Study protocol

Title:

Bupivacaine Liposome Plus Bupivacaine or Ropivacaine for PENG Block on Post Operative Pain Management in Patients Undergoing Hip Arthroplasty: a Prospective, Randomized, Single Blind, Active Controlled Study

Principal Investigator: Prof. Wei Mei

Institution: Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

Sponsor: Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

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1. Brief summary

The goal of this clinical trial is to study the analgesic effect of liposomal bupivacaine plus bupivacaine for PENG block in postoperative pain management following hip replacement surgery. It will also assess the safety of liposomal bupivacaine for this purpose. The main questions it aims to answer are:

1)Is liposomal bupivacaine plus bupivacaine superior to ropivacaine in terms of analgesic efficacy, duration of pain relief, opioid consumption, and patient satisfaction?
2) What medical problems do participants encounter when using liposomal bupivacaine plus bupivacaine for PENG block in postoperative pain management following hip replacement surgery?

Researchers will compare liposomal bupivacaine plus bupivacaine to ropivacaine (a routinely used regional anesthetic in clinical practice) to determine if liposomal bupivacaine plus bupivacaine is more effective for pain management following hip replacement surgery.

Participants will:
1) Receive liposomal bupivacaine plus bupivacaine or ropivacaine as a regional anesthetic for PENG block under ultrasound guidance.
2) Undergo hip replacement surgery under spinal anesthesia.
3) Have pain relief, opioid analgesic consumption, and incidence of complications assessed at multiple time points within 72 hours after surgery.

2. Background and rationale

Pain management plays a crucial role in the perioperative period. The concept of multimodal analgesia has become globally popular due to its ability to improve analgesic effects and reduce opioid use and associated side effects. Recently, several expert consensuses, such as the "Expert Consensus on Postoperative Pain Management in Adults (2017)," "Chinese Thoracic Surgery Perioperative Pain Management Expert Consensus (2018)," and "Chinese Expert Consensus on Multimodal Analgesia with Low Opioids in Elderly Patients during the Perioperative Period (2018)," unanimously emphasize the importance of multimodal analgesia. The core is to achieve optimal analgesic effects and reduce opioid dependence by combining different types of analgesic drugs and techniques in the perioperative period (1-3).

Local anesthetics and regional blocks are important components of multimodal analgesia. For large surgeries such as hip arthroplasty, multimodal analgesia has been recognized as an essential pain management strategy. Acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and local anesthetics such as bupivacaine and ropivacaine, through incision infiltration or peripheral nerve blocks, have been widely used to improve analgesic outcomes.

However, existing local anesthetics such as bupivacaine and ropivacaine, although effective, have a limited duration of action when administered as a single injection. In surgeries with moderate to severe postoperative pain, such as hip arthroplasty, these short-action local anesthetics may lead to postoperative breakthrough pain, posing higher demands for pain management. Currently, the use of sustained-release formulations or continuous catheter techniques could extend the duration of action of local anesthetics (4). Liposomal bupivacaine is an important innovation where this formulation encapsulates bupivacaine in multivesicular liposomes using DepoFoam technology, enabling slow drug release and effectively prolonging analgesia duration up to 72 hours (5). This ultra-long-acting local anesthetic offers clear advantages in reducing opioid use, enhancing analgesic satisfaction, reducing complications, and shortening hospital stays, and has been applied in the Enhanced Recovery After Surgery (ERAS) concept.

Liposomal bupivacaine, as the first approved ultra-long-acting local anesthetic, has gained broad international recognition. Several international guidelines, such as the 2017 ASCRS/SAGES Clinical Practice Guidelines for Enhanced Recovery After Colon Surgery, the 2017 ERAS Expert Consensus on Best Perioperative Management of Breast Reconstruction, the 2018 ERAS/ESTS Guidelines for Enhanced Recovery After Lung Surgery, and the 2019 ERAS Guidelines for the Perioperative Management of Gynecologic Cancer, all recommend the use of liposomal bupivacaine in multimodal analgesia (6-9). Liposomal bupivacaine achieves long-lasting analgesia with a single injection, reducing the need for postoperative continuous catheters, and avoiding catheter-related risks such as infection, catheter dislodgement, and migration (7). On November 30, 2022, liposomal bupivacaine injection was approved for market in China (National Drug Approval No. H20223899) (10).

The pericapsular nerve group (PENG) block is a new regional anesthesia technique that mainly targets the branches of the obturator nerve and femoral nerve to the hip joint capsule to provide effective analgesia for the hip joint (11). Its advantages include precise analgesia, quick onset, preservation of lower limb motor function. PENG block is typically performed under ultrasound guidance to ensure accurate drug placement.

This study aims to compare the postoperative analgesic efficacy of liposomal bupivacaine versus ropivacaine for pericapsular nerve group (PENG) block in patients undergoing hip arthroplasty. Given the significant trauma associated with hip arthroplasty, moderate to severe postoperative pain is common. Traditional local anesthetics such as ropivacaine have been used; however, due to their short duration of action, postoperative pain can often rebound. This study intends to use the PENG block technique to precisely inject liposomal bupivacaine and ropivacaine at key nerves around the hip joint capsule, comparing their differences in analgesic efficacy, duration, opioid usage, and patient satisfaction.

Driven by the global ERAS concept, reducing postoperative hospital stay and improving patients' postoperative quality of life has become a significant focus in modern surgical development. The introduction of liposomal bupivacaine holds critical implications for enhancing the quality of postoperative pain relief, reducing opioid use, and shortening hospital stays. Previous studies have shown its significant advantages in managing postoperative pain following major surgeries (12).

