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Addition of Dexamethasone and Buprenorphine to Bupivacaine Sciatic Nerve Block: A Randomized, Controlled Trial

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Abstract

Background and Objectives—Sciatic nerve block provides analgesia after foot and ankle surgery, but block duration may be insufficient. We hypothesized that perineural dexamethasone and buprenorphine would reduce pain scores at 24 hours.

Methods—Ninety patients received ultrasound-guided sciatic (25 mL 0.25% bupivacaine) and adductor canal (10 mL 0.25% bupivacaine) blockade, with random assignment into 3 groups (30 patients per group): control blocks + intravenous dexamethasone (4 mg) (control); control blocks + intravenous buprenorphine (150 mcg) + intravenous dexamethasone (intravenous buprenorphine); nerve blocks containing buprenorphine + dexamethasone (perineural). Patients received mepivacaine neuraxial anesthesia and postoperative oxycodone / acetaminophen, meloxicam, pregabalin, and ondansetron. Patients and assessors were blinded to group assignment. The primary outcome was pain with movement at 24 hours.

Results—There was no difference in pain with movement at 24 hours (median score 0). However, the perineural group had longer block duration vs control (45.6 vs 30.0 hr). Perineural patients had lower scores for “worst pain” vs control (median 0 vs 2). Both intravenous buprenorphine and perineural groups were less likely to use opioids on the day after surgery, vs control (28.6%, 28.6%, 60.7%, respectively). Nausea after intravenous buprenorphine (but not perineural buprenorphine) was severe, frequent, and bothersome.

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Conflicts of Interest:

In the past, Dr. Kahn has received money from Helwig, Henderson, Ryan, LaMagna & Spinola, LLP for expert testimony outside of the submitted work. The remaining authors have no disclosures.

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This report was previously presented, in part, at the American Society of Regional Anesthesia and Pain Medicine Meeting in April 2014 and at the Anesthesiology Annual Meeting in October 2014.

Conclusions—Pain scores were very low at 24 hours after surgery in the context of multimodal analgesia and were not improved by additives. However, perineural buprenorphine and dexamethasone prolonged block duration, reduced the worst pain experienced, and reduced opioid use. Intravenous buprenorphine caused troubling nausea and vomiting. Future research is needed to confirm and extend these observations.

INTRODUCTION

Prolongation of peripheral nerve block may reduce pain, opioid use, and opioid-related side effects. Sciatic nerve blocks in the popliteal fossa provide analgesia for about 14 hours; increasing the concentration of local anesthetic does not prolong the duration of analgesia.¹ Perineural clonidine prolongs duration of analgesia to approximately 18 hours.²

A meta-analysis found that addition of dexamethasone to local anesthetics prolonged brachial plexus blockade.³ However, recent studies using systemic dexamethasone controls failed to show major benefits from perineural dexamethasone.⁴⁻⁶ Systemic dexamethasone provides analgesia when used at more than 0.1 mg/kg,⁷ emphasizing the need for systemic controls.

Pain scores after bupivacaine sciatic nerve block were improved by buprenorphine, a partial mu-opioid agonist, administered either perineural or intramuscular.⁸ After sciatic block, perineural buprenorphine provided longer duration of analgesia than did intramuscular buprenorphine, judged both by pain scores and time until additional opioid analgesic administration. Buprenorphine also prolongs the duration of analgesia after axillary nerve blockade,⁹ subclavian perivascular brachial plexus block,¹⁰ and intraoral nerve blockade.¹¹

Addition of multiple adjuvants to local anesthetic (“multimodal perineural analgesia”) may prolong analgesia after single injection peripheral nerve blockade.¹² We hypothesized that addition of dexamethasone and buprenorphine to a bupivacaine sciatic nerve block in the popliteal fossa, in the context of multimodal analgesia, would improve analgesia, specifically by reducing pain scores at 24 hours.

METHODS

After approval from Hospital for Special Surgery's institutional review board, and informed written consent, 90 patients (age 18–75) scheduled for discharge after foot or ankle surgery (with one of 2 co-investigator surgeons) with planned use of spinal anesthesia and sciatic nerve blockade entered the study (Fig. 1). Common reasons for exclusion were no popliteal block planned (n=170), no research staff available for follow-up (n=74), planned admission for postoperative intravenous opioid analgesia (n=27). This study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02198235), NCT02198235.

Exclusion criteria follow: surgery that would cause significant pain at sites outside the distal lower extremity (eg, iliac crest bone graft was an exclusion criterion, but iliac crest bone marrow aspiration was not grounds for exclusion), bilateral surgery, regular use of opioid analgesics for > 3 months, regular use of steroids for > 3 months, contraindication to performance of the popliteal fossa nerve block with 0.25% bupivacaine (eg, alleged

bupivacaine sensitivity, low body weight), contraindications to dexamethasone or buprenorphine (eg., allergy, insulin dependent diabetes mellitus), altered pain perception or, lack of sensation in the operative leg, inability of the patient to describe postoperative pain (eg, psychiatric disorder, dementia), non-English-speaking patients (questionnaires were in English).

