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Buprenorphine Enhances and Prolongs the Postoperative Analgesic Effect of Bupivacaine in Patients Receiving Infragluteal Sciatic Nerve Block

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ABSTRACT

Background: Results from previous studies have shown favorable effects from the addition of buprenorphine to local anesthetics used for interscalene or axillary perivascular brachial plexus blocks. The main objective of the current study was to determine whether addition of buprenorphine could enhance bupivacaine analgesia after infragluteal sciatic nerve block.

Methods: One hundred and three consenting adult patients for elective foot and ankle outpatient surgeries were prospectively assigned randomly, in double-blind fashion, to one of three groups. Group 1 received 0.5% bupivacaine with epinephrine 1:200,000 for infragluteal sciatic block plus 1 ml normal saline intramuscularly. Group 2 received bupivacaine sciatic block along with intramuscular buprenorphine (0.3 mg). Group 3 received bupivacaine plus buprenorphine for infragluteal sciatic block and 1 ml normal saline intramuscularly.

Results: Although patients receiving buprenorphine either for sciatic block or intramuscularly had less pain in the postanesthesia care unit compared with patients receiving only bupivacaine, the individual pair-wise comparison of the analysis of variance model showed no statistical difference. However, only buprenorphine added to bupivacaine for sciatic block prolonged postoperative analgesia. Patients receiving a combination of buprenorphine and bupivacaine for sciatic block had lower numeric rating pain scores and received less opioid medication at home than patients in the other two groups.

Conclusions: The results show that buprenorphine may enhance and prolong the analgesic effect of bupivacaine when used for sciatic nerve blocks in patients undergoing foot and ankle surgery under general anesthesia but does not do so to the extent shown in previous studies using brachial plexus models with mepivacaine and tetracaine.

What We Already Know about This Topic

- Whether opioids prolong peripheral nerve block duration by a clinically meaningful degree is uncertain

What This Article Tells Us That Is New

- In sciatic nerve blocks, buprenorphine added to bupivacaine enhances and prolongs postoperative analgesic effects but to a minor degree

PERIPHERAL nerve blocks are useful techniques for providing perioperative analgesia after outpatient surgery. Different adjuncts have been proposed to enhance and prolong the effect of local anesthetics (LAs) in upper extremity peripheral nerve blocks, including epinephrine, bicarbonate, clonidine, neostigmine, tramadol, and opioids.[1–5] Discovery of multiple opiate receptor sites present on primary afferent nerve fibers[6] increased interest in using opioid analgesics as adjuvants to LAs. However, the efficacy and mechanism of action of peripherally applied opioids in postoperative pain remains controversial.[4,7,8] One difficulty is in determining whether the analgesic action of peripherally administered opioids is mediated by interaction at peripheral opioid receptor sites, by interaction within the substantia

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gelatinosa of the dorsal horn of the central nervous system after systemic absorption, or by facilitating and enhancing the analgesic properties of LAs.

Results from previous studies[1–3,9,10] have shown favorable effects from the addition of buprenorphine to LAs for upper extremity peripheral and neuraxial nerve blocks. However, opioid analgesics have not been studied as LA adjuvants for sciatic nerve block. It is unclear whether the sciatic nerve, surrounded by dense connective tissue, would be an unfavorable anatomical site where anatomical barriers would limit usefulness of perineural additives to LAs. Therefore, the purposes of this study were (1) to determine whether the addition of buprenorphine could enhance bupivacaine analgesia when used for sciatic nerve block placed for postoperative analgesia, and (2) to evaluate whether the observed benefit of the perineural buprenorphine was peripherally mediated by comparing it with the analgesic effect provided by a systemic intramuscular injection of buprenorphine in patients receiving sciatic nerve blocks.

Materials and Methods

After Loyola University Medical Center Institutional Review Board (Maywood, Illinois) approval of the protocol, written informed consent was obtained from 103 consecutive adult patients scheduled to receive a sciatic nerve block as a component of their anesthetic management for outpatient foot and ankle surgery.

