg epinephrine were infiltrated periarticularly during operation → 21 hr postoperatively: 200 mg ropivacaine, 30 mg ketorolac, and 0.1 mg epinephrine were injected intraarticularly
Andersen ⁷ (2010)	RCT	40	67 ± 5 years	40 patients > 18 years of age undergoing elective, unilateral, primary TKA	Hypersensitivity to study drugs, Contraindications to spinal anesthesia and epidural analgesia, regular narcotic use, general anesthesia, Inability to communicate in Danish, Drug-treated diabetes, Neuropathic pain or sensory disorders in the leg to be operated on, RA, Pregnancy, Severe obesity (BMI > 40), Treatment with tricyclic antidepressants, antiepileptic drugs and/or antacids	7	<u>Group A:</u> intraoperative wound infiltration with 150 mL ropivacaine (2 mg/mL), 1 mL ketorolac (30 mg/mL) and 0.5 mL epinephrine (1 mg/mL) (total volume 152 mL) combined with intra-articular infusion (4 mL/h) of 190 mL ropivacaine (2 mg/mL) plus 2 mL ketorolac (30 mg/mL)

OUTCOMES

The outcomes of the studies that were measured included total morphine used postoperatively and the average knee pain intensity at rest and upon movement postoperatively.

The outcomes were measured by total PCA-morphine consumption recordings during specific intervals in the postoperative period and with an average pain assessment VAS/NRS score (0-100 mm VAS) at rest and upon movement (analyzed with Mann-Whitney U-test).

RESULTS

The three randomized controlled trials chosen for this systematic review compare local infiltration analgesia (LIA) against three differing control interventions: femoral nerve block, placebo injections and epidural analgesia.

The first study (Affas et al) was conducted over a twenty-four hour period postoperatively from an elective TKA. Forty patients were randomized into either experimental group LIA, receiving peri- or intra-articular infiltration analgesia with a mixture containing 150 mL ropivacaine (2 mg/mL), 1 mL ketorolac (30 mg/mL) and 5 mL epinephrine (0.1 mg/mL) or group F, in which patients received a femoral nerve block directly after spinal analgesia [30 mL ropivacaine (2 mg/mL) was injected followed by 15 mL of the same concentration every 4 hours for 24 hours (total dose 240 mg/24 hours)].⁵ The primary outcome for this study was average pain intensity 24 hours postoperatively between group LIA and group F; measurements were recorded using NRS (numeric rating scale) from 0-10 (0 = no pain and 10= worst pain imaginable), on an hourly basis postoperatively if the patient was awake. If the patient were asleep, the NRS score was recorded as a "0".⁵ The secondary outcome, or total morphine use 24 hours post-TKA was quantified by the intravenous PCA pump and analyzed by the Mann-Whitney U-test.

All of the 40 patients who entered the study completed the operation and trial. Data was analyzed under strict intention-to-treat (sITT).⁵ A value of $p < 0.05$ was chosen to indicate statistical significance and confidence intervals of 95%. For the primary outcome of the study

comparing average pain NRS at rest and upon movement, the study revealed similar low average pain intensity scores at rest among Group F and group LIA. Group F had an average NRS score at rest of 2.1 (95% CI: 1.4-2.9) compared to group LIA with 1.6 (95% CI: 1.0-2.3) (Table 2). However, average pain NRS at rest was slightly lower in group LIA, the small difference did not show statistical significance (p-value not reported). The average pain NRS upon movement between groups F and LIA similarly showed comparable results, and therefore not yielding statistical significance between the control and experimental. The secondary outcome, total morphine (in milligrams) consumption in the first 24 hours postoperatively, also yielded similar amounts in both groups, indicating similar analgesic effects for both methods and did not reach statistical significance.⁵ Total morphine (mg) per kilogram in group F was 0.4 (95% CI: 0.3-0.5) whereas group LIA was 0.3 (95% CI: 0.2-0.4). Statistical significance was found for an NRS score greater than 7 upon movement, as for group LIA, only 1 of 20 patients compared to group F where 7 of 19 patients reported these values (p-value 0.04). Further studies need to be conducted to explore and confirm this clinical finding.⁵ The Number Needed to Treat was calculated to be 4, therefore for every 4 patients, 1 more patient had reduced pain intensity (NRS score) at rest as compared to the control or femoral block analgesia (Table 4).

Table 2: Primary outcome comparing average pain NRS at rest and upon movement between femoral block and LIA⁵

	Femoral block (n= 20)	LIA (n= 20)
Average pain NRS at rest	2.1 (1.4-2.9)	1.6 (1.0 -2.3)
Average pain NRS upon movement	2.4 (1.5 – 3.2)	2.4 (1.7- 3.0)

Table 3: Secondary outcome comparing total morphine use (mg) between femoral block and LIA⁵

	Femoral block (n=20)	LIA (n = 20)
Total morphine (mg)	32 (23-41)	24 (16-31)
Total morphine (mg/kg)	0.4 (0.3 – 0.5)	0.3 (0.2 – 0.4)

Table 4: Pain intensity (NRS) at rest (throughout 24 h observation)

CER	EER	Relative risk reduction (RRR)	Absolute risk reduction (ARR)	Number needed to treat (NNT)
35%	60%	71.4%	60% - 35% = 25%	1/25% = 4

The second study (Essving et al) was conducted over a 3-month period postoperatively.

