Cover Page
Document type: Study protocol and Statistical Analysis Plan
Study title: Single Shot Lumbar Erector Spinae Plane (ESP) Block in Total Hip Replacement (THR)
NCT number: NCT04388553
Document date: 10 Dec 2020

Glossary of Terms (in alphabetical order)

ANZCA - Australian and New Zealand College of Anesthetists
ASA - American Society of Anesthesiologists
BMI - body mass index
CI - confidence interval
CONSORT - Consolidated Standards of Reporting Trials
ESP - erector spinae plane
ESPB - erector spinae plane block
GA - general anesthesia
MRC - Medical Research Council
NRS - numeric rating scale
OR - odds ratio
PCA - patient controlled analgesia
POD1 - first postoperative day
Prn - pro re nata
SD - standard deviation
THR - total hip replacement

INTRODUCTION

Total hip replacement (THR) improves quality of life in pathologies like osteoarthritis, rheumatoid arthritis and avascular necrosis[1]. Postoperative complications, for instance, venous thromboembolism and chest infection may be prevented by early mobilization which is facilitated by effective pain management[2,3].

Multimodal analgesia is applied to these patients, with a combination of opioid and non-opioid oral analgesics and regional block. Each of the components has its own limitations; for opioid, postoperative nausea and vomiting and respiratory depression restrict its use; non-steroidal anti-inflammatory drugs are contraindicated in those with renal impairment; and adjuvants like gabapentinoid can lead to dizziness and sedation in some patients. Regional techniques like femoral nerve block, lumbar plexus block and epidural anesthesia have shortcomings like incomplete coverage of nerves innervating the hip joint, limb weakness, invasiveness of the procedure and/or potential hemodynamic instability. Newer plane blocks like Pericapsular Nerve Group block[4] and Supra-inguinal Fascia Iliaca block[5] are emerging as candidates for analgesia after THR. Erector spinae plane block (ESPB) has been described in hip surgery by Tulgar in a case report[6]. However, the evidence of lumbar ESPB was limited mainly to case reports at the time of this study being designed. We postulated that compared to no block, a single shot lumbar ESPB at L1 would reduce postoperative fentanyl use and postoperative pain scores (primary outcomes) in a multicenter, double-blinded, randomized clinical trial in patients undergoing unilateral THR.

METHODS

This was a multicenter, double-blinded, randomized (with a randomization ratio of 1:1), controlled, parallel-group study conducted in Hong Kong. The study was carried out from July 2020 to November 2021 in two tertiary centers, which were situated in New Territories West and had an annual caseload of around 450 total joint replacements. Patients were counselled on the potential risks of general anesthesia (GA) and ESPB during the pre-anesthetic assessment, after which written informed consent would be obtained if they agreed to be recruited. This study was approved by the New Territories West Cluster Research Ethics Committee (reference number: NTWC/REC/20007), and was registered prior to patient enrollment at ClinicalTrials.gov (NCT04388553, Principal investigator: Anyon Chan, Link to registration page: https://clinicaltrials.gov/ct2/show/NCT04388553, Date of registration: May 14, 2020). The full trial protocol can also be accessed via ClinicalTrials.gov. This manuscript was constructed in the format suggested by the Consolidated Standards of Reporting Trials (CONSORT) guideline[7].

Eligibility criteria

To be eligible for the study, patient must be above 18 years old, under American Society of Anesthesiologists (ASA) class 1-3 and underwent primary elective unilateral THR. They should understand and accept the risks for GA and ESPB. They should also be able to use postoperative patient-controlled analgesia (PCA) and express their pain intensity in Numeric Rating Scale (NRS).

Patients with the following conditions were excluded from this study: 1) emergency case, 2) bilateral THR, 3) revision THR, 4) THR done under neuraxial technique, 5) contraindication for ESPB (i.e. patient refusal, mentally incapacitated, injection site infection, local spine pathology or surgery, coagulopathy with International Normalized Ratio > 1.4 or thrombocytopenia < 75 x 10^9/L), 6) regular strong opioid (e.g. fentanyl, morphine, oxycodone, methadone, heroin etc.), 7) severe obstructive sleep apnea syndrome (Apnea-Hypopnea Index ≥ 30), 8) severe obesity (Body Mass Index (BMI) ≥ 35).