Prior to study start, a research assistant not otherwise associated with the study prepared opaque numbered envelopes containing group assignment; each envelope was opened after the patient signed consent. Blocked randomization with a blocking factor of 2 was used. This was a parallel 1:1:1 ratio study, conducted at an orthopedic teaching hospital. The intraoperative anesthesiologist was not blinded to group assignment, but the patient and the research assistant collecting the data were both blinded. All patients received a sciatic and an adductor canal block with 0.25% bupivacaine. Sciatic nerve block (25 mL) in the popliteal fossa was performed with the patient prone, using ultrasound guidance. The nerves were traced to the level immediately proximal to the union of the tibial and peroneal branches. A 22-gauge, 102-mm Chiba needle (Hakko Co Ltd, Tokyo, Japan) was introduced, in-plane from the lateral side, to pierce the fascia surrounding the 2 nerve bundles. Local anesthetic was injected between the bundles, with the goal of separating, but not injecting into, the nerve bundles. This nerve block can be described as subparaneural,¹³ intraneural but extrafascicular¹⁴ or paraneural.¹⁵ Ultrasound- guided adductor canal blockade was performed 6 to 8 cm above the knee, using 10 mL of the same solution used for the sciatic block.

Patients were randomized to 1 of 3 groups (n = 30 / group): (1) control nerve blocks + IV dexamethasone (4 mg) (“IV dexamethasone”); (2) control nerve blocks + IV buprenorphine (150 mcg) + IV dexamethasone (4 mg) (“IV buprenorphine +dexamethasone”); (3) nerve blocks containing buprenorphine (150 mcg) + dexamethasone (4 mg) (“perineural buprenorphine + dexamethasone”). Perineural buprenorphine and dexamethasone represent “off-label” usage, but, as discussed in other papers, perineural use is described in multiple textbooks and publications.^{8,16}

Patients received a standardized anesthetic and analgesic protocol. Intravenous sedation was provided with midazolam and propofol (no opioids, no ketamine). Neuraxial anesthesia was performed (spinal or combined spinal-epidural) with 60 mg subarachnoid mepivacaine. Epidural 2% lidocaine (5–10 mL at a time) was used as needed to maintain intraoperative blockade. Intravenous intraoperative medications included famotidine (20 mg), ondansetron (4 mg), and ketorolac (30 mg, reduced to 15 mg if < 60 kg or >70 y.o.).

Postoperative medications included oxycodone / acetaminophen (5 mg / 325 mg) 1–2 orally every 4 hours as needed, meloxicam 15 mg orally every night at bedtime (POD 0,1, reduced to 7.5 mg if > 70 y.o.), pregabalin 50 mg orally every night at bedtime for 5 days, and ondansetron 8 mg orally every day as needed for nausea.

The primary outcome was pain with movement at 24 hours from the nerve block (Numerical Rating Scale, NRS, of 0–10). Secondary outcomes (based on IMMPACT recommendations¹⁷) included NRS pain scores at rest and with movement (preoperatively,

PACU, 24 and 48 hours), physical functioning (BPI: Brief Pain Inventory; 0–10 scale; 24 hr), patient global impression of change (satisfaction) (24 hr; 0–10 scale), and spontaneously reported symptoms and adverse events (24 hr; “Have you noticed any problems with the pain management? If yes, what are they?”).

Duration of analgesia from the nerve blocks was assessed by asking the following questions at 24 and 48 hours (and POD3 if needed): “At what time did you start to have pain in the foot?” “When did the nerve block stop providing pain relief?” “When did you first need to take a pain pill?” and “When did the nerve block entirely wear off?”

Additional outcome measures included opioid usage (PACU, 24, 48 hr), ORSDS (Opioid Related Symptom Distress Scale; 24 hr),¹⁸ and quality of sleep (assessed for the first 2 postoperative nights). Block-related complications were assessed at one month by asking if there were post-procedural impaired movement or sensation on the operative leg. Study data were collected and managed using REDCap electronic data capture tools hosted at Hospital for Special Surgery.¹⁹ REDCap (Research Electronic Data Capture) is a secure, web-based application to support data capture for research studies.

Data were analyzed after 15 patients/group. Study discontinuation was planned if patients in a group had pain at 24 hours that statistically significantly exceeded pain in the IV dexamethasone group by 2 units. The stopping criteria were not met,^a so the study was completed as designed.

A sample size of 27 patients in each of 3 treatment groups would provide 80% power at a 2-sided alpha level of 0.05 to detect a 1.5 point difference in NRS pain score with movement (3.2 vs 1.7 with common within-group standard deviation of 1.9²⁰) between the control (IV dexamethasone) and each experimental group (IV buprenorphine + dexamethasone and perineural buprenorphine + dexamethasone) using pairwise independent-samples t-tests. Assuming a 10% drop-out rate, we planned to enroll 30 patients per group for a total of 90 patients in the study.