Buprenorphine is not approved for neuraxial or peripheral administration by the United States Food and Drug Administration. However, it has been well described as a LA adjuvant in several regional anesthesia and pain management textbooks.[5,11–13] All study participants were advised of this off-label use of buprenorphine.

Excluded from the study were patients who had hemostatic abnormalities, chronic pain syndromes, or preexisting neuropathy or neuromuscular disease that could interfere with data collection. Patients were also excluded if they were receiving long-term opioid analgesic therapy or reported a history of allergy to amino-amide LA drugs or opioids.

All patients received 2 mg/50 kg midazolam premedication, followed by a single-injection sciatic nerve block using an infragluteal-parabiceps approach, as described previously,[14] followed by general inhalational anesthesia without opioid supplementation. Sciatic nerve block was performed in the prone or lateral decubitus position using a 10-cm, 21-gauge insulated needle and peripheral nerve stimulator guidance. The needle was positioned at the gluteal fold, just lateral to the long head of the biceps femoris muscle, and was directed until plantar flexion (53%) or inversion (45%) of the ipsilateral foot was obtained at 0.20–0.40 mA stimulation.[14] Once the appropriate evoked motor response was obtained, bupivacaine 0.5%, with or without buprenorphine, was incrementally injected as follows.

Using a double-blind protocol, patients were randomly assigned to one of three groups using computer-generated randomization numbers, which were kept in sealed envelopes. Patients in group 1 (LA control) received LA (0.5% bupivacaine with epinephrine 1:200,000), 0.45 ml/kg for infragluteal block, plus 1 ml normal saline intramuscularly into the gluteus maximus muscle. Patients in group 2 (intramuscular control) received the same LA regimen along with intramuscular buprenorphine 0.3 mg (1 ml). Patients in group 3 (additive) received both LA and buprenorphine (0.3 mg) for infragluteal sciatic nerve block and 1 ml normal saline intramuscularly into the gluteus muscle. The anesthesiologist who injected the same volumes of solutions, as well as the anesthesiologist assigned for evaluation in the operating room and in the postanesthesia care unit (PACU), was unaware of the assigned group for each patient.

Assessments for the onset of sensory and motor block were performed every 2 min for 20 min by two trained observers working simultaneously and commencing from the time of completion of injection of the total dose of anesthetic for sciatic block. In most cases, both observers had the same assessment, and in cases wherein those assessments were different, the average values of the data were used. Sensory block assessments were performed in the distributions of the superficial peroneal nerve, deep peroneal nerve, posterior tibial nerve, and sural nerve. A three-level scale was used to grade the intensity of sensory block using pinprick stimulation: 0 = normal sensation (pin prick felt as sharp); 1 = blunt sensation (pin prick felt but not sharp); and 2 = no sensation (pin prick not felt at all). Motor block intensity of the foot was graded on a four-level scale: 0 = full movement (no discernible weakness); 1 = decreased movement (moves foot); 2 = diminished movement (moves toes only); and 3 = no movement (complete motor block). Motor block assessments performed included plantar flexion (representing a tibial nerve component), dorsiflexion of the foot at the ankle (representing a deep peroneal nerve component), and toe movements (representing both tibial and peroneal components). A complete block was defined as one associated with grade 2 sensory anesthesia and grade 3 motor block in the distribution of both the posterior tibial as well as peroneal nerves. Once the block assessments had been completed and no less than 20 min had elapsed, patients were placed supine and were transported to the operating room where standard American Society of Anesthesiologists monitors were applied, baseline vital signs were monitored and recorded, and oxygen was administered by facemask for denitrogenation of the lungs. Then, propofol was administered in a 2 mg/kg dose for anesthesia induction, followed by insertion of a laryngeal mask airway (LMA-Unique, LMA North America, Inc., San Diego, CA). Anesthesia maintenance was accomplished using oxygen, nitrous oxide, and sevoflurane with the patients breathing spontaneously.

