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RESEARCH ARTICLE **OPEN ACCESS**

Efficacy and Adverse Effect of Continuous Femoral Nerve Block and Intrathecal Morphine with Patient-Controlled Epidural Analgesia Post-total Knee Arthroplasty: A Randomised Controlled Trial

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Abstract:

Introduction: Achieving adequate analgesia after total knee arthroplasty (TKA) can be a challenging task. This study investigates the efficacy and adverse effects of continuous femoral nerve block using a patient-controlled analgesia machine (FNB-PCA) in comparison to intrathecal morphine (ITM) with patient-controlled epidural analgesia (PCEA) using bupivacaine in patients undergoing unilateral TKA under spinal anesthesia.

Materials and Methods: Forty patients with ASA I-II scheduled for unilateral TKA were randomized into two groups. Group ITBM+Ep received 250 mcg of intrathecal morphine and 15 mg of hyperbaric bupivacaine, and group ITB-FNB received FNB with 30 ml of 0.375% Bupivacaine with 5 mcg/ml of epinephrine with 15 mg bupivacaine administered intrathecally. Post-operative analgesia for group ITBM+Ep was maintained by PCEA with bupivacaine, while group ITB-FNB used PCA. Visual analogue scales (VAS) on rest and movement, hemodynamics, and side effects were recorded post-operatively.

Results: A decrease in VAS at rest between group ITBM+Ep and ITB-FNB from the 24^{th} - 48^{th} hour was statistically significant ($P<0.05$). VAS on movement showed no statistical difference between both groups from the 1^{st} until the 6^{th} hour ($P >0.05$), but VAS was significantly different starting the 12^{th} hour ($P <0.05$). Group FNB was associated with less hypotension, nausea, vomiting, and pruritus ($P <0.05$).

Conclusion: This study concludes that ITB-FNB-PCA provides superior analgesia on rest and movement with a significant reduction in side effects in comparison to ITBM+Ep with PCEA for patients who underwent TKA. Further trials comparing different anesthetic techniques with larger sample sizes are necessary to establish “gold standard” management after TKA.

Clinical Trial Registration Number: 194/K-LKJ/ETIK/VI/2022

Keywords: Arthroplasty, Bupivacaine, Epidural, Femoral, Intrathecal, Morphine.

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1. INTRODUCTION

Achieving adequate analgesia after total knee arthroplasty (TKA) can be a challenging task. Patients often experience severe pain, which relates to complications including immobility, prolonged hospital stay, and poor functional outcomes, as well as reduced patient satisfaction [1, 2]. Regional anesthesia techniques have been shown to be effective in suppressing surgical stress

response, including pain, based on metabolic, hormonal, and hemodynamic parameters [3]. This includes the use of peripheral nerve blocks and neuraxial techniques.

Epidural analgesia has been gaining popularity as an anesthetic modality in orthopaedic surgery [4, 5]. A systematic review comparing epidural blockade and systemic opioid analgesia has found that epidural blockade correlates with less complications post-operatively, including less blood loss and thromboembolic compli- cations [6]. However, patients with a history of using anticoagulants may limit the options for epidural analgesia. Intrathecal morphine (ITM) may also be used to improve postoperative analgesia after TKA. ITM has been shown to be associated with several adverse effects, including postoperative nausea and vomiting, pruritus, and urinary retention [7].

Peripheral nerve blocks with or without the use of a continuous catheter offer an alternative to neuraxial techniques, which may be safer in the setting of peri-operative anticoagulation with efficacy at least equal or superior to that of epidural analgesia [8]. Femoral nerve block (FNB) is a commonly used technique in patients undergoing TKA due to its simplicity, low risk of complications, and high success rate. When used alone, FNB is performed on the anterior aspect of the thigh and for postoperative analgesia in femur and knee surgery [9-11].

Providing analgesia after TKA is pivotal as it relates to complications and patient dissatisfaction. Despite TKA being commonly performed, pain after TKA remains a major concern without a “standard” anesthetic manage- ment plan [12]. Therefore, this study aims to investigate and compare the effectiveness and side effects of ITM and continuous FNB for pain management after TKA.

2. METHODS

This study was approved by Institutional Research Ethics (approval number 194/K-LKJ/ETIK/VI/2022). This study was conducted in a hospital in Tangerang, Indonesia, from August to December 2022. Written and verbal consent was given by all participants following a thorough explanation of the procedure and research. This study was conducted in accordance with ethical standards as written in the Declaration of Helsinki. Forty patients with ASA I-II scheduled for single TKA were enrolled in the clinical study. Patients were excluded if they were <40 or >80 years old, ASA III-IV, had a history of allergy to local anaesthetics, had a history of opioid dependence, or had contraindications for spinal anaesthesia and femoral nerve block. Patients were excluded if a failed femoral nerve block or intrathecal anaesthetic was experienced. Demographic data included gender, age, weight, height, and the ASA physical status classification was recorded for each patient. The Consort flow diagram is presented in the Supplementary material.