Non-normally distributed ordinal outcomes are reported as both means with standard deviations and medians with first and third quartiles and compared between the control and each experimental group using Fisher-Pitman permutation tests.²¹ This non-parametric test involves calculating the *t* test statistic for all possible permutations of group labels among data from pairs of treatment arms and comparing the observed *t* statistic to the distribution of *t* statistics from all permutations. Normality of continuous variables was assessed via histograms, quantile-quantile (q-q) plots, and Shapiro-Wilk tests. The generalized estimating equations (GEE) method^{22,23} with an autoregressive [AR(1)] correlation structure was used to compare NRS pain score between groups in the PACU, at 24, and 48 hours after adjustment for holding area score. Binary outcomes are presented as risk difference and relative risk with respect to the control group and compared using χ^2 or Fisher exact tests, as appropriate. The Kaplan-Meier method was used to calculate the median and 95%

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confidence intervals (log-log transformation) for time-to-event outcomes in the presence of censored data. Hazard ratios were obtained via Cox proportional hazards models. All statistical tests were two-sided with a P value < 0.05 considered statistically significant. Adjustment for multiple comparisons was not performed because each of the experimental group/control group comparisons were defined *a priori*. Statistical analyses were performed with SAS Version 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

Ninety patients were enrolled (Fig. 1, Table 1), from October 2012 to January 2014. The primary endpoint was analyzed in 83 patients (Fig. 1). Patient characteristics are described in Table 1. The epidural was dosed in 11 of 90 patients.

There was no evidence of a difference in the primary outcome of pain with movement at 24 hours between either the IV buprenorphine + dexamethasone group (median [Q1, Q3]: 0 [0, 2]) and IV dexamethasone group (0 [0, 4]) or between the perineural buprenorphine + dexamethasone group (0 [0, 2.5]) and IV dexamethasone group ($P = 0.149$ and 0.390 , respectively) (Fig. 2). There was evidence of lack of normality for NRS pain scores at rest and with movement (Shapiro-Wilk tests $P < 0.05$). Histograms and q-q plots of residuals revealed positively skewed data. Pain scores were presented as median (Q1, Q3) but, for reference, mean $\pm$ SD scores (24 hr NRS with movement) were 1.9 ± 2.6 (IV dexamethasone), 1.0 ± 1.6 (IV buprenorphine + dexamethasone) and 1.3 ± 2.1 (perineural buprenorphine + dexamethasone). Longitudinal modeling of NRS pain with movement with adjustment for preoperative score via the GEE method also did not show a difference between IV buprenorphine + dexamethasone and IV dexamethasone or between perineural buprenorphine + dexamethasone and IV dexamethasone at 24 hours (Table 2).

The median (Q1, Q3) pain with movement was 0 (0, 0) for all groups on the day of surgery after resolution of the spinal and rose to 4 (0, 6), 4 (2, 5), 4 (3, 6) in the IV dexamethasone, IV buprenorphine + dexamethasone, and perineural buprenorphine + dexamethasone groups, respectively, by 48 hours (Table 2). Pain at rest followed a similar pattern, but with lower magnitude of pain (Table 2). No difference between groups in pain with movement or at rest was found via GEE analysis on the day of surgery after resolution of the spinal, 24 hours, or 48 hours (Table 2).

BPI worst pain favored administration of buprenorphine, both IV and perineural (Table 2). Satisfaction scores were 10 (9, 10) [median (Q1, Q3)] for all groups. There were no unexpected spontaneously reported adverse events at 24 hours; answers focused on opioid use, pain location and persistent numbness.

The median (95% CI) time to block regression (for the question “When did the nerve block entirely wear off?”) was 30.0 hours (24.1, 45.2) for IV dexamethasone, 37.9 hours (30.7, 43.9) for IV buprenorphine + dexamethasone, and 45.6 hours (33.9, 53.8) for Perineural Buprenorphine + dexamethasone (Figure 3). There was evidence of a lower hazard rate (i.e., chance of block regression occurring in the next moment) in the Perineural Buprenorphine + dexamethasone group compared with the IV dexamethasone group (hazard ratio [95% CI]:

0.50 [0.26, 0.97]; $P = 0.041$) but no evidence of a difference between the IV Buprenorphine + dexamethasone and IV dexamethasone group (0.75 [0.41, 1.39]; $P = 0.354$). Other block duration questions did not achieve statistical significance (Table 3).

The percentage of patients needing opioids in the first 24 hours was lower for patients receiving buprenorphine: 60.7% of IV dexamethasone patients needed opioids, vs 28.6% for IV Buprenorphine + dexamethasone, 28.6% for Perineural Buprenorphine + dexamethasone (difference [95% CI]: 32% [6.1, 52.8]; $P = 0.016$) (Table 4).

Nausea in the PACU was noted with IV Buprenorphine + dexamethasone, but not with Perineural Buprenorphine + dexamethasone (Table 4). Patients in the IV Buprenorphine + dexamethasone group demonstrated higher rates of nausea and vomiting at 24 hours as compared with IV dexamethasone (Table 4). Patients in the perineural buprenorphine + dexamethasone group did not have higher rates of nausea and vomiting compared with IV dexamethasone. Other ORSDS data also indicated increased distress in the IV buprenorphine + dexamethasone group (Table 4).

Difficulty sleeping POD1 was uncommon: 2/21 (IV dexamethasone); 0/27 (IV buprenorphine + dexamethasone); 2/28 (perineural buprenorphine + dexamethasone). At the POD 30 phone call, 2 patients commented on numbness. One patient (IV buprenorphine + dexamethasone) had decreased sensation at the surgical scar. One patient (perineural buprenorphine + dexamethasone) reported that “part of foot feels a little bit numb,” but was not more specific. When this patient returned to the surgeon's office at 6 months the symptoms were entirely resolved. Two patients (both in IV dexamethasone) reported uncomfortable swollen operative feet.