The pain score was the primary outcome in our study. In the PACU, the pain intensity (0–10 numeric rating scale [NRS]), as well as recovery of sensation (superficial, deep peroneal, posterior tibial, and sural nerves) and motor function (toe movement), were monitored upon arrival at 15-,

30-, and 45-min intervals and at discharge by the attending anesthesiologist staffing the recovery room. Additional study variables that were recorded included patient age, weight, sex, American Society of Anesthesiologists physical status, type of surgical procedures, block performance time (time from initiation of block procedure to completion of LA injection), depth of needle insertion at which the injection was made, twitch amplitude, duration of surgery, perioperative adverse events, perioperative use of opioid analgesics, and duration of PACU stay.

Assessments of sensory function in the foot (normal sensation, blunted sensation, or no sensation), motor function (ability to move foot), pain intensity (0–10 NRS), use of analgesics, and adverse events continued to be monitored at home *via* telephone interview at 1-h intervals for the first 6 h, and at 12, 24, 36, and 48 h after discharge. Patients were instructed to use the surgeon's prescribed opioid analgesic (hydrocodone plus acetaminophen) when pain in the operated extremity was greater than or equal to 3 of 10 on the NRS.

Finally, overall satisfaction with the anesthesia experience and specifically with pain control was elicited on postoperative day 2 by telephone interview. The patients rated satisfaction with one of the following descriptors: complete satisfaction, satisfied, somewhat satisfied, dissatisfied, or complete dissatisfaction.

Statistical Analysis

The sample size estimate for this study (n = 24 patients in each group) was determined to detect a difference in postoperative pain scores at $\alpha = 0.05$ and power = 0.90, given that the pain score was the primary outcome in our study. We considered a difference of 50% in pain scores after 24 h to be clinically significant. Expected mean (SD) pain scores were 3.0 (2.0) and 1.5 (1.5) for control and treated groups, respectively. To allow a larger SD than anticipated and account for potential dropouts, we included 34 patients per group.

Statistical analysis was performed using SPSS software (IBM SPSS Statistics 18, Chicago, IL). NRS pain scores in the PACU and at home, as well as opioid medication use at home, are expressed as mean ± SD. The other data are expressed as median and interquartile range (range between the 25th and 75th percentiles) or as number of subjects. A repeated-measures analysis of variance (ANOVA) was performed to compare NRS pain scores and opioid medication use by using *post hoc* analysis with Bonferroni correction. The study group was treated as a between-subject factor and time was treated as a within-subject factor. Kruskal-Wallis test and Mann–Whitney U-test were used to compare quantitative parameters. The Fisher exact test was used to analyze categorical data. A *P* value less than 0.05 was considered to be statistically significant. The nature of the significance testing was two-tailed. Whenever *P* values were significant, we also reported effect size to supplement the reported *P* values. The effect size statistics were partial η squared in repeated measures ANOVA and *r* statistics in Mann–Whitney analysis.

Table 1. Demographic Characteristics of Patients

	Group 1 LA Control	Group 2 IM Control	Group 3 Additive	Statistical Difference *P*
Sex				
Males	17	12	16	—
Females	17	23	18	0.369
Age, yr	42 [21]	48 [15]	46 [21]	0.575
Height, cm	168 [16]	165 [10]	170 [16]	0.132
Weight, kg	100 [37]*	84 [27]	90 [32]	0.037
ASA				
1	9	5	13	—
2	19	23	20	—
3	6	7	1	0.060
N	34	35	34	—

Values are reported as median [interquartile range] or number of subjects. Group 1: LA Control = local anesthetic block + IM placebo; group 2: IM Control = local anesthetic block + IM buprenorphine; group 3: Additive = local anesthetic/buprenorphine block + IM placebo.

