TITLE: Ultrasound Guided Fascia Iliaca Nerve Block with Bupivacaine and Adjuvant Ketamine vs. Bupivacaine alone in patients with hip or femur fracture: a double blind randomized clinical trial

INTRODUCTION

An ageing population, increased activity level, bone fragility and co-morbidities are contributing to the increasing incidence of proximal femoral fractures (PFF).(1) The incidence of hip fracture is predicted to increase to 101,000 by 2020. Falls in the elderly osteoporotic population resulting in hip fracture is the commonest reason for admission to the orthopedic ward. (2) Multi-disciplinary care for the hip fracture patient has reduced one month mortality to 8.2% in recent years but significant morbidity still exists.(3) Analgesia is a key component in the pre-hospital, preoperative and post-operative time periods for the hip fracture patient. Opioids are often required to provide adequate analgesia but can cause nausea, constipation, and confusion (delirium) in the older patient.(4)

BACKGROUND

The fascia-iliaca compartment block (FICB) is a relatively new component of the hip fracture analgesia armamentarium. The National Institute of Health and Care Excellence (NICE) recommends the use of simple oral analgesia including opioids, with fascia-iliac blocks used as an adjunct.(5) FICB provided superior analgesia to intramuscular morphine in a randomized controlled trial of 48 hip fracture patients.(6) The analgesic effects were significant both at rest and 15 degree flexion of the hip. In a different study, 24/30 patients who received a FIB were able to assume a semi-recumbent position pre-operatively due to improved hip flexion which provided comfort whilst waiting for surgical intervention.(7) FICB significantly reduced the incidence of delirium in intermediate risk patients.(8) FICB administered in the emergency department by an emergency physician provided significant decrease in pain from 15 minutes - 8 hours post block when compared to standard parenteral medications. Post block analgesic requirements for patients in the FIB group were minimal.(9)

SIGNIFICANCE

Ketamine is a noncompetitive antagonist of the N-methyl-D aspartate receptor (NMDAR). It is used for premedication, sedation, induction, and maintenance of general anesthesia.(10) Central, regional, and local anesthetic and analgesic properties have

been reported for ketamine. Intravenous (IV) administration of low-dose ketamine decreases postoperative opioid use and improves analgesia.(11) The addition of ketamine to epidural lidocaine or bupivacaine increases the duration of regional anesthesia and postoperative analgesia.(12) It has been seen that peri-incisional use of 0.3-0.5% ketamine combined with local anesthetic in surgical wounds enhances analgesia by a peripheral mechanism.(13)

Several studies have been performed to evaluate the effect of added ketamine to local anesthetics for nerve block and regional anesthesia. Ketamine did not enhance the onset time and duration of sensory and motor blockade when added to ropivacaine for the interscalene brachial plexus block.(14) Addition of ketamine to ropivacaine infusion via the femoral nerve catheter after repairing an anterior cruciate ligament (ACL) injury/tear could not improve postoperative pain control.(16). However, addition of ketamine to lidocaine for supraclavicular brachial plexus block resulted in greater pain relief and longer time to first request for analgesia. (17)

We are conducting this study to evaluate the effect of ketamine added to bupivacaine at the onset on the duration of sensory and motor block in ultrasound –guided fascia iliaca compartment block for patients presenting to the ED with hip or femur fractures

STUDY OBJECTIVES

1. To compare the onset of motor and sensory block between two groups while in the ED
2. To compare the time for a first rescue analgesia between two groups
3. To compare the change in pain score between two groups for up to 24
4. To evaluate and compare the rates of the side effects between two groups and an overall need for rescue analgesia.
5. Assess functional outcome in elderly TBI patients above age 65, following discharge.

HYPOTHESIS

1. The administration of ketamine as an adjunct to bupivacaine for ultrasound guided fascia –iliaca nerve block will result in greater and longer lasting analgesia, longer lasting motor and sensory block, and overall less requirements for an opioid rescue analgesia.

STUDY DESIGN

Subjects: Patients aged 18 years and older with isolated hip or femur fracture confirmed on x-ray.

Eligibility:

Patients aged 18 years and older with isolated hip or femur fracture confirmed on x-ray.

Exclusion Criteria

- Polytrauma
- Unstable vitals signs
- Allergy to Bupivacaine or Ketamine
- Inability to give consent
- Altered mental status
- Known end stage renal disease or hepatic dysfunction
- Received > 2 doses of Morphine in ER prior to regional nerve block
- Patients with failed nerve block (30 minute onset)
- ≥ 100kg

Design:

A randomized double-blind prospective superiority trail.

- Each patient will receive Morphine for analgesia prior to regional nerve block.
    - Patients < 65 years will receive Morphine 0.1 mg/kg every four hours as needed for 2 doses
    - Patients > 65 years will receive Morphine 0.05 mg/kg every four hours as needed for 2 doses
- **Treatment group:** will receive an ultrasound guided regional nerve block with Bupivacaine (0.5% or 5 mg/ml) 2.5 mg/kg (max dose 175 kg) + Ketamine (50 mg/ml) 2 mg/kg. Each patient will be given a volume of 40 mL - this will be a mixture of Bupivacaine, Ketamine and 0.9% NS to make up the full 40 ml.
- **Control group:** will receive an ultrasound guided regional nerve block with Bupivacaine 0.5% only. Each patient will be given a volume of 40 ml - this will be a mixture of Bupivacaine and 0.9% NS to make up the full volume of 40 mL
- The patients will be followed with respect to accrual time, follow up time, and total time of the block as well as a need for rescue analgesia as follows: every 15 minutes for the first hour; every 30 minutes for the next hour; every 1 hour for next 4 hours; every 4 hours for next 18 hours with end point of 24 hours or up until they are taken to surgery, whichever comes first.

- Evaluation of the sensory blocks: will be performed every 5 minutes after administration of the local anesthetic. The sensory block will be quantified as: 0 = Anesthesia (no sensation), 1 = Analgesia (decreased [dull] sensation), and 2 = no block (normal sensation), by using the pinprick test and comparing with the contralateral limb. The time elapsed from the injection to the onset of analgesia in the central sensory region of femoral nerve block will be taken as time of onset of the sensory block.
- Rescue Analgesia: If pain is not relieved and the participant requires rescue analgesia a weight-based dose of Morphine will be given at 0.1 mg/kg.
  In addition, an antidote (lipid emulsion) that will be given to patients who need it when they develop severe side effects.

Data Collection: Patient demographic, clinical and injury information, pain score, onset of motor and sensory block, rescue analgesia and side effects will be collected by using a data collection form by trained research assistant and associates.

Data Analysis: Statistical Analyses will include frequency distributions, t-test and chi-square for comparison between and within the groups and Cox Linear Regression Analysis. P<.05 will denote statistical significance. Statistical analyses will be conducted via SPSS version 24. Antonios Likourezos or equivalent will perform the statistical analyses.

Sample Size:
A sample size of 110 patients (55 per group) will be needed to detect a 20 % difference in time to first rescue analgesia with alpha= 0.05 and SD of 2.5. We would recruit 120 patients (60 in each group) to account for any missing data and loss to follow-up.

Expected Outcomes:
Primary Outcome: time to first rescue analgesia post-regional nerve blockade in each group
Secondary Outcomes:

- Change in pain score as measured by Visual Analog Scale: Patient to be approached at the following intervals: every 15 minutes for the first hour; every 30 minutes for the next hour; every 1 hour for next 4 hours; every 4 hours for next 18 hours with end point of 24 hours or up until they are taken to surgery, whichever comes first.