Study Protocol and Statistical Analysis Plan

Official title：Analgesic Effect of Ropivacaine Combined with Methylene Blue in Fascia Iliaca Block for Patients Undergoing Hip Arthroplasty

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For inclusion in this study, patients of either sex had to meet the requirements for hip replacement surgery, be in the age range of 65–85 years, have a body mass index (BMI) in the range of 18–28 kg/m^2, be categorized as American Society of Anesthesiologists (ASA) grade II to III, have no history of analgesic or local anesthetic allergies, and have no history of alcoholism or narcotic drug abuse. Patients were excluded if they met any of the following criteria: refusal by patient or family member to participate in the study, having a serious mental illness or inability to communicate clearly with researchers, severe coagulopathy, allergy to local anesthetics, severe psychiatric illness or other communication disorder, history of neurological disease such as Guillain-Barré syndrome, infection at the puncture site, delay in awakening post-surgery for more than 60 min, post-surgical use of an analgesic pump, and inability to follow-up at the required time points.

Randomization and Blinding

Using a computer-generated random sequence, a person who was not involved in the experimental operation divided the patients into two groups in which FICB was achieved with either methylene blue and ropivacaine (MB+R group) or ropivacaine only (R group). All serial numbers were encoded sequentially, kept, and scheduled for each experiment by someone other than the researcher. Because methylene blue is a blue liquid, exposure to the color could expose the experimental group. Thus, blinding was achieved by having different researchers perform different steps in the study to avoid the color affecting the experiment. The steps of the experimental procedure,

including the extraction of the liquid medicine, performance of the nerve block, and postoperative follow-up, were performed by different anesthesiologists, who were only responsible for independent experimental procedures, did not know the information about the patient outside the experiment, and did not communicate with each other about the patient and the experiment. Catheterization was not performed for any patient to prevent the color of the urine from exposing the experimental group.

Operative Procedures

Nerve Block

Before general anesthesia induction, FICB was performed under ultrasound guidance using the Edge II ultrasound device (Sonosite, USA). With the patient in supine position and the surgical area disinfected, the high-frequency ultrasound probe was placed perpendicular on the inguinal ligament. The probe was slowly moved until the "bowtie sign" created by the internal oblique and sartorius muscles was observed. This sign corresponds to the confluence of the fascia lata and fascia iliaca, which represents the fascia iliaca compartment. With an in-plane technique in the caudal to cranial direction, the needle tip was inserted deep to the fascia iliac. After confirming it could be withdrawn without blood, local anesthetic drugs in a volume of 30 ml were injected. Patients in the MB+R group received 0.25% ropivacaine (Product Batch Number: EE2344, Zhejiang Xianju Pharmaceutical Co., Ltd.) and 0.05% methylene blue (Product Batch Number: 2310032, Jichuan Pharmaceutical Group Co., Ltd.), and those in the R group received only 0.25% ropivacaine (same batch number).

Induction and Maintenance of Anesthesia

After successful nerve block, all patients were transferred to the operating room where they received routine monitoring of heart rate (HR), electrocardiogram (ECG), oxygen saturation (SpO_2), etc. Radial artery puncture catheterization was performed under local anesthesia for invasive arterial pressure monitoring. For anesthesia induction, patients received an intravenous injection of propofol 1.0–2.0 mg/kg, rocuronium bromide 0.6 mg/kg, and sufentanil 0.2–0.3 μg/kg. The specifications of mechanical ventilation after endotracheal intubation were: tidal volume (VT) 6–8 ml/kg, respiratory rate (RR) 10–12 times/min, positive end expiratory pressure (PEEP) 3–5 cmH_2O, and end-expiratory carbon dioxide partial pressure ($PETCO_2$) 35~45 mmHg. Anesthesia was maintained by inhalation of 1.5%–2.0% sevoflurane along with intravenous infusion of remifentanil at 0.05–0.2 μg/kg/min and intermittent administration of rocuronium bromide 5–10 mg according to the intraoperative situation to maintain muscle relaxation. Blood pressure (BP) and HR fluctuation within 20% of baseline values was allowed according to the intraoperative situation. If BP dropped by >20% of the baseline value or if systolic BP was <90 mmHg, ephedrine 6 mg was given. If the HR was <50 beats/minute, an intravenous bolus of atropine 0.5 mg was given. All operations among included patients were performed by the same surgical team with the same surgical method, and the surgical method was hip replacement with posterolateral approach in the lateral decubitus position. The inhalation of sevoflurane and infusion of remifentanil was stopped 5 min before the end of the operation. After surgery, the patient was transferred to a recovery room, and

the endotracheal tube was removed once the patient was awake and spontaneous breathing had resumed. According to our pre-test experience, many patients refuse the use of analgesic pumps due to the relatively high cost, certain drug-related side effects, and the option of FICB. Thus, we did not include cases with post-surgical use of an analgesic pump in this study. In this study, fascia iliaca block was used to administer postoperative analgesia to patients. If the patients were not satisfied with the effect of fascia iliaca block, additional opioids were used for supplemental analgesia. At the same time, to avoid the effect of drugs on the level of patients' inflammatory factors, the use of non-steroidal analgesic drugs was prohibited.

Study Outcomes

Primary Outcomes

As a measure of pain, Visual Analog Scale (VAS) scores at both rest and with activity (passive straight leg raise at 45°) were recorded at the following time points: before block and at 2, 6, 12, 24, and 48 h postoperatively. The VAS score is a common way to assess pain using a sliding ruler about 10 cm long, marked with 10 scales on one side and "0" and "10" at each end. A score of 0 indicates no pain; a score of 10 indicates the most severe pain that is unbearable. The higher the score, the greater the degree of pain. In this study, a dedicated anesthesiologist assessed the pain of each included participant at different time points before and after surgery.

Secondary Outcomes

As indicators of inflammation, the values of hypersensitive C-reactive protein

(hs-CRP), procalcitonin (PCT), and the neutrophil-to-lymphocyte ratio (NLR) also were recorded on postoperative days 1 and 2.

HR and mean arterial pressure (MAP) values were recorded at the following time points: operating room entry (T1), immediately before skin incision (T2), 1 min after skin incision (T3), skin suture (T4), and 30 min after extubation (T5). The requirement of supplemental analgesia was noted within 48 h postoperatively, along with the number of times patients got out of bed to perform activities within 48 h postoperatively and the distance walked after the patient's first attempt to get out of bed. Any occurrence of adverse reactions such as nausea, vomiting, and arrhythmia within 48 h postoperatively also was recorded. Any drug-related nerve damage after surgery was noted. Nerve deficits were defined according to sensory findings: 0—no nerve damage, 1—minor sensory paresthesia, 2—complete sensory parasthesia, 3—complete motor defect with or without sensory paresthesia, and 4—complex regional pain syndrome. Two researchers who were blinded to the group allocation assessed these outcomes.

Statistical Methods

SPSS 25.0 software was used for statistical analysis. Normally distributed data were expressed as mean ± SD, and group comparisons were performed using independent samples *t*-test. Data with a skewed distribution were expressed as median (*M*) and interquartile range (IQR), and non-parametric tests were used for comparisons. Friedman's test was used for intra-group comparisons. Count data were expressed as

number (%), and comparisons between groups were performed using the χ^2 test. $P<0.05$ was considered statistically significant.