* Statistically significant difference between LA control and IM control groups ($P = 0.039$; $r = 0.3$).

ASA = American Society of Anesthesiologists; IM = intramuscular.

Results

One hundred and three patients participated in the study, consisting of 45 men and 58 women with a median (interquartile range) age of 45 (18) yr. Aside from one failed block (group 1), there were no drop-outs and no patients lost to follow-up. There was no significant difference between the three groups with respect to age, sex, height, or physical status (table 1). Patients in group 1 (LA control) had a slight but statistically significant greater weight compared with the intramuscular control group ($P = 0.039$; $r = 0.3$) (table 1). All patients were undergoing various elective foot and ankle surgical procedures (table 2). There were no differences between the three groups in duration of surgery, time to complete the block, percentage of failed blocks, depth of needle insertion, twitch amplitude needed to evoke a brisk plantar flexion or an inversion of the foot, or time spent in the PACU (table 3).

The pain score was the primary outcome in our study, which we evaluated in the PACU and at home for the first 48 h after discharge. Patients receiving buprenorphine added to the bupivacaine for infragluteal sciatic nerve block had approximately 50% lower NRS pain scores in the PACU than patients in the control group (fig. 1). This beneficial, antinociceptive effect, however, was similar to that observed in the group with the systemic (intramuscular) injection of buprenorphine (group 2). However, the repeated-measures ANOVA showed that both factors (time and group) were statistically significant but interaction (group × time) was not (fig. 1). The *post hoc* test did not find any significant difference in the group factor, and we found significant dif-

Table 2. Types of Surgical Procedures

	Group 1 LA Control	Group 2 IM Control	Group 3 Additive	Statistical Difference *P*
Ankle Arthroscopy	6	1	3	—
Arthroscopy plus Ligament Reconstruction	5	2	2	—
Achilles Tendon Reconstruction	0	2	5	—
Fusion	7	12	8	—
Ligament-Tendon Reconstruction	3	3	6	—
ORIF	8	7	2	—
Osteotomy	4	3	5	—
Tendon Transfer	0	2	0	—
Excisions	1	3	3	—
N	34	35	34	0.115

Values are reported as number of subjects.

Group 1: LA Control = local anesthetic block + intramuscular (IM) placebo; group 2: IM Control = local anesthetic block + IM buprenorphine; group 3: Additive = local anesthetic/buprenorphine block + IM placebo.

ORIF = open reduction with internal fixation.

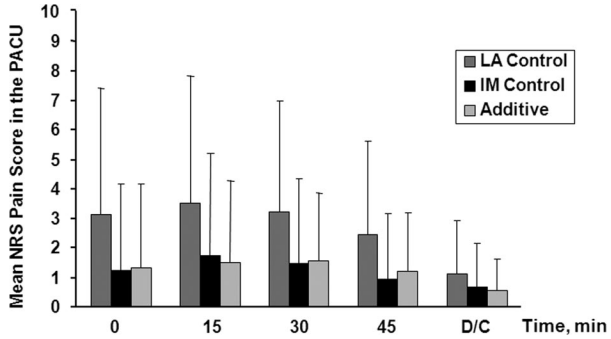

Fig. 1. The numeric rating scale (NRS) pain score in the postanesthesia care unit (PACU) (by repeated-measures analysis of variance). Plots show mean NRS pain scores (mean ± SD) at different time points in the PACU. A between-subject factor group was significant at level $P = 0.026$ (partial η squared 0.071), and a within subject factor time was significant at level P less than 0.0005 (partial η squared 0.236). However, an interaction (group × time) was not significant. The *post hoc* comparisons with Bonferroni correction on factor group was not found to be significant. The *post hoc* comparisons with Bonferroni correction on factor time was significant between adjacent time points (30 and 45 min: P less than 0.0005, partial η squared = 0.160; 45 min and D/C: $P = 0.001$, partial η squared = 0.134). Group 1: LA control = local anesthetic block + intramuscular placebo; group 2: intramuscular control = local anesthetic block + intramuscular buprenorphine; group 3: additive = local anesthetic/buprenorphine block + intramuscular placebo. D/C = discharge time.

ferences between adjacent times (30–45 min and 45 min-discharge time) in the time factor.

