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Original contribution

Perineural dexamethasone successfully prolongs adductor canal block when assessed by objective pinprick sensory testing: A prospective, randomized, dose-dependent, placebo-controlled equivalency trial

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ABSTRACT

Study objective: To determine whether perineural dexamethasone prolongs peripheral nerve blockade (PNB) when measured objectively; and to determine if a 1 mg and 4 mg dose provide equivalent PNB prolongation compared to PNB without dexamethasone.
Setting: Multiple studies have reported that perineural dexamethasone added to local anesthetics (LA) can prolong PNB. However, these studies have relied on subjective end-points to quantify PNB duration. The optimal dose remains unknown. We hypothesized that 1 mg of perineural dexamethasone would be equivalent in prolonging an adductor canal block (ACB) when compared to 4 mg of dexamethasone, and that both doses would be superior to an ACB performed without dexamethasone.
Design: This was a prospective, randomized, double-blind, placebo-controlled equivalency trial involving 85 patients undergoing a unicompartmental knee arthroplasty.
Interventions: All patients received an ACB with 20 ml of 0.25% bupivacaine with 1:400,000 epinephrine. Twelve patients had 0 mg of dexamethasone (placebo) added to the LA mixture; 36 patients had 1 mg of dexamethasone in the LA; and 37 patients had 4 mg of dexamethasone in the LA.
Measurements: The primary outcome was block duration determined by serial neurologic pinprick examinations. Secondary outcomes included time to first analgesic, serial pain scores, and cumulative opioid consumption.
Main results: The 1 mg (31.8 ± 10.5 h) and 4 mg (37.9 ± 10 h) groups were not equivalent, TOST [Mean difference (95% CI); 6.1 (−10.5, −2.3)]. Also, the 4 mg group was superior to the 1 mg group (*p*-value = 0.035), and the placebo group (29.7 ± 6.8 h, p-value = 0.011). There were no differences in opioid consumption or time to analgesic request; however, some pain scores were significantly lower in the dexamethasone groups when compared to placebo.
Conclusion: Dexamethasone 4 mg, but not 1 mg, prolonged the duration of an ACB when measured by serial neurologic pinprick exams.
Clinical trial registration: NCT02462148

1. Introduction

Peripheral nerve blockade (PNB) has become a mainstay for providing postoperative analgesia for a variety of surgical procedures. In addition to reducing the need for opioid medications, the main analgesic goal following joint replacement surgery is to allow for early participation in physical and occupational therapy. Unfortunately, while single injection PNBs provide effective initial postoperative analgesia, pain may become significant after the PNB resolves. Although analgesic duration can be extended by placing an indwelling perineural catheter, this technique requires additional time, procedural skill, and resources. It would be particularly advantageous to identify local anesthetic (LA) adjuvants that can prolong single injection PNBs with a duration of action similar to a perineural infusion. Additives that have

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been previously studied include: clonidine, buprenorphine, tramadol, midazolam, and neostigmine [1].

Recent investigations have shown particular interest in whether dexamethasone, a glucocorticoid steroidal medication, prolongs PNB. Both intravenous (IV) and perineural (off-label) routes of administration have garnered interest in prolonging PNB. These studies followed the findings that IV dexamethasone in doses ≥0.1 mg/kg provided significant analgesic effects and opioid sparing [2]. While several studies have since concluded that both the IV and perineural routes prolong PNB, some feel that the perineural route is superior [3,4,6–10]. A recent systematic review and meta-analysis concluded that the use of perineural dexamethasone as an additive to LA may prolong the duration of PNB with bupivacaine by an additional 3 h compared to a PNB with the addition of IV dexamethasone [11]. However, given the rather modest benefit of perineural dexamethasone versus IV administration and the fact that there are concerns related to the relative safety of perineural administration (off-label use and the theoretical possibility of neurotoxicity in humans), the authors suggest that the IV route may be preferred.

It is important to note that essentially all previous studies investigating the influence of dexamethasone on PNB duration have utilized subjective end-points as surrogate markers to define PNB duration or duration of analgesia, such as time-to-first-analgesic-request, opioid consumption, or patient-determined block duration (defined by either the onset of pain or time to first movement). While these outcomes are clinically relevant, it should be recognized that they do not necessarily equate to block duration. For example, a recent study involving IV (not perineural) dexamethasone (4 mg and 8 mg) found that neither dose prolonged PNB duration when measured by an objective serial pinprick endpoint [12]. However, 8 mg of IV dexamethasone did prolong the time-to-first analgesic when compared to placebo.

The aim of this study was to determine whether perineural dexamethasone prolongs an adductor canal block (ACB) performed with bupivacaine when an objective method of determining block duration was employed. Given that there has been evidence of equivalence utilizing 4 mg and 8 mg of perineural dexamethasone, we set out to determine if an even lower 1 mg dose, which is theoretically safer, could be equally effective given concerns that higher than necessary doses of perineural dexamethasone are being utilized [13,14]. It was hypothesized that 1 mg and 4 mg of perineural dexamethasone would be equally effective at prolonging an ACB when measured objectively by serial pinprick examination and that both doses would be superior to placebo.