The 48 patients were randomized into group A (LIA) and group P (placebo) by the hospital pharmacy (each group containing 24 patients); group A received 400 mg ropivacaine, 30 mg ketorolac and 0.5 mg epinephrine periarticularly during the TKA and group P, no injections were given. Twenty- one hours postoperatively, group A received 200 mg ropivacaine, 30 mg ketorolac and 0.1 mg epinephrine intraarticularly and group P received the same volume of saline.⁶

One of the 48 randomized patients in group P was withdrawn from the analysis of the study due to disorientation postoperatively. Results were deemed statistically significant at a p-value <0.05. Statistical significance was found for the primary endpoint of median morphine consumption during the first 48 hours postoperatively in group A versus group P (p < 0.001) with a median difference of 69 mg (95% CI: 47-86) (Table 5).⁶ The secondary endpoint, median VAS pain score at rest and upon movement, was also found to be statistically significantly reduced in group A compared to group P (Table 6).⁶ The pain intensity scores were recorded at 3, 6, 12, 21, 22 and 27 hours postoperatively.

Table 5: Consumption of analgesics⁶

	Group A median (range)	Group P median (range)	p-value
Morphine IV (mg)			
0-24 hrs	17 (1-74)	65 (36 -131)	< 0.001
24-48 hrs	0.5 (0-17)	22 (0-52)	< 0.001
0-48 hrs	18 (1-74)	87 (36-160)	< 0.001
Tramadol orally (mg)			
0-24 hrs	0 (0-200)	0 (0-100)	0.01
24-48 hrs	375 (0-400)	200 (0-200)	0.04
0-48 hrs	400 (0-500)	200 (0-500)	0.008
Total analgesics^a (mg)			
0-48 hrs	54 (4-114)	109 (37 -211)	< 0.001

^aTotal analgesic consumption was calculated by converting oral tramadol to the equivalent dose of IV morphine (100 mg tramadol orally = 10 mg morphine IV).⁶

Table 6: Postoperative pain ratings VAS (0-100 mm) significance at rest and on flexion 60° between Group A and Group P⁶

Time (hrs) post-operative	VAS at rest (p-value)	VAS on flexion 60° (p-value)
3	< 0.001	< 0.001
6	< 0.001	< 0.001
12	< 0.001	< 0.001
21	0.005	N/A
22	0.003	< 0.001
27	0.002	0.005

The third and final study (Andersen et al) exhibits efficacy of LIA by demonstrating reduced morphine consumption and pain intensity postoperatively (48 h following TKA) as compared to the control group which employed continuous epidural infusion combined with intravenous ketorolac treatment. Of the 40 patients in the study, 21 were analyzed in group A [intraoperative wound infiltration with 150 mL ropivacaine (2 mg/mL), 1 mL ketorolac (30 mg/mL), and 0.3 mL epinephrine (1 mg/mL) combined with intraarticular infusion (4 mL/h) of 190 ropivacaine (2 mg/mL) plus 2 mL ketorolac (30 mg/mL)] compared to group E which received epidural infusion [(4 mL/h) of 192 mL ropivacaine (2 mg/mL) combined with 6 intravenous administrations of 0.3 mL ketorolac (30 mg/mL)] for 24 hours postoperatively.⁷ The statistical analysis used p-values to determine significance at 3 different time intervals in the post-operative period and showed statistical significance for the reduction in pain intensity scores and morphine consumption in favor of LIA therapy. P-values of <0.05 were considered statistically significant. Morphine consumption during the 0-48 hour postoperative period was statistically significantly reduced in group A compared to group E with a p-value of 0.01 (Table 7).⁷ Pain intensity was measured using a visual analog scale (VAS) scoring from 0-100 mm at select intervals postoperatively. The experimental group A was found to have statistically significant reduction in pain intensity postoperatively at rest and upon movement at 2-24 hours, 24-48 hours, and 48-72 hours postoperatively (Table 8).

