International Journal of Surgery 36 (2016) 44–55

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Review

# Liposomal bupivacaine infiltration versus femoral nerve block for pain control in total knee arthroplasty: A systematic review and meta-analysis

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## HIGHLIGHTS

- A meta-analysis is performed to evaluate the efficiency of FNB compared with local LB for pain management after TKA.
- Only high quality studies were selected.
- LB infiltration could significantly reduce the morphine equivalents consumption compared FNB.

## ARTICLE INFO

*Article history:*
Received 17 July 2016
Received in revised form
28 September 2016
Accepted 6 October 2016
Available online 11 October 2016

*Keywords:*
Liposomal bupivacaine
Femoral nerve block
Total knee arthroplasty
Meta-analysis

## ABSTRACT

*Objective:* Total knee arthroplasty (TKA) usually results in postoperative pain. The objective of this meta-analysis was to compare the effectiveness and safety of liposomal bupivacaine (LB) infiltration and femoral nerve block (FNB) for pain control in total knee arthroplasty.
*Methods:* We systemically searched electronic databases, including Embase (1980–2016.7), MEDLINE (1966–2016.7), PubMed (1966–2016.7), ScienceDirect (1985–2016.7), Web of Science (1950–2016.7) and Cochrane Library for potentially relevant articles. All calculations were conducted using Stata 11.0.
*Results:* One randomized controlled trials (RCTs) and five non-RCTs involving 1289 participants met the inclusion criteria. The result of the meta-analysis revealed that there were no significant differences in terms of postoperative pain scores at POD 0 (SMD = −0.047, 95% CI: -0.276 to 0.182, P = 0.688), POD1 (SMD = −0.038, 95% CI: -0.273 to 0.197, P = 0.749) or POD 2 (SMD = −0.043, 95% CI: -0.192 to 0.107, P = 0.575). Significant differences were found between groups in morphine equivalent consumption at POD 1 (SMD = 0.625, 95% CI: 0.068 to 1.183, P = 0.028) and POD 2 (SMD = 0.410, 95% CI: 0.024 to 0.796, P = 0.037) between groups. There were no significant differences regarding the incidence of adverse effects such as nausea (RD = −0.01, 95% CI: -0.04 to −0.075, P = 0.914) or vomiting (RD = 0.006, 95% CI: -0.049 to 0.062, P = 0.821).
*Conclusions:* Liposomal bupivacaine infiltration provides similar postoperative pain relief to femoral nerve block following total knee arthroplasty. In addition, liposomal bupivacaine infiltration could significantly reduce the consumption of morphine equivalents compared to femoral nerve block without an increased risk of adverse events.


## 1. Introduction

Total knee arthroplasty is a common surgical treatment for patients experiencing osteoarthritis of the knee joint. It has been estimated that more than approximately 700,000 of these procedures have been performed in the United States [1]. Appropriate postoperative pain control is crucial for early ambulation and better functional outcomes that usually are achieved following postoperative rehabilitation [2–4]. Furthermore, optimal pain management may decrease the length of stay and the risk of adverse events, such as deep vein thrombus (DVT) and pulmonary embolism (PE).

Postoperative pain management has been a topic of interest for a few decades and remains controversial. Various attempts have been made including systemic opiates, local infiltration analgesia

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http://dx.doi.org/10.1016/j.ijsu.2016.10.007
1743-9191/

and patient-controlled analgesia with oral narcotics. Although they have been shown to be effective for pain relief, adverse effects, such as vomiting, respiratory depression, urinary retention and nausea may be associated with these analgesia methods [5,6].

Femoral nerve block (FNB) was reportedly reduces postoperative pain and is considered to be an effective way to manage perioperative pain and decrease opioid consumption; therefore it is widely used following TKA [7]. However, FNB has been criticized due to the associated weakness in quadriceps muscle strength which results in an increased risk of postoperative falls [8]. To avoid motor weakness, periarticular injections are also considered to be an alternative method for postoperative pain management following TKA. Generally, a local anaesthetic drug is used for wound infiltration to provide a pain relief. Liposomal bupivacaine (LB) is a long-acting, local anaesthetic that is administered via single-dose infiltration to produce postsurgical analgesia [9]. In the acting process, bupivacaine is encapsulated into multivesicular liposomes, resulting in a slow and controlled release from the liposomes. Liposomal bupivacaine has a long analgesia duration of 72 h, especially following TKA [10]. Currently, controversy surrounds which analgesia method is optimal. Therefore, we performed a meta-analysis to evaluate the efficiency and safety of liposomal bupivacaine infiltration compared to a femoral nerve block for pain control in total knee arthroplasty.