DISCUSSION

Addition of buprenorphine and dexamethasone to bupivacaine for sciatic nerve blockade in the popliteal fossa did not improve pain with movement at 24 hours. Pain scores at 24 hours were low; median scores were 0 in all 3 groups, suggesting that attempts to improve pain at 24 hours are unlikely to succeed. Previous work at the authors' institution found that duration of analgesia after sciatic nerve blockade lasted 14 to 18 hours.^{1,2,20} The power analysis (based on previous work²⁰) assumed NRS means of 3.2 (control) vs 1.7 (experimental); observed mean pain scores at 24 hours were lower (1.9 and 1.3, respectively), with median pain scores of 0. Low pain scores may be attributable to the multimodal analgesic regimen of neuraxial anesthesia, nerve blockade, non-steroidal anti-inflammatory, pregabalin, acetaminophen and opioids. Additionally, the use of a subparaneural injection site²⁴ prolongs duration of analgesia from a sciatic nerve block in the popliteal fossa.

Some secondary outcomes suggest beneficial aspects of perineural buprenorphine / dexamethasone. The perineural buprenorphine + dexamethasone group experienced longer block duration than the IV dexamethasone group (45.6 hr vs 30.0 hr) and was spared the nausea prominently associated with IV buprenorphine + dexamethasone on POD1 (19.2% vs 57.7%). Patients in the perineural buprenorphine + dexamethasone group had lower scores

for “worst pain” compared with IV dexamethasone (mean of 1.6 vs 3.4). Both experimental groups (IV buprenorphine + dexamethasone and perineural buprenorphine + dexamethasone) were less likely to use additional opioids in the first day after surgery, compared with IV dexamethasone (28.6%, 28.6%, 60.7%, respectively). Preoperative administration of either IV or perineural buprenorphine, a potent opioid, is expected to reduce postoperative consumption of additional opioids. The mean duration of pain relief from 0.2 mg intramuscular buprenorphine is 5.6 hours.²⁵ It is unproven that these differences (longer block duration, lower “worst pain” and decreased use of additional opioids) represent clinically significant value.

Nausea after IV buprenorphine + dexamethasone was often severe, frequent and bothersome, despite prophylactic and on-demand antiemetics. Because of the high impact of nausea and the low yield of analgesia, intravenous buprenorphine should be avoided in this patient population. Addition of buprenorphine to the nerve block did not cause increased or extensive nausea and vomiting.

Use of dexamethasone as an adjunct for peripheral nerve blockade remains controversial, despite extensive recent study. Low dose dexamethasone had no effect on in vitro ropivacaine-induced toxicity following a 24-hour exposure, but higher doses increased rates of neuron cell death.²⁶ On the other hand, a different in vitro model system found dexamethasone protective against bupivacaine-induced neuron injury.²⁷ It has been suggested that these in vitro data need to be viewed critically and that perhaps the use of prolonged infusions of ropivacaine via perineural catheters should be re-evaluated.²⁸ Some clinical studies that found benefit of perineural dexamethasone lack systemic controls.³ Three recent studies that question the benefit of perineural dexamethasone (compared with intravenous control) present interesting methodologic issues. One⁶ found that perineural dexamethasone (8 mg) did not improve quality of recovery (QoR40). However, perineural dexamethasone prolonged analgesia (compared with both saline and IV controls) and reduced pain on POD1. Another⁵ found that perineural dexamethasone (8 mg, combined with 8 mg IV; total dose 16 mg) did not reduce pain at 48 hr, the primary outcome. However, sciatic perineural dexamethasone reduced pain for the first 24 hours. Thirdly⁴, perineural dexamethasone (10 mg) did not reduce time to analgesic use, compared with systemic dexamethasone (1405 vs 1275 min), but it was suggested that the study was underpowered for this comparison.²⁹ All of these studies used dexamethasone doses (8, 10, 16 mg) that were higher than used in this study (4 mg). Systemic dexamethasone doses greater than 0.1 mg/kg (as used in these three studies) are expected to have analgesic effects⁷. A meta-analysis indicates that the 4 mg dose used in the current study is not expected to have major systemic analgesic effect⁷; however this population-based statement would not necessarily apply to each patient.

Buprenorphine has been extensively studied as an adjunct for peripheral nerve blockade.^{8-11,28} Clinical concentrations of buprenorphine had no effect on in vitro ropivacaine-induced toxicity following a 24-hour exposure.²⁶ Buprenorphine, both perineural and intramuscular, improved analgesia after bupivacaine sciatic nerve blockade.⁸ Compared with control, perineural buprenorphine prolonged analgesia (from 6–12 hr to 24–36 hr), with decreased opioid use in the first 12 hours at home (from c 6 mg to c 2 mg

hydrocodone).⁸ Similarly, in this study, combined perineural administration of dexamethasone and buprenorphine (compared with control) prolonged analgesia (from 30 to 45.6 hr), reduced worst pain score (from 2 to 0), and decreased use of additional opioids on POD1 (from 60.7% of patients to 32.1%). Study differences include the primary anesthetic, use of ultrasound, prophylactic antiemetics, and multimodal analgesia.