Randomization

Simple randomization method was employed. Allocation concealment was achieved by drawing randomly from a set of sealed opaque envelopes with allocation inside on the day before surgery, followed by attaching it to the pre-anesthetic assessment form by the investigator. The envelope was opened by the attending anesthetist after the patient was put under GA to ensure patient blinding. If the operation was cancelled or the patient could not use PCA postoperatively, for instance, postoperative mechanical ventilation or delirium, the envelope would be put back into the pool. A CONSORT diagram illustrates the participant flow (Figure 1).

Intervention

After the patient was put under GA (maintained with nitrous oxide and either sevoflurane or desflurane), the envelope was opened. For the treatment arm, lumbar ESPB was performed by 4 designated anesthetists. For the control arm, no injection was performed and a plaster was applied to the target skin puncture site to blind the assessor. A curved probe (Fujifilm Sonosite Edge (Washington, United States); 2-5 MHz) was placed sagittally on the flank to look for the 12_{th} rib, which was traced medially to the transverse process of the T12. The probe was then moved one spinal level caudad to locate the L1 vertebra with the L1 transverse process in the middle of the probe. A 10 cm Pajunk Sonoplex® needle (Geisingen, Germany) was inserted in an in-plane manner to aim at the tip of the L1 transverse process. After hitting the bone, 0.5-1ml normal saline was used for hydrolocating the plane between the erector spinae muscle and the transverse process beneath it. Forty mL of 0.25% levobupivacaine (or a maximum of 2mg/kg body weight made up to the same volume) was injected into the ESP. After the block, the injection site was also covered with a plaster like the control arm. If the block was technically challenging and the anatomy was difficult to identify, the procedure would be aborted and the patient would be excluded from the study with the assignment envelope returned. After the injection, the surgeon was instructed not to infiltrate any local anesthetics into the wound. Intraoperatively, both arms received intravenous fentanyl (4 μg/kg in the first hour, 2 μg/kg in the second hour and then 1 μg/kg/hour onward) as the only analgesic and 4mg intravenous ondansetron was given. Patients from both arms were prescribed intravenous PCA fentanyl as the first-line analgesia with the following setting for at least 24 hours postoperatively: 1) bolus dose of 40% of the corrected body weight in μg fentanyl (ideal body weight in kg = body height in cm -105 (female) or -100 (male), corrected body weight = (total body weight - ideal body weight) x 0.4 + ideal body weight); 2) no background infusion; 3) lock-out time of 6 minutes; and 4) 1 hour limit of 120 - 200 μg (to be decided by the attending anesthetist). Preoperative regular oral analgesics (paracetamol 0.5 - 4 g daily, non-steroidal anti-inflammatory drugs like ibuprofen 200 - 400 mg daily or diclofenac 25 - 100 mg daily, tramadol 50 - 200 mg daily and gabapentinoids like gabapentin 100 - 900 mg daily or pregabalin 25 - 150 mg daily) were continued postoperatively unless contraindicated. Oral tramadol 50mg was prescribed as the rescue analgesic and intravenous metoclopramide 10mg was prescribed as the rescue antiemetic. Patients were instructed to request prn tramadol from ward nurse if pain control was inadequate despite intravenous fentanyl PCA.

Outcome assessment

Patients were followed up on POD1 by independent assessors from the acute pain service team consisting of a nurse and an anesthetist, who were not involved in the intraoperative care of the patient and was blinded by being instructed not to look at the anesthetic record. The primary outcomes, namely the amounts of PCA fentanyl used 12-hour and 24-hour postoperatively (in μg) and the pain intensity at rest and on movement on POD1, were assessed. NRS with a scale from 0 to 10 was adopted for pain assessment. NRS 0 means no pain while NRS 10 means the worst pain experienced[8]. The secondary outcomes were the rates of postoperative nausea (defined as feeling of having an urge to vomit)[9] and postoperative vomiting (defined as forcing the contents of the

stomach up through the oesophagus and out of the mouth)[9] from the end of operation till the follow-up on POD1 as recalled by the patient, the need of rescue antiemetic and analgesia in the first 24 hours postoperatively, along with knee flexion power of the operated limb in Medical Research Council (MRC) scale. The oral morphine equivalents of fentanyl and prn tramadol used at 12 hours and 24 hours postoperatively were calculated according to the opioid conversion table from the Faculty of Pain Medicine of Australian and New Zealand College of Anaesthetists (ANZCA)[10]. Of note, the use of antiemetic was not a surrogate of postoperative nausea or vomiting.