Patients were randomized and placed into two groups, which was performed using graphpad software. The patient was given 1-2 mg of midazolam intravenously. Patients were positioned in the lateral decubitus position to conduct the intrathecal blocks in the L3-L4 or L4-L5 interspace. ITBM+Ep group was administered 250 mcg of intrathecal preservative-free morphine and 15 mg of hyperbaric bupivacaine. An epidural catheter was also inserted using a G18 Touhy needle at L2-L3 level using loss of resistance technique, and the catheter was threaded into the space 3-5 cm.

The second group received a continuous femoral nerve block prior to the intrathecal injection (group ITB-FNB). After generous skin and subcutaneous tissue infiltration of local anesthetic agent, a Gauge 20-Touhy needle (Contiplex, BBraun) with an electrode at the bevel edge and a lead wire connected to a nerve stimulator unit was used. A high-frequency ultrasound transducer was placed on the femoral crease. The femoral nerve was then identified lateral to the femoral artery and between the two layers of fascia iliaca. The needle was then inserted, aiming at 30 to 45 degrees cephalad “in-plane” with ultrasound pointing towards the ASIS. The tip was then gradually advanced beyond the tip of the needle for a distance of approximately 3-5 cm. Identification of the femoral nerve was confirmed by the “patellar dancing” sign. Thirty ml of 0.375% Bupivacaine with 5 mcg/ml of epinephrine were injected slowly after aspiration. A sensory level of cold temperature was identified prior to performing an intrathecal blockade in the femoral nerve distribution. The patient was also administered 15 mg of hyperbaric bupivacaine intrathecally. Intrathecal blocks, placement of epidural catheter, and femoral nerve blocks were conducted by a single experienced anesthesiologist.

Estimated blood loss and surgery duration were recorded intraoperatively. In the post-anaesthetic care unit (PACU), the ITBM+Ep group was started on patient-controlled epidural analgesia (PCEA) bupivacaine when there was a regression of sensory blockade below T8 level and initial recovery of motor function. Bupivacaine PCEA 0.2% was started with the following settings: continuous infusion at 5ml/hr with PCA bolus of 3 ml with lockout setting of 20 minutes. The average duration of epidural analgesia was 48 hours. ITB-FNB group was provided with PCA-ITB-FNB with a continuous infusion of bupivacaine 0.125% 5 ml and a PCA dose of 2.5 ml with a lockout setting of 30 minutes, starting 6 hours after the initial FNB. Group ITB-FNB would receive a continuous infusion of local anaesthetic until 48 hours post-operatively. The site of the femoral catheter was examined daily for signs of infection and was then removed on the 2nd post-operative day.

While at the post-anesthetic care unit (PACU), a visual analogue scale (VAS) was used by nurse assistants to assess patients’ pain scales. All patients were given Ketorolac 30mg IV every 6 hours. Data were collected at 0, 1, 2, 4, 6, 12, 24, and 48 hours at rest and on movement post-operatively. Time 0 was the time at which the patient arrived in the PACU. Data included systolic blood pressure, where hypotension is defined as a more than 30% decrease in baseline systolic blood pressure reading. Patients were also asked on a numeric scale if they experienced nausea, vomiting, or pruritus. The scale was (1) none, (2) mild, (3) moderate, and (4) severe. Patients were also asked about the pain experienced using VAS. VAS was then categorised into 3 categories: *mild pain* with a VAS of 1-3, *moderate pain* with a VAS of 4-6, and *severe pain* with a VAS of 7-10. Postoperative nausea and vomiting were managed with

ondansetron 4 mg twice daily intravenously. Diphenhydramine 10 mg was administered intravenously to manage any pruritus experienced by patients.

Follow-up was conducted one week after discharge *via* teleconsultation or text by the nursing staff, where satisfaction regarding their anaesthetic experience was rated using a scale as follows: (1) unsatisfactory, (2) satisfactory, (3) very good, and (4) outstanding.

A minimum of 16 patients per group would provide 80% power for this study, as calculated using a power analysis. Univariate analysis was accomplished using Kruskall Wallis ANOVA, Fisher's Exact test, Chi-square, and Student's t-test. The correlation was considered significant if the *P* value was < 0.05.