Safety data about combinations of local anesthetic and combined adjuncts are limited. A recent laboratory study with a similar drug combination (bupivacaine, clonidine, buprenorphine, dexamethasone) demonstrated both in vivo safety (ie, absence of any test article related changes in nerves after sciatic nerve blockade in rats), as well as in vitro chemical compatibility and stability.³⁰ Additionally, quality assurance data are available after administration of combined multiple additives for nerve blockade in over 1300 clinical cases.³¹

Strengths of the study include use of a randomized controlled trial design, including a systemic control group. Systemic controls were used for dexamethasone and buprenorphine. Numerous outcomes were measured (following IMMPACT guidelines as applied to acute pain studies), covering pain, use of analgesics, physical functioning, satisfaction, symptoms and adverse events, and participant disposition.¹⁷

Weaknesses of the study include the assumption of higher pain scores at 24 hours for the power analysis. Pain scores at 24 hours were substantially lower than predicted, and no difference was seen between groups at 24 hours. The study examined the concept of multimodal perineural analgesia, so it is not possible to determine whether the effects were due to buprenorphine, dexamethasone, or the combination. Different doses or combinations of the adjuvants may have different effects. All 3 groups received 4 mg dexamethasone; an additional control group that did not receive dexamethasone would have helped clarify the analgesic role of systemic dexamethasone. Both intravenous and perineural study drugs were administered intraoperatively to sedated patients by unblinded physicians; data collection was performed by blinded researchers. Blinding could potentially have been improved by remote preparation of study drugs and blinding of study physicians.

Further research is needed to confirm that perineural buprenorphine and dexamethasone (1) reduce the worst pain experienced, (2) prolong time until block resolution, and (3) reduce need for postoperative opioids. Before recommending use of these additives it would be necessary to demonstrate clinically meaningful benefit. Studies are needed to assess whether both buprenorphine and dexamethasone are needed, and if so, in which combination. Large-scale clinical trials are needed to evaluate safety. Direct comparison of safety and efficacy of perineural catheters vs single-injection nerve blockade with additives would be of interest.

In conclusion, median pain scores were zero at 24 hours after foot and ankle surgery in the context of a multimodal analgesic, and were not improved by either perineural or intravenous administration of buprenorphine, 150 mcg, and dexamethasone, 4 mg. Perineural buprenorphine and dexamethasone reduced the worst pain experienced, prolonged block duration, and reduced postoperative opioid use. Intravenous buprenorphine

caused troubling nausea and vomiting, despite antiemetics. Future research is needed to confirm and extend these observations.

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REFERENCES

1. YaDeau JT, Wukovits BU, LaSala VR, et al. Similar analgesic effect after popliteal fossa nerve blockade with 0.375% and 0.75% bupivacaine. *HSS J.* 2007; 3:173–176. [PubMed: 18751790]
2. YaDeau JT, LaSala VR, Paroli L, et al. Clonidine and analgesic duration after popliteal fossa nerve blockade: a randomized, double-blind, placebo-controlled study. *Anesth Analg.* 2008; 106:1916–1920. [PubMed: 18499632]
3. Choi S, Rodseth R, McCartney CJ. Effects of dexamethasone as a local anaesthetic adjuvant for brachial plexus block: a systematic review and meta-analysis of randomized trials. *Br J Anaesth.* 2014; 112:427–439. [PubMed: 24413428]
4. Desmet M, Braems H, Reynvoet M, et al. I.V. and perineural dexamethasone are equivalent in increasing the analgesic duration of a single-shot interscalene block with ropivacaine for shoulder surgery: a prospective, randomized, placebo-controlled study. *Br J Anaesth.* 2013; 111:445–452. [PubMed: 23587875]
5. Fredrickson MJ, Danesh-Clough TK, White R. Adjuvant dexamethasone for bupivacaine sciatic and ankle blocks: results from 2 randomized placebo-controlled trials. *Reg Anesth Pain Med.* 2013; 38:300–307. [PubMed: 23698496]
6. Rahangdale R, Kendall MC, McCarthy RJ, et al. The effects of perineural versus intravenous dexamethasone on sciatic nerve blockade outcomes: a randomized, double-blind, placebo-controlled study. *Anesth Analg.* 2014; 118:1113–1119. [PubMed: 24686045]
7. De Oliveira GS Jr, Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. *Anesthesiology.* 2011; 115:575–588. [PubMed: 21799397]
8. Candido KD, Hennes J, Gonzalez S, et al. Buprenorphine enhances and prolongs the postoperative analgesic effect of bupivacaine in patients receiving infragluteal sciatic nerve block. *Anesthesiology.* 2010; 113:1419–1426. [PubMed: 21042200]
9. Candido KD, Winnie AP, Ghaleb AH, Fattouh MW, Franco CD. Buprenorphine added to the local anesthetic for axillary brachial plexus block prolongs postoperative analgesia. *Reg Anesth Pain Med.* 2002; 27:162–167. [PubMed: 11915063]
10. Candido KD, Franco CD, Khan MA, Winnie AP, Raja DS. Buprenorphine added to the local anesthetic for brachial plexus block to provide postoperative analgesia in outpatients. *Reg Anesth Pain Med.* 2001; 26:352–356. [PubMed: 11464356]
11. Modi M, Rastogi S, Kumar A. Buprenorphine with bupivacaine for intraoral nerve blocks to provide postoperative analgesia in outpatients after minor oral surgery. *J Oral Maxillofac Surg.* 2009; 67:2571–2576. [PubMed: 19925973]
12. Ibinson JW, Mangione MP, Williams BA. Local anesthetics in diabetic rats (and patients): Shifting from a known slippery slope toward a potentially better multimodal perineural paradigm? *Reg Anesth Pain Med.* 2012; 37:574–576. [PubMed: 23086347]
13. Tran DQ, Gonzalez AP, Bernucci F, Pham K, Finlayson RJ. A randomized comparison between bifurcation and prebifurcation subparaneural popliteal sciatic nerve blocks. *Anesth Analg.* 2013; 116:1170–1175. [PubMed: 23492960]