Although there was no difference in analgesic efficacy between the local and systemic (intramuscular) injections of buprenorphine (groups 2 and 3), the pain follow-up after discharge showed a longer duration of analgesia in patients who received buprenorphine as a block component (group 3: additive) (fig. 2). The repeated-measures ANOVA of NRS pain scores at home showed that besides both factors (group and time), the interaction between time and group was also significant (fig. 2). The *post hoc* analysis showed significant differences between additive and the two control groups (LA control and intramuscular control). The *post hoc* analysis within groups on adjacent times showed differences in the LA control group between 6 and 12 h, in the intramuscular control group between 12 and 24 h, and in the additive group between 24 and 36 h (fig. 2).

The opioid medication use at home showed that patients from group 3 (additive) used less pain medication than patients in the other two groups (LA control and intramuscular control) (fig. 3). The repeated-measures ANOVA of opioid medication use at home showed that time and group factors and interaction between time and group were significant. The *post hoc* analysis showed significant differences between the additive group and the two control groups (LA control and intramuscular control). The *post hoc* analysis within groups on adjacent times in LA control and intramuscular control groups showed differences between 6 and 12 h and between 12 and 24 h in the additive group (fig. 3).

The mean time until patients receiving LA block with buprenorphine added (group 3) required opioid analgesics was approximately 6 h longer *versus* patients in the other two

Table 3. Duration of Surgery (Surgical Time), Time to Complete the Block (Block Time), Depth of Needle Insertion (Needle Depth), Twitch Amplitude, Failed Blocks, and Time in the Postanesthesia Care Unit (PACU Time)

	Group 1 LA Control	Group 2 IM Control	Group 3 Additive	Statistical Difference *P*
Surgical time, min	64 [39]	62 [32]	54 [35]	0.378
Block time, min	5 [4]	5 [4]	4 [5]	0.560
Needle depth, cm	5 [2]	4 [4]	4 [3]	0.440
Twitch amplitude, mA	0.34 [0.10]	0.35 [0.07]	0.35 [0.08]	0.957
Failed blocks	1/34	0/35	0/34	0.660
PACU time, min	87 [41]	100 [55]	98 [51]	0.133

Values are reported as median [interquartile range] or number of subjects.

Group 1: LA Control = local anesthetic block + intramuscular (IM) placebo; group 2: IM Control = local anesthetic block + IM buprenorphine; group 3: Additive = local anesthetic/buprenorphine block + IM placebo.