Table 7: Total Morphine consumption postoperatively (mg)⁷

Time Postoperatively	Group A (n=21)	Group E (n= 19)	p-value
0-24 h	7.5 (2.5-15)	18 (13-32)	0.05
24-48 h	5 (0-8.8)	15 (5-23)	0.03
0-48 h	11 (3.8 – 23)	33 (20-40)	0.01

Table 8: Pain Intensity score (VAS, 0-100 mm) at rest and during walking postoperatively⁷

	Group A (n =21)	Group E (n= 19)	p-value
Rest: 2-24 h	7 (3-25)	30 (10-44)	0.009
24-48 h	5 (2-21)	33 (9-38)	0.02
48-72 h	7.5 (2.5-21)	23 (14-42)	0.02
Walking: 2-24 h	13 (4-41)	37 (12-53)	0.05
24-48 h	14 (7-35)	41 (27-51)	0.02
48-72 h	17 (4.5-36)	41 (24-53)	0.02

SAFETY

In the study by Affas et al, it was reported that none of the patients in the study endured cardiac side effects to either of the control or experimental interventions (no patients had prolonged QT interval at the ECG 2 hours and 24 hours postoperatively).⁵ In the study by Essving et al, no major surgical complications were reported, as well as a statistically significant lower incidence of nausea, pruritus and sedation in group A compared to group P (Table 9).⁶ The most common side effect, nausea, had a number needed to harm (NNH) of -3, which means for every 3 people treated with LIA, one less person experiences nausea as compared to the placebo. Table 9 displays others adverse events of LIA therapy compared to the placebo. A negative NNH value actually correlates with fewer ADRs for the experimental compared to the control. In the study by Andersen et al, the adverse events reported included nausea, vomiting, and pruritus, and were similar between both control and experimental groups.⁷ Group A (LIA) had significantly lower incidence of constipation (p= 0.004) and shorter time with urinary retention (p= 0.03).⁷ One patient in Group A also developed a deep infection after spinal abscess; two patients in group E were treated with antibiotics due to wound complications during the follow-up period.⁷

Table 9: Analysis of ADRs among placebo and experimental group in RCT by Essving et al⁶

Side effect (0-24 hrs)	Relative Risk	Absolute Risk	Number Needed to	P-value
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post-operatively)	Increase (RRI)	Increase (ARI)	Harm (NNH)	
Nausea (0-24 hrs)	-0.46	-32.5	-3	0.03
Vomiting (0-24 hrs)	-0.46	-0.18	-6	0.2
Pruritus (0-24 hrs)	-0.9	-0.35	-3	0.004
Sedation (0-24 hrs)	-1	-0.22	-5	0.02

DISCUSSION

This systematic review investigated three randomized controlled trials for the safety and effectiveness of local infiltration analgesia as a postoperative pain management method after unilateral TKA. The studies by Essving et al and Andersen et al demonstrated local infiltration analgesia as a safe and effective means of postoperative pain management. Statistical significance was not reached in the study conducted by Affas et al, however, a NNT of 4 and paucity of adverse reactions demonstrates LIA as a safe and efficacious method of postoperative analgesia.⁵

Local infiltration analgesia (LIA) is a multimodal method of postoperative pain management following lower extremity orthopedic surgical procedures (total knee and hip arthroplasties).⁸ This analgesic technique has gained attention and popularity among the orthopedic world since its introduction by Kerr and Kohan in 2008.⁸ Currently, the most commonly used methods of intraoperative analgesia during a TKA include an indwelling epidural catheter and long-acting femoral nerve blocks. Epidural analgesia has proved its efficacy as a postoperative pain management method following TKA, however not without common side effects including urinary retention, hypotension and muscular weakness.⁵ Femoral nerve blocks provide adequate postoperative analgesia as well, but can cause an unpleasant numbness of the lower extremity.⁵ Local infiltration analgesia has been called into question, regarding a safe plasma level for the combination of local anesthetic agents infiltrated peri- and intraarticularly.⁸ Concerns have also been presented regarding the risk of infection with the presence of an indwelling intra-articular catheter. In the study by Essving et al, none of the

patients had any evidence of systemic analgesic toxicity and no evidence of postoperative infections in the 3-month follow-up period presented, helping reassure the questions of the LIA method's safety.⁶

A limitation of the RCTs chosen for this systematic review is the lack of detail regarding significant side effects and safety of the LIA therapy drugs. Another limitation of the RCTs chosen were the sample sizes; each of the RCTs had between 40-48 patients participating, which in the future, may necessitate further studies to solidify the evidence of LIA efficacy. Also, only one of the RCTs was double-blinded, where two studies were not (Affas and Andersen), which may have interfered with the patients and operators postoperative expectations.

CONCLUSION

Statistical significance for local infiltration analgesia's superiority to femoral nerve block analgesia was not seen statistically in the RCT by Affas et al, however the other two RCTs (Essving and Andersen) indicated that LIA provided safe and effective postoperative pain management compared to placebo infiltration and epidural analgesia (statistical significance $p < 0.05$).^{5,6,7} Therefore, I agree with such studies in that local infiltration analgesia is a safe and effective method for postoperative pain management after unilateral total knee arthroplasty, as revealed by this review. Future studies should focus on accumulating more participants to increase credibility of the study as well as delve further into determining the appropriate dose for patient safety of the locally infiltrated analgesic agents. Due to the rapidly increasing average age of our US population, total knee arthroplasties have become a prevalent surgical procedure in our society. The low cost of LIA and ease of administration should also be taken into consideration when the surgical team and patient are consulting regarding postoperative pain management.

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