14. Sala-Blanch X, Vandepitte C, Laur JJ, et al. A practical review of perineural versus intraneural injections: a call for standard nomenclature. *Int Anesthesiol Clin.* 2011; 49:1–12. [PubMed: 21956073]
15. Franco CD. Connective tissues associated with peripheral nerves. *Reg Anesth Pain Med.* 2012; 37:363–365. [PubMed: 22683708]
16. Parrington SJ, O'Donnell D, Chan VW, et al. Dexamethasone added to mepivacaine prolongs the duration of analgesia after supraclavicular brachial plexus blockade. *Reg Anesth Pain Med.* 2010; 35:422–426. [PubMed: 20814282]
17. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain.* 2005; 113:9–19. [PubMed: 15621359]
18. YaDeau JT, Liu SS, Rade MC, Marcello D, Liguori GA. Performance characteristics and validation of the Opioid-Related Symptom Distress Scale for evaluation of analgesic side effects after orthopedic surgery. *Anesth Analg.* 2011; 113:369–377. [PubMed: 21525182]
19. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009; 42:377–381. [PubMed: 18929686]
20. YaDeau JT, Paroli L, Kahn RL, et al. Addition of pregabalin to multimodal analgesic therapy following ankle surgery: a randomized double-blind, placebo-controlled trial. *Reg Anesth Pain Med.* 2012; 37:302–307. [PubMed: 22476240]
21. Pitman EJG. Significance tests which may be applied to samples from any populations. *Supplement to the Journal of the Royal Statistical Society.* 1937; 4:119–130.
22. Ma Y, Mazumdar M, Memtsoudis SG. Beyond repeated-measures analysis of variance: Advanced statistical methods for the analysis of longitudinal data in anesthesia research. *Reg Anesth Pain Med.* 2012; 37:99–105. [PubMed: 22189576]
23. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: A generalized estimating equation approach. *Biometrics.* 1988; 44:1049–1060. [PubMed: 3233245]
24. Choquet O, Noble GB, Abbal B, Morau D, Brinquier S, Capdevila X. Subparaneural versus circumferential extraneural injection at the bifurcation level in ultrasound-guided popliteal sciatic nerve blocks: a prospective, randomized, double-blind study. *Reg Anesth Pain Med.* 2014; 39:306–311. [PubMed: 24918330]
25. Dobkin AB, Esposito B, Philbin C. Double-blind evaluation of buprenorphine hydrochloride for post-operative pain. *Can Anaesth Soc J.* 1977; 24:195–202. [PubMed: 321103]
26. Williams BA, Hough KA, Tsui BY, Ibinson JW, Gold MS, Gebhart GF. Neurotoxicity of adjuvants used in perineural anesthesia and analgesia in comparison with ropivacaine. *Reg Anesth Pain Med.* 2011; 36:225–230. [PubMed: 21519308]
27. Ma R, Wang X, Lu C, et al. dexamethasone attenuated bupivacaine-induced neuron injury in vitro through a threonine-serine protein kinase B-dependent mechanism. *Neuroscience.* 2010; 167:329–342. [PubMed: 20038443]
28. Candido KD, Knezevic NN. All adjuvants to local anesthetics were not created equal: Animal data evaluating neurotoxicity, thermal hyperalgesia and relevance to human application. *Reg Anesth Pain Med.* 2011; 36:211–212. [PubMed: 21508791]
29. Sondekoppam RV, Uppal V, Ganapathy S. Intravenous or perineural dexamethasone for interscalene brachial plexus block: The equivalence not yet proven. *Br J Anaesth.* 2014; 112:175–176. [PubMed: 24318708]
30. Williams BA, Butt MT, Zeller JR, Coffee S, Pippi MA. Multimodal perineural analgesia with combined bupivacaine-clonidine-buprenorphine-dexamethasone: safe in vivo and chemically compatible in solution. *Pain Med.* 2015; 16:186–198. [PubMed: 25339320]
31. Williams BA, Ibinson JW, Mangione MP, et al. Research priorities regarding multimodal peripheral nerve blocks for postoperative analgesia and anesthesia based on hospital quality data extracted from over 1,300 cases (2011–2014). *Pain Med.* 2015; 16:7–12. [PubMed: 25377071]

Figure 1.
CONSORT diagram of patient flow through the study

Figure 2.