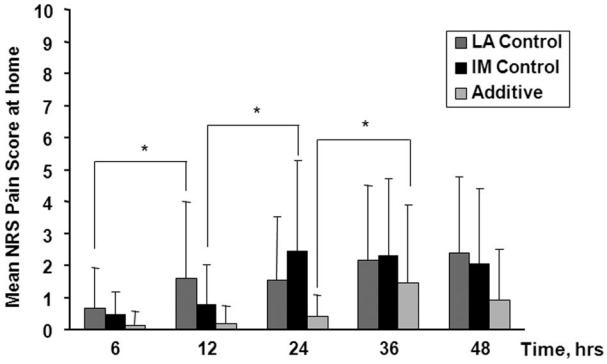

Fig. 2. The numeric rating scale (NRS) pain score after discharge (by repeated-measures analysis of variance). Plots show mean NRS pain scores (mean ± SD) at different time points after discharge. A between-subject factor group was significant at level $P = 0.02$ (partial η squared = 0.115), and a within-subject factor time was significant at level P less than 0.0005 (partial η squared = 0.432). An interaction (group × time) was also significant at level $P = 0.001$ (partial η squared = 0.130). The *post hoc* comparisons with Bonferroni correction on factor group was found to be significant between the additive and LA control groups ($P = 0.005$) and between the additive and intramuscular control groups ($P = 0.009$). The *post hoc* comparisons with Bonferroni correction on factor time was significant between adjacent time points (6 and 12 h: $P = 0.004$, partial η squared = 0.113; 12 and 24 h: $P = 0.012$, partial η squared = 0.086). Because the interaction (group × time) was significant, we also analyzed differences within groups across times with Bonferroni correction. In the LA control group, we found differences between 6 and 12 h ($P = 0.036$, partial η squared = 0.190). In the intramuscular control group, we found differences between 12 and 24 h ($P = 0.001$, partial η squared = 0.324). In the additive group, we found differences between 24 and 36 h ($P = 0.028$, partial η squared = 0.202). * Statistically significant difference within groups between certain times (P less than 0.05). Group 1: LA control = local anesthetic block + intramuscular placebo; group 2: intramuscular control = local anesthetic block + intramuscular buprenorphine; group 3: additive = local anesthetic/buprenorphine block + intramuscular placebo.

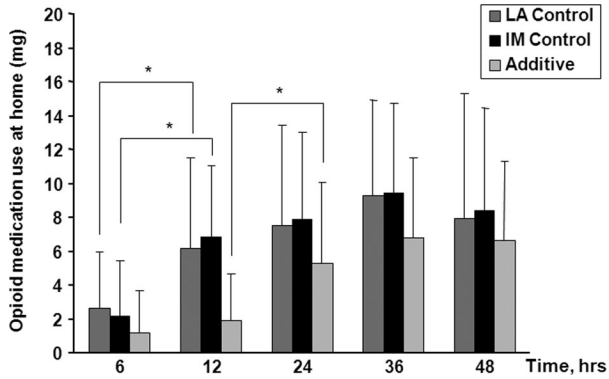

Fig. 3. Opioid medication use at home (by repeated-measures analysis of variance). Plots show mean hydrocodone dose in milligrams (mean ± SD) at different time points at home. A between-subject factor group was significant at level $P = 0.013$ (partial η squared = 0.083), a within-subject factor time was significant at level P less than 0.0005 (partial η squared = 0.640), and interaction (group × time) was significant at level $P = 0.001$ (partial η squared = 0.130). The *post hoc* comparisons with Bonferroni correction on factor group was found to be significant between the additive and LA control groups ($P = 0.046$) and between the additive and intramuscular control groups ($P = 0.022$). The *post hoc* comparisons with Bonferroni correction on factor time were significant between adjacent time points (6 and 12 h: P less than 0.0005, partial η squared = 0.367; 12 and 24 h: P less than 0.0005, partial η squared = 0.195; 24 and 36 h: P less than 0.0005, partial η squared = 0.137). Because the interaction (group × time) was significant, we also analyzed differences within groups across times with Bonferroni correction. In the LA control group, we found differences between 6 and 12 h (P less than 0.0005, partial η squared = 0.403). In the intramuscular control group, we found differences between 6 and 12 h (P less than 0.0005, partial η squared = 0.546). In the additive group, we found differences between 12 and 24 h (P less than 0.0005, partial η squared = 0.399). * Statistically significant difference within groups between certain times (P less than 0.05). Group 1: LA control = local anesthetic block + intramuscular placebo; group 2: intramuscular control = local anesthetic block + intramuscular buprenorphine; group 3: additive = local anesthetic/buprenorphine block + intramuscular placebo.

groups (23.9 ± 17.6 h in 71% of patients). The mean time until patients from the other two groups (groups 1 and 2) required opioid analgesics were 17.8 ± 17.1 h in 80% of patients and 17.7 ± 17.5 h in 87% of patients, respectively. Twenty-nine percent of patients from group 3, 20% of patients from group 1, and 13% of patients from group 2 did not require opioid analgesics.