## 2. Methods

### 2.1. Search strategy

We systematically searched electronic databases including Embase (1980–2016.7), MEDLINE (1966–2016.7), PubMed (1966–2016.7), ScienceDirect (1985–2016.7), Web of Science (1950–2016.7) and Cochrane Library for potentially relevant articles. Grey academic studies were also identified from the references of identified studies. There was no language restriction. The following terms were used as key words in combination with Boolean operators AND or OR: "Total knee replacement OR arthroplasty", "Liposomal bupivacaine", "femoral nerve block" and 'pain control". The retrieval process is presented in Fig. 1.

### 2.2. Inclusion and exclusion criteria

Studies were considered eligible if they met the following criteria: 1) Published clinical randomized controlled trials (RCTs) or non-randomized controlled trials (non-RCTs); 2) Patients undergoing TKA surgery, where the experimental group received femoral nerve block for postoperative analgesia and the control group received topical use liposomal bupivacaine infiltration; 3) Reported surgical outcomes, including postoperative pain scores, morphine equivalent consumption, length of stay, and drug-related adverse effects, such as nausea and vomiting. Dosage and types of for femoral nerve block were not limited in our search process. Studies were excluded from the meta-analysis if they had incomplete data, cases report, and review articles.

### 2.3. Selection criteria

Two reviewers (XBM and WJZ) independently reviewed the abstracts of the potential studies. After an initial decision, the full text of the studies that potentially met the inclusion criteria were reviewed before a final decision was made. A senior reviewer was consulted in cases involving disagreement.

### 2.4. Data extraction

A standard form for data extraction was printed. Two reviewers independently extracted the relevant data from the included studies. When incomplete data were encountered, the corresponding author was consulted. The following data were extracted: first author names, publication year, study design, comparable baseline, anesthesia methods, dosage and type of anaesthetic drug and intervening procedures. Outcome parameters included the postoperative pain scores at different periods, the cumulative morphine equivalent consumption, length of stay, and drug-related adverse effects such as nausea and vomiting. Other relevant data were also extracted from individual studies.

### 2.5. Quality assessment

The quality assessment of the included studies was performed by two reviewers independently (XBM and WJZ). The modified Jadad score which was based on the Cochrane Handbook for Systematic Reviews of Interventions was used for the assessment of the RCTs. Studies with scores greater than four points were considered to be high-quality. We created a "risk of bias" table that included the following key points: random sequence generation, allocation concealment, blinding, incomplete outcome data, free of selective reporting and other bias. The Methodological Index for Non-Randomized Studies (MINORS) scale was used to assess non-RCTs with scores ranging 0 to 24. Consensus was reached through a discussion.

### 2.6. Data analysis and statistical methods

All calculations were completed in Stata 11.0 (The Cochrane Collaboration, Oxford, United Kingdom). Statistical heterogeneity was assessed based on the value of P and $I^2$ using a standard chi-square test. When $I^2 > 50\%$, $P < 0.1$ was considered to indicate significant heterogeneity. A random-effect model was used in the meta-analysis. Otherwise, a fixed-effect model was utilized. If possible, a sensibility analysis was conducted to explore the origins of the heterogeneity. The results of any test with a dichotomous outcomes was expressed as a risk difference (RD) with a 95% confidence interval (CI). For continuous outcomes, the mean difference (MD) or standard mean difference (SMD) with a 95% confidence interval (CI) was used in the assessment.

## 3. Results

### 3.1. Search results

A total of 288 studies were reviewed initially. After the title and abstract of each one was reviewed, 282 reports were excluded from the meta-analysis because they did not meet the inclusion criteria. No grey reference was obtained. Ultimately, six studies [11–16] that were published between 2015 and 2016 were included in the meta-analysis. Five of them were non-RCTs, whereas one was an RCT.

### 3.2. Risk of bias assessment

Demographic characteristics and details about the included studies are summarized in Table 1. The modified Jadad score, which was based on the Cochrane Handbook for Systematic Reviews of Interventions was used for the assessment of the RCTs (Table 2). For the RCT study, a clear inclusion and exclusion criteria were provided. In addition, a detailed randomization procedure was described. The randomization sequence was generated via computer. Allocate concealment was achieved using a sealed envelope.