Pain Scores (NRS). 2A. Pain with movement. 2B. Pain at rest.

The diamond, square, triangle, and circle indicate the means, the bottom and top areas of each box indicate the 1st and 3rd quartiles, respectively. The horizontal line within the box indicates the median, and the lines extending out of the bottom and top represent the minimum and maximum values that lie within 1.5 times the interquartile range (3rd quartile minus 1st quartile) below and above the 1st and 3rd quartiles, respectively.

Figure 3. Kaplan-Meier plot showing the proportion of patients in each group not yet reporting that the block entirely wore off by time elapsed after end of block administration. Survival curves are shown with 95% Hall-Wellner bands.

Table 1

Demographics

	IV Dexamethasone (n = 30)	IV Buprenorphine + Dexamethasone (n = 30)	Perineural Buprenorphine + Dexamethasone (n = 30)
Age (Years), mean $\pm$ SD	51 $\pm$ 16	51 $\pm$ 15	53 $\pm$ 14
Gender (Male / Female) (%)	40.0% / 60.0%	46.7% / 53.3%	43.3% / 56.7%
BMI, mean $\pm$ SD	27.2 $\pm$ 5.7	26.3 $\pm$ 4.4	26.3 $\pm$ 5.2
Race (n)			
Caucasian	23	24	26
Other	7	6	4
ASA (1/2/3) (n)	19/9/2	17/12/1	15/14/1
Operation Type:			
ORIF Ankle Fracture	3	2	3
Achilles Tendon Repair	1	1	3
Forefoot/Midfoot Reconstruction	9	7	8
Midfoot Reconstruction	2	3	5
Hindfoot Reconstruction	9	5	9
Forefoot Reconstruction	3	2	1
Peroneal Tendon Surgery	1	8	0
ORIF Calcaneous Fracture	0	1	1
Ankle Arthroscopy	2	1	0

Abbreviations: ASA = American Society of Anesthesiologists physical status classification system; BMI = Body Mass Index; IV Dexamethasone = control nerve blocks + IV dexamethasone (4 mg); IV Buprenorphine + Dexamethasone = control nerve blocks + IV buprenorphine (150 mcg) + IV dexamethasone (4 mg); Perineural Buprenorphine + Dexamethasone = nerve blocks containing buprenorphine (150 mcg) + dexamethasone (4 mg); ORIF = open reduction internal fixation; SD = standard deviation

Numeric Rating Scale (NRS) Pain Scores

Table 2

IV Dexamehasone						IV Buprenorphine + Dexamehasone						Perineural Buprenorphine + Dexamehasone					
	N	Mean ± SD	Median (Q1, Q3)		N	Mean ± SD	Median (Q1, Q3)	Unadjusted analysis <i>P</i> ^a	Adjusted analysis <i>P</i> ^b		N	Mean ± SD	Median (Q1, Q3)	Unadjusted analysis <i>P</i> ^a	Adjusted analysis <i>P</i> ^b		
NRS with Movement																	
Pre-op	30	5.0 ± 3.2	5 (3, 8)		29	4.2 ± 3.1	5 (2, 7)	0.350	---		30	4.8 ± 3.6	5 (1, 8)	0.850	---		
PACU	27	0.9 ± 2.2	0 (0, 0)		26	0.2 ± 0.5	0 (0, 0)	0.094	0.090		24	0.7 ± 2.1	0 (0, 0)	0.760	0.814		
24 hours	27	1.9 ± 2.6	0 (0, 4)		28	1.0 ± 1.6	0 (0, 2)	0.149	0.178		28	1.3 ± 2.1	0 (0, 2.5)	0.390	0.362		
48 hours	26	3.7 ± 3.1	4 (0, 6)		26	3.7 ± 2.0	4 (2, 5)	0.999	0.959		25	4.3 ± 2.8	4 (3, 6)	0.475	0.424		
NRS at Rest																	
Pre-op	30	1.9 ± 2.4	1 (0, 4)		29	1.2 ± 2.2	0 (0, 1)	0.235	---		30	1.6 ± 2.7	0 (0, 3)	0.725	---		
PACU	27	0.9 ± 2.2	0 (0, 0)		27	0.2 ± 0.6	0 (0, 0)	0.124	0.191		27	1.0 ± 2.7	0 (0, 0)	0.914	0.853		
24 hours	27	1.8 ± 2.5	0 (0, 4)		28	0.9 ± 1.3	0 (0, 2)	0.105	0.150		28	0.8 ± 1.6	0 (0, 1)	0.098	0.081		
48 hours	26	2.7 ± 2.7	2 (0, 4)		27	2.4 ± 2.0	3 (1, 3)	0.730	0.909		25	3.3 ± 2.6	3 (2, 5)	0.460	0.390		
BPI Worst Pain																	
24 hours	27	3.4 ± 3.6	2 (0, 7)		26	1.2 ± 2.0	0 (0, 2)	0.010	---		26	1.6 ± 2.5	0 (0, 3)	0.043	---		

Abbreviations: BPI = Brief Pain Inventory; IV Dexamehasone = control nerve blocks + IV dexamehasone (4 mg); IV Buprenorphine + Dexamehasone = control nerve blocks + IV buprenorphine (150 mcg) + IV dexamehasone (4 mg); Perineural Buprenorphine + Dexamehasone = nerve blocks containing buprenorphine (150 mcg) + dexamehasone (4 mg); NRS = Numeric Rating Scale; PACU = post anesthesia care unit; SD = standard deviation

^aUnadjusted analysis *P* values obtained via Fisher-Pitman permutation tests.