Vomiting was a more frequent adverse event in patients receiving buprenorphine (groups 2 and 3) (table 4). Other side effects or complications such as urinary retention (total three patients), pruritus (total six patients), or fatigue (total nine patients) were less frequent than vomiting. None of the patients developed respiratory depression or ileus. Satisfaction with the anesthesia experience and with pain control was measured 48 h after discharge by telephone interview. There were no differences in satisfaction with the anesthesia experience ($P = 0.817$), specifically with pain control ($P = 0.761$) among the three groups, although the patients receiving buprenorphine (groups 2 and 3) had more adverse effects than patients receiving bupivacaine only (group 1).

Discussion

Buprenorphine is a partial μ opioid agonist and κ and δ antagonist, which produced antihyperalgesia in a human volunteer study of electrically-induced pain.[15] These effects were longer lasting and more pronounced than were the analgesic effects.[15] Buprenorphine is not approved for neuraxial or peripheral administration by the U.S. Food and Drug Administration. However, it has been well described as an adjuvant in several regional anesthesia and pain management textbooks.[5,11–13] Results from previous studies[1–3,9,10] have shown favorable effects from the addition of buprenor-

Table 4. Postoperative Vomiting (POV) and Patient's Satisfaction

	Group 1 LA Control	Group 2 IM Control	Group 3 Additive	Statistical Difference *P*
Operating Room POV	0	2	0	0.327
PACU POV	3	8	6	0.320
Postoperative Day 1 POV	2	9	8	0.070
Postoperative Day 2 POV	2	2	5	0.459
Satisfied/Complete Satisfied with Anesthesia Experience	34	34	33	0.817
Satisfied/Complete Satisfied with Pain Control	33	33	32	0.761

Values are reported as number of subjects.

Group 1: LA Control = local anesthetic block + intramuscular (IM) placebo; group 2: IM Control = local anesthetic block + IM buprenorphine; group 3: Additive = local anesthetic/buprenorphine block + IM placebo.

PACU = postanesthesia care unit.

phine to LAs used for upper extremity peripheral (interscalene or axillary perivascular brachial plexus) and for central neuraxial nerve blocks (caudal). However, opioid analgesics have not been studied as LA adjuvants for sciatic nerve block. Therefore, the purpose of this study was to determine the effects of buprenorphine added to bupivacaine using an infragluteal sciatic nerve block model.

Results of the current study show that the addition of buprenorphine to bupivacaine sciatic nerve block enhanced and prolonged postoperative analgesia. However, in the PACU, buprenorphine was equally effective whether it was given locally or systemically. The *post hoc* analysis with Bonferroni correction showed that interaction (group × time) was not significant. However, after adjustment, these comparisons were determined to have lower than calculated power. The follow-up after discharge revealed that only patients receiving buprenorphine added to bupivacaine for sciatic block had lower NRS pain scores and received less opioid medications than patients in the other two groups. The *post hoc* analysis with Bonferroni correction showed that the additive group was significantly different in NRS pain scores and opioid medication use than the other two control groups (LA control and intramuscular control).