The ultimate aim of this study is to systematically compare the effects of liposomal bupivacaine and ropivacaine in postoperative pain management following hip arthroplasty. This will provide reliable evidence to optimize pain management protocols, improve patients' postoperative quality of life, and support the further promotion and application of the multimodal analgesia concept. Through this study, we hope to provide robust data to aid clinicians in selecting analgesic drugs and implementing analgesic techniques, particularly for major trauma surgeries such as hip arthroplasty. This will also help achieve rapid postoperative recovery and reduced opioid use while ensuring effective pain control.

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3. Study Objective

1) To compare the analgesic efficacy of liposomal bupivacaine plus bupivacaine to ropivacaine for PENG block in patients undergoing hip arthroplasty, as measured by pain scores, opioid consumption, and patient satisfaction.
2) To assess the safety profile of liposomal bupivacaine compared to ropivacaine for PENG block in terms of adverse events.
3) providing practice evidence for clinicians to select appropriate pain management strategies for hip arthroplasty.

4. Study Design

1) Randomized, single-blind, active controlled study.
2) Patients undergoing elective total hip arthroplasty will be randomized to receive either liposomal bupivacaine plus bupivacaine or ropivacaine for PENG block.
3) Outcome measures will be collected at multiple time points within 72 hours postoperatively.

5. Study Population

1) Inclusion criteria:

a) ASA I~II
b) Normal coagulation
c) Clinical diagnosis of hip fracture.

2) Exclusion criteria:

a) Presence of severe systemic diseases or ASA grade III or higher
b) Allergy to amide local anesthetics.

6. Study Procedure

1) Participants Screening

Participants meeting the inclusion criteria are screened, and written informed consent is obtained.

Record basic information of the Participants, including age, gender, ASA classification, condition, comorbidities, etc.

2) Grouping

Randomization

Participants are randomized into two groups using a random allocation method:
the experimental group and the control group.

3) Interventions:

a) **Intervention Protocol**:

Experimental Group:

Ultrasonography-guided PENG block with 15ml liposomal bupivacaine.

Formulation: 10ml 1.33% liposomal bupivacaine + 5ml 0.75% bupivacaine hydrochloride.

Control Group:

Ultrasonography-guided PENG block with 15ml 0.4% ropivacaine.

Formulation: 6ml 1% ropivacaine + 9ml saline.

b) Additional Analgesia Protocol:

Intraoperatively: sufentanil(0.1-0.15μg/Kg) + Ketorolac (Flurbiprofen Ester, 0.5-1mg/Kg)

Postoperatively: Intravenous sufentanil patient-controlled analgesia (PCA).

Sufentanil 1 mcg/mL

Total volume: 100 mL

Base rate: 1 mL/hour

Bolus: 2 mL

Lockout time: 10 minutes

c) Spinal Anesthesia

30 minutes after PENG block,

Position the patient in a left lateral decubitus position with hips and knees flexed.

Perform spinal anesthesia using 12.5-15mg of 0.5% plain bupivacaine at the L3/4 level.

10 minutes after the spinal anesthesia, test sensory level (should be around T10)

start the hip arthroplasty surgery

7. Data Collection and Management

1) Patient Demographics and Baseline Characteristics

a) Collect detailed demographic information including age, gender, weight, height, and ASA classification.

b) Document relevant comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and cardiovascular disease.

2) Pain Assessment

Employ a Numeric Rating Scale (NRS) to assess pain intensity at the following time points:

a) Pre-PENG block

b) 30 minutes post-PENG block

c) Upon arrival to the Post-Anesthesia Care Unit (PACU)

d) 6, 12, 24, 36, 48, 60, and 72 hours postoperatively

3) Opioid Consumption

a) Record the total amount of opioids administered (e.g., morphine equivalents) during the first 72 postoperative hours.

b) Specify the route of administration (e.g., intravenous, oral, patient-controlled analgesia).

4) Length of Stay

Document the duration of the patient's hospital stay from surgery completion to discharge.

5) Adverse Events

a) Monitor the occurrence of peripheral nerve block-related adverse events and opioid related adverse events, including:
   - Local infection at the injection site
   - Nerve injury
   - Systemic local anesthetic toxicity
   - Nausea
   - Vomiting
   - Constipation
   - sedation

b) Utilize standardized reporting forms to document the onset, severity, and management of any adverse events.

6) Data Management

a) Implement a secure, electronic data management system to collect, store, and analyze study data.
b) Employ data entry protocols to ensure accuracy and consistency.
c) Conduct regular data audits to verify data integrity.
d) Obtain appropriate ethical approval for data collection and storage.
e) Adhere to relevant data privacy and confidentiality regulations.
f) Assign a dedicated data manager responsible for overseeing data collection, entry, and quality control.

8. Statistic Method

1) Sample Size Calculation

A sample size of 60 patients (30 per group) was determined based on a combination of expert opinion, literature review, and statistical assumptions.

2) Statistical Methods

a) **Descriptive Statistics:** Descriptive statistics, including mean, standard deviation, and frequency, will be used to summarize patient demographics, baseline characteristics, and clinical outcomes.

b) Primary Outcome

The primary outcome-- total opioid consumption-- will be compared between the liposomal bupivacaine + bupivacaine and ropivacaine groups using an independent t-test.

c) Secondary Outcomes:

mean NRS pain scores at specific time point, and length of hospital stay will be compared between the groups using an independent t-test.

The incidence of adverse events will be compared using the Chi-square test or Fisher's exact test, as appropriate.

d) **Missing Data:** If missing data occur, appropriate imputation methods (e.g., mean imputation, multiple imputation) will be used to handle missing values.
e) **Safety Analysis:** All adverse events will be summarized descriptively.

3) Data Analysis Software

Data analysis and graphing will be performed using Origin Lab.