3. RESULTS

Forty patients who underwent TKA in a tertiary hospital in Tangerang, Indonesia, during August-December 2022 were recruited in this trial. Twenty received spinal bupivacaine with continuous femoral nerve block, and 20 patients received spinal bupivacaine with ITM. The femoral nerve block was successful in all 20 patients. The demographics of patients enrolled in the two groups were similar (Table 1).

VAS scores at the different time intervals are shown in Table 2. There was no statistical difference from the VAS score at rest from the 1st hour until the 12th hour (P value >0.05). A decrease in VAS score at rest from the 24th until the 48th hour was statistically significant (P value <0.05). VAS score on movement showed that there was no statistical difference between the 2 groups from the 1st hour until the 6th hour (P value >0.05), but there was a statistical difference starting on the 12th hour until the 48th hour (P value <0.05). Patients from the ITB-FNB showed superior pain relief than the ITBM+Ep group.

Table 1. Patient demographics.

-	ITBM+Ep (n=20)	ITB-FNB (n=20)
Mean Age ± SD (years)	60±10	58±10
Height ± SD (cm)	170±12	168±10
Weight ± SD (kg)	59±9	61±9
Gender		
Male	8	10
Female	12	10
Intraoperative blood loss ± SD (ml)	260±90	250±86
Duration of surgery ± SD (min)	162±18	170±16
ASA class I/II		
ASA I	4	5
ASA II	16	15

Note: Values are mean (SD).

Table 2. VAS scores in ITBM+Ep with PCEA *vs* ITB-FNB (Student's t-test).

Time (hr)	ITBM+Ep Mean (SD)	ITB-FNB Mean (SD)	P value
VAS rest			
1	0.0 (0.0)	0.0 (0.0)	1.0000
2	0.7 (1.4)	0.9(2.0)	0.761
4	1.8(2.3)	1.9(1.5)	0.8715
6	2.3(2.5)	2.1(1.4)	0.7566
12	2.5(2.0)	2.6(2.5)	0.8896
24	3.3(2.7)	2.7(2.3)	0.0112
48	3.5(3.0)	3.0(2.8)	0.0097
VAS movement			
1	0.0 (0.0)	0.0 (0.0)	1.0000
2	1.1 (2.0)	1.1(2.0)	1.0000
4	2.6(2.7)	2.7(1.8)	0.8911
6	3.0(2.9)	3.1(2.0)	0.8997
12	3.8(2.4)	3.4(3.0)	0.0193
24	5.0(2.8)	4.5(2.8)	0.0202
48	5.9(3.5)	3.8(3.0)	0.0110

Note: Values are mean (SD).

Table 3. Post-operative side effects (Fischer's exact test and Chi-square).

-	ITBM+Ep (n=20)	ITB-FNB (n=20)	*P* value
***Hypotension**	15 (75)	10(50)	0.0138
Moderate-Severe Nausea	15(75)	3(15)	0.0005
Moderate-Severe Vomiting	16(80)	3(15)	0.0001
Moderate-Severe Pruritus	14(70)	1(15)	0.0001

Note: Values are number (%).
* <30% of baseline systolic blood pressure.

Table 4. Satisfaction 1 week post discharge.

-	ITBM+Ep (n=20)	ITB-FNB (n=20)
Outstanding	7	10
Very satisfied	6	8
Satisfied	3	2
Unsatisfied	4	0

Table **3** shows the side effects experienced in both groups. Incidence of hypotension, nausea, vomiting, and pruritus were more frequent in the ITBM+Ep group (P value <0.05). Administration of antiemetics and anti-pruritic medication were also more frequent.

During follow-up, 20% of patients in the ITBM+Ep group had an "unsatisfactory" experience. No patients in the ITB-FNB group were unsatisfied (Table **4**). All patients with unsatisfactory experience had nausea, vomiting, or pruritus post-procedure.

4. DISCUSSION

This study found that the VAS score at rest after TKA was significantly less at the 24th hour in group ITB-FNB compared to ITBM+Ep (2.7 *vs* 3.3, p=0.01). VAS score recorded during movement was also lower in group ITB-FNB at the 12th hour (3.4 *vs* 3.8, p=0.01). This shows that ITB-FNB provided superior analgesia in comparison to ITBM+Ep in patients who underwent TKA. Furthermore, post-operative side effects, such as hypotension, nausea, vomiting, and pruritus, were significantly lower in group ITB-FNB (10 *vs*. 15 (p=0.01), 13 *vs*. 15 (p<0.001), 3 *vs*. 16 (p<0.001), and 1 *vs* 14 (p<0.001) respectively). No patients in group ITB-FNB reported an "unsatisfactory" anesthetic experience, in comparison to four patients in group ITBM+Ep.