^bAdjusted analysis *P* values obtained via generalized estimating equations (GEE) method with adjustment for pre-operative score.

Table 3

Time to event

	IV Dexamethasone			IV Buprenorphine + Dexamethasone			Perineural Buprenorphine + Dexamethasone			
Event	N	Median time to event (95% CI)	N	Median time to event (95% CI)	Hazard ratio (95% CI)	P	N	Median time to event (95% CI)	Hazard ratio (95% CI)	P
Foot/ankle started having pain	28	20.7 (18.0, 30.2)	28	29.8 (25.3, 39.4)	0.81 (0.46, 1.43)	0.456	28	30.3 (27.0, 37.2)	0.71 (0.39, 1.28)	0.258
Nerve block stopped providing pain relief	28	25.0 (18.2, 34.7)	28	32.2 (28.5, 40.5)	0.74 (0.41, 1.34)	0.3217	28	32.3 (28.4, 45.6)	0.66 (0.36, 1.23)	0.1936
Pain medication needed to be taken	28	25.5 (18.0, 34.7)	28	30.0 (26.8, 40.5)	0.91 (0.50, 1.67)	0.761	28	35.3 (30.3, 55.8)	0.59 (0.31, 1.14)	0.1163
Nerve block entirely wore off	28	30.0 (24.1, 45.2)	28	37.9 (30.7, 43.9)	0.75 (0.40, 1.38)	0.3539	28	45.6 (33.9, 53.8)	0.50 (0.26, 0.97)	0.0412

Time to event calculated from end of block administration to patient report of event. Data were censored at the time of last interview if the event did not occur during the assessment period.

Abbreviations: CI = confidence interval; IV Dexamethasone = control nerve blocks + IV dexamethasone (4 mg); IV Buprenorphine + Dexamethasone = control nerve blocks + IV buprenorphine (150 mcg) + IV dexamethasone (4 mg); Perineural Buprenorphine + Dexamethasone = nerve blocks containing buprenorphine (150 mcg) + dexamethasone (4 mg)

Table 4

Side effects

		IV Dexamethasone			IV Buprenorphine + Dexamethasone					Perineural Buprenorphine + Dexamethasone				
	Time Point	N	Count (%) Or median (Q1, Q3)	N	Count (%) Or median (Q1, Q3)	Risk Difference (95% CI)	Relative Risk (95% CI)	P	N	Count (%) Or median (Q1, Q3)	Risk Difference (95% CI)	Relative Risk (95% CI)	P	
	Opioid Use	28	17 (60.7)	28	8 (28.6)	-32.1% (-52.8, -6.1)	0.5 (0.2, 0.9)	0.016	28	8 (28.6)	-32.1% (-52.8, -6.1)	0.5 (0.2, 0.9)	0.016	
	Nausea Treated	30	0 (0)	28	5 (17.9)	17.9% (2.7, 37.6)	N/A	0.021	30	1 (3.3)	3.3% (-8.3, 16.7)	N/A	0.483	
	ORSDS Composite Score	27	0.2 (0, 0.4)	26	2.1 (1.1, 4.6)	N/A	N/A	0.033	26	0.1 (0, 0.4)	N/A	N/A	0.756	
	Nausea Occurrence ^a	27	6 (22.2)	26	15 (57.7)	35.5% (9.1, 55.9)	2.6 (1.2, 5.7)	0.008	26	5 (19.2)	-3.0% (-24.4, 19.0)	0.9 (0.3, 2.5)	0.788	
	Among patients with nausea, % 'frequent' or 'almost constant'	6	0 (0)	15	8 (53.3)	53.3% (7.9, 75.2)	N/A	0.046	5	0 (0)	N/A	N/A	N/A	
	Among patients with nausea, % 'severe' or 'very severe'	6	0 (0)	15	9 (60.0)	60.0% (14.1, 80.2)	N/A	0.019	5	0 (0)	N/A	N/A	N/A	
	Among patients with nausea, % 'quite a bit' or 'very much' bothersome	6	0 (0)	15	12 (80.0)	80.0% (33.6, 93.0)	N/A	0.002	5	0 (0)	N/A	N/A	N/A	
	Emesis Occurrence ^a	27	0 (0)	26	7 (26.9)	26.9% (8.8, 46.1)	N/A	0.004	26	1 (3.8)	3.8% (-9.0, 18.9)	N/A	0.491	

Abbreviations: CI = confidence interval; IV Dexamethasone = control nerve blocks + IV dexamethasone (4 mg); IV Buprenorphine + Dexamethasone = control nerve blocks + IV buprenorphine (150 mcg) + IV dexamethasone (4 mg); Perineural Buprenorphine + Dexamethasone = nerve blocks containing buprenorphine (150 mcg) + dexamethasone (4 mg); PACU = post anesthesia care unit

^aNausea and emesis occurrence determined via the Opioid Related Symptom Distress Scale (ORSDDS)