Statistical analysis

The data were collected by the investigator and analyzed by SPSS® 26 package. Per-protocol analysis was planned because it reflects treatment efficacy better, and any patient who deviated from the protocol (for instance, technically challenging block, postoperative mechanical ventilation and delirium) would not be analyzed. Since data of the primary outcomes, the oral morphine equivalents and the knee flexion power were not normally distributed as evidenced by skewed appearance of the histograms and p values of Shapiro-Wilk test smaller than 0.05, we used Mann-Whitney U test to compare these outcomes between treatment group and control group, while the Hodges-Lehmann estimator was employed to compute the median difference and the 95% confidence interval (CI). The proportions of postoperative nausea, postoperative vomiting and need of rescue antiemetic between two arms were compared by Chi-square test, whereas the proportions of those requiring rescue analgesia between both groups were analyzed by 2-sided Fisher's exact test (due to presence of expected count less than 5). Multivariable regression would be employed to adjust the outcomes should there be any major discrepancy (absolute standardized difference > 0.46 with n=35 in both groups as suggested by Austin[11]) in the perioperative factors between treatment and control groups.

Sample size estimation

A pilot study was done by retrospectively examining cases of primary unilateral THR in the two tertiary centers from January to December 2019 with postoperative PCA (infusion-plus-bolus and bolus only). The mean fentanyl use upon follow-up on the first day postoperatively (POD1) without regional block (including femoral nerve block/fascia iliaca block/lumbar plexus block/lateral cutaneous femoral nerve block/gluteal nerve block) or local anesthetics infiltration (n=36) was 664 μg, whereas that with regional block or local anesthetics infiltration (n=20) was 368 μg. To detect a reduction of fentanyl use by 300 μg which was comparable to data from the pilot study (Standard Deviation (SD) 438 μg), along with a reduction in pain score (in NRS) by 2 points (SD 2.42 for rest pain and 2.48 for movement pain) on POD1, a sample size of 35 patients was required for both treatment and control arm ($\kappa = 1$) with type 1 error (α) of 0.05 and power ($1-\beta$) of 80% in two-sample t-test assuming equal variance and normality of data distribution[12]. Secondary outcomes were not taken in account of sample size calculation, and were considered to be exploratory only. No interim analysis was planned.

REFERENCES

1. Świtoń A, Wodka-Natkaniec E, Niedźwiedzki Ł, Gaździk T, Niedźwiedzki T. Activity and Quality of Life after Total Hip Arthroplasty. *Ortop Traumatol Rehabil*. 2017;19(5):441-450.
2. Chandrasekaran S, Ariaretnam SK, Tsung J, Dickison D. Early mobilization after total knee replacement reduces the incidence of deep venous thrombosis. *ANZ J Surg*. 2009;79(7-8):526-529.
3. Zhang XY, Ma JB. The efficacy of fascia iliaca compartment block for pain control after total hip arthroplasty: a meta-analysis. *J Orthop Surg Res*. 2019;14(1):33.

4. Pascarella G, Costa F, Del Buono R et al. Impact of the pericapsular nerve group (PENG) block on postoperative analgesia and functional recovery following total hip arthroplasty: a randomised, observer-masked, controlled trial. Anaesthesia. 2021 Nov;76(11):1492-1498.
5. Gasanova I, Alexander JC, Estrera K et al. Ultrasound-guided suprainguinal fascia iliaca compartment block versus periarticular infiltration for pain management after total hip arthroplasty: a randomized controlled trial. Reg Anesth Pain Med. 2019 Feb;44(2):206-211.
6. Tulgar S, Ermis MN, Ozer Z. Combination of lumbar erector spinae plane block and transmuscular quadratus lumborum block for surgical anaesthesia in hemiarthroplasty for femoral neck fracture. *Indian J Anaesth*. 2018;62(10):802-805.
7. Moher D, Hopewell S, Schulz KF et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg. 2012;10(1):28-55.
8. Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA. Studies with pain rating scales. Ann Rheum Dis. 1978 Aug;37(4):378-81.
9. World Health Organization. ICD-11: International classification of diseases (11th revision). 2019.
10. Australian and New Zealand College of Anaesthetists. PM01 (Appendix 2): Opioid dose equivalence - Calculation of Oral Morphine Equivalent Daily Dose (oMEDD). 2021.
11. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009 Nov 10;28(25):3083-107.
12. Chow SC, Shao J, Wang H. Sample Size Calculations in Clinical Research, Second Edition. Chapman & Hall/CRC; 2008.