2. Methods

This double-blind, prospective, randomized, placebo-controlled, equivalency trial was performed at a single, tertiary-care academic medical center. Institutional Review Board approval was granted prior to initiation of the study, and it was registered at clinicaltrials.gov (NCT02462148). Federal Drug Administration Investigational New Drug Exemption (IND 125810) was obtained for the off-label use of dexamethasone prior to the beginning of this study. Written informed consent was obtained from all subjects.

Patients, 18 to 90 years of age, presenting to Wake Forest Baptist Medical Center for primary medial or patellofemoral unicompartmental knee replacement surgery were eligible. Subjects were excluded if they had contraindications to regional anesthesia (allergy to amide local anesthetics, coagulopathy, or infection in the area of the anticipated ACB), peripheral neurologic dysfunction or neuropathy, insulin or non-insulin dependent diabetes mellitus, systemic corticosteroid use within 30-days of surgery, chronic opioid use (≥40 mg of oxycodone equivalents daily or any extended release opioid), pregnancy, allergy or adverse reaction to dexamethasone (i.e., psychosis), or the inability to comprehend or reliably participate in the study.

The study was conducted from July 2015 to August 2017. It was originally designed to include 115 patients; however, surgical personnel changes resulted in a significant decline in eligible procedures and difficulty recruiting, and a decision was made to terminate the study after enrollment of 85 patients. All patients underwent block randomization utilizing sequentially numbered, opaque, sealed envelopes where both the patient and study observers making patient assessments were blinded to group assignment. Twelve patients received an ACB performed by personnel blinded to group allocation with 0.25% bupivacaine with 1:400,000 epinephrine (an intravascular marker). Thirty-six patients received the same ACB mixture (bupivacaine with epinephrine) with the addition of 1 mg (0.1 ml) of preservative free dexamethasone. Thirty-seven patients received the same block mixture with 4 mg (0.4 ml) of preservative free dexamethasone. All study patients received a PNB volume of 20 ml. All study drug preparations were prepared by an anesthesiologist who was not involved in patient assessment to preserve blinding.

Unless contraindicated, each patient received the following oral preoperative medications for analgesia: acetaminophen 1 g, celecoxib 400 mg, and pregabalin 150 mg. Monitoring throughout the PNB procedure included pulse oximetry, electrocardiogram, noninvasive blood pressure, and end-tidal carbon dioxide. Prior to the procedure, patients were sedated with fentanyl and midazolam at the discretion of the anesthesiologist. All blocks were performed at approximately the midpoint of the thigh (halfway between the patella and the anterior superior iliac spine) using ultrasound guidance with a short axis in-plane approach, and a 21 g needle (Arrow Stimuquik, Teleflex Medical, Wayne, PA). This location was chosen so that the most distal block could be performed to preserve motor function while still performing a block within the adductor canal. The injection of the local anesthetic mixture was placed deep to the sartorius fascia and anterior to the superficial femoral artery as described by Kirkpatrick et al. [15].

Following ACB placement, block success was determined by performing pinprick sensory assessment using a 25 g Whitacre spinal needle at a location on the antero-medial lower extremity 3 to 5 cm superior to the medial malleolus in the expected distribution of the saphenous nerve. The following scale was used: (2 = absence of sensation; 1 = able to feel pressure, but not sharp pinprick; 0 = sharp pinprick). Pinprick assessment was performed at 15 min and, if necessary, 30 min following block placement. If clinical time constraints precluded this, then assessment occurred following resolution of spinal or general anesthesia in the postoperative anesthesia care unit (PACU). Once block success was confirmed (scale score of 1 or 2), a mark was made in order to standardize the location of subsequent serial sensory exams.

All patients received either a spinal anesthetic (12.5 mg bupivacaine with 20 μg of fentanyl) or general anesthetic (IV induction with propofol followed by inhalational anesthetic) per the attending anesthesiologist. Neither intraoperative IV dexamethasone nor ketamine were administered. However, alternative antiemetics could be utilized at the discretion of the intraoperative anesthesia care team. Unless contraindicated, all patients were started on a postoperative regimen consisting of acetaminophen 1 g every 6-h and celecoxib 200 mg twice daily. Patients taking pregabalin or gabapentin preoperatively were continued on this postoperatively.

Starting 6 h following block placement, serial neurologic pinprick examinations were performed at the previously marked site every 2 h until block resolution occurred (pinprick assessment score = 0), including throughout the night. Time “zero” for each patient was block placement, which determined the 2 h incremental checks. The pin-prick pressure utilized throughout the study was the required pressure to illicit a sharp sensation (score of 0) in the contralateral, non-surgical leg at the same location above the medial malleolus. Any patient discharged from the hospital with an ongoing block was provided a safety pin to utilize for self-assessment and they were instructed to perform this examination every 2 h and to record their results. At the time that the safety pin was given to the patient, they were asked to see if their