TKA often causes severe post-operative pain, which relates to immobility, prolonged hospital stay, poor functional outcomes, and patient dissatisfaction [1, 2]. Although TKA is a relatively common orthopedic procedure, pain management remains a challenge for anesthesiologists [12]. Various anesthetic techniques have been proposed and practiced over the years. However, consensus regarding the most effective analgesia with minimal side effects has yet to exist. Regional anesthesia, including neuraxial techniques and peripheral nerve blocks, are options that may be employed by anesthesiologists for patients undergoing TKA [3].

Existing literature has found that neuraxial techniques are appropriate for any lower extremity procedure in most patients. ITM is effective postoperative analgesia for major orthopaedic procedures [7, 13-15]. Adding morphine to an IT anesthetic is relatively simple to perform as its use does not require an additional procedure. However, this technique has a higher incidence of side effects, including hypotension, sedation, nausea, vomiting, pruritus, urinary retention, and delayed respiratory depression [7]. This aligns with the findings of this trial, which showed that group ITBM+Ep had a higher incidence of adverse effects, including hypotension, nausea, vomiting, and pruritus, in comparison to group ITB-FNB.

Peripheral nerve blocks with or without continuous catheter use offer an alternative technique to neuraxial techniques, which may be safer in the setting of peri-operative anticoagulation with efficacy at least equal or superior to that of epidural analgesia [2, 8-11]. This study demonstrates a similar finding where the effectivity of femoral nerve block has comparable effectivity for providing pain relief in patients after TKA by a significant reduction in VAS score following the 12th hour (at movement) and 24th hour (at rest). This study employs VAS to quantify and evaluate the analgesic effect of ITM and FNB. Using this scoring method may allow patients to compare differences in pain intensity. The VAS scoring system has been previously validated [16, 17]. The use of a femoral nerve catheter allows site-specific analgesia, which explains why lower VAS scores are documented in the ITB-FNB group. This technique also has no concerns about spinal hematoma, unlike continuous epidural analgesia [8]. FNBs are also relatively easy to perform and have a lower risk of complications. When used alone, it is well suited for surgery performed on the anterior aspect of the thigh and for post-operative management of knee surgery. However, a need for an indwelling catheter raises concerns as this may become a source of infection [18]. Placing a continuous catheter also requires expertise, which makes it relatively complex, subject to the

anesthesiologist's experience, and requires a longer duration to perform compared with a single injection procedure [19].

Prior studies comparing the efficacy and adverse effects of ITM and FNB in patients after TKA exist with varying results. A retrospective analysis involving 54 patients revealed that patients with ITM had lower pain scores and use of morphine post-operatively [20]. A meta-analysis conducted by Li *et al.* found that both FNB and ITM were equally effective modalities for pain control after TKA [8]. This differs from another meta-analysis conducted by Tang *et al.*, which found that ITM was associated with immediate analgesia and opioid-sparing effects [20]. Our results, however, revealed higher patient satisfaction in the ITB-FNB group, which may be attributed to this reduction in side effects and higher post-operative analgesia [21].

There are several limitations of this study. Confounding factors, including the success of physical therapy, amount of local anaesthetic consumed (PCA), time to discharge, anesthesiologist's experience, and cost analysis, were not analysed in this article. Furthermore, this study was limited by the resources available. Hence, a limited sample size with short follow-up data was available for analysis in this study. Adverse effects, including pain, nausea, vomiting, and pruritus, were categorically measured and were subject to patient bias. Further trials with larger sample sizes investigating various internal and external factors that may contribute to patients' satisfaction should be conducted to establish the use of ITB-FNB for managing analgesia after TKA.

CONCLUSION

This study concludes that ITB-FNB provided superior analgesia, with less complications, including hypotension, nausea, vomiting, and pruritus. Further trials with a larger sample size and investigation regarding other confounding factors that may affect patient satisfaction are necessary to establish the use of ITB-FNB as routine practice for managing patients undergoing TKA.

AUTHORS' CONTRIBUTIONS

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

TKA	=	Total Knee Arthroplasty
FNB	=	Femoral Nerve Block
PCA	=	Patient Controlled Analgesia
ITM	=	Intrathecal Morphine
PCEA	=	Patient Controlled Epidural Analgesia
VAS	=	Visual Analogue Scale

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethical Committee of Pelita Harapan University with registration number 194/K-LKJ/ETIK/VI/2022 on June 6, 2022.

HUMAN AND ANIMAL RIGHTS

All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Written and verbal consent was obtained from participants in this study.

STANDARDS OF REPORTING

CONSORT guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

SUPPLEMENTARY MATERIALS

Supplementary material is available on the Publisher's website.

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