Unlike other studies wherein buprenorphine was added to LAs for interscalene or axillary brachial plexus blocks, we were unable to demonstrate a multifold augmentation (*i.e.*, two to three times longer) of the duration of postoperative analgesia.[1,3] One of the reasons may be the discrepancies inherent in monitoring patients' pain and opioid analgesics use in the postoperative period of an outpatient surgical population compared with the surgical populations in previous studies that were performed as inpatient surgeries.[1,3] Here, we relied strictly upon telephone follow-up interviews for the first 48 h. In addition, there is a difference in the neural size and structure and surrounding connective tissue of the sciatic nerve *versus* the brachial plexus. The connective tissue and adipose content surrounding the sciatic nerve may be one reason for reduced effectiveness of a highly lipophilic substance such as buprenorphine when injected perineurally. The results of this study showed that 0.5% bupivacaine alone (group 1) had more than 1 h shorter analgesia than 0.625% levobupivacaine in a previous study[14] (17.7–17.8 *vs.* 19 h) using the same infragluteal approach. We believe that this difference is due to the higher concentration of levobupivacaine used in that previous study, as well as a slightly longer half-life of levobupivacaine (information from Purdue Pharma, L.P., Stamford, CT). However, in the current study there was an approximately 6-h prolonged duration of analgesia in the group receiving bupivacaine and buprenorphine together. These patients reported lower NRS pain scores in the first 24 h, and almost 40% of them had no pain even 48 h after surgery, which is atypical after foot and ankle surgeries where there is osseous manipulation.

There continues to be controversy regarding whether the analgesic effects of peripherally-injected opioids are peripherally or centrally mediated,[4,8,16] and one accepted mechanism to reconcile this is to use systemic opioid-control groups. Results of the current study support a previous supposition[1] that buprenorphine may prolong postoperative analgesia *via* peripheral mechanisms. Obara *et al.*[17] showed that the peripherally-selective opioid receptor antagonist naloxone-methiodide inhibited all agonist-induced antinociceptive activity in a rat model, indicating that all analgesic effects were mediated by peripheral opioid receptors. They also showed an improved effect of opioids on inflammatory pain *versus* neuropathic pain, because inflammation enhanced the transport or migration of opioid receptors.[17]

Opioid analgesics may have a direct anti-inflammatory effect on opioid receptors presented on different cells involved in host defense and the immune response.[18] It has been shown that opioids reduce cytokine expression and neutrophil infiltration in animal models.[19] Tissue inflammation and release of inflammatory cytokines are two main reasons postulated for the development of acute postoperative pain.[20] Because inflammation enhances transport of opioid receptors,[17] there is a possibility that the analgesic effects of buprenorphine are due to an increased number of active opioid receptors in the periphery. Martin *et al.*[20] showed that combined sciatic and femoral nerve blocks using LAs (without added opioids) inhibited inflammation after total knee arthroplasty but with no changes in tissue and plasma cytokine concentrations. Binder *et al.*[21] showed that the anti-inflammatory effects of peripherally active, selective opioid agonists were delayed, and it may be that a delayed anti-inflammatory effect of buprenorphine is responsible for the prolonged effect of locally administered buprenorphine in the current study. Machelska *et al.*[22] demonstrated an im-

portant role of opioids in modulating the inflammatory process. They showed that in the early stages of inflammation (*i.e.*, the first couple of hours), both peripheral and central opioid mechanisms contribute to the antinociception, whereas only the peripheral mechanism is effective in later stages.[22] The fact that the initial enhancing effect of buprenorphine was the same in both groups (receiving buprenorphine locally or systemically) in terms of both onset and efficacy demonstrates a similar pattern of antinociception in the current study as that described above (results, fig. 1).

Although we have shown that buprenorphine increases the risk of vomiting in patients receiving buprenorphine (local or systemic), this was not unexpected and is likely related to use of general anesthesia after the sciatic nerve block. However, this effect would have been minimized if patients received standard perioperative antiemetic treatment. Our study protocol did not designate antiemetic therapy in the perioperative period to avoid potentially engendering analgesic effects of antiemetic drugs, such as glucocorticoids, on postoperative pain. We observed no toxic effects of buprenorphine either acutely or delayed in onset during our 3-month follow up. The results from studies conducted on animal models and in healthy volunteers have shown that buprenorphine is largely devoid of systemic or neural toxicity when used in dosages commensurate with those employed here.[23,24]

There are several limitations of this study. The major limitation was our inability to directly observe and monitor patients' pain in the extended postoperative period. All surgeries were done in an outpatient center, and patients were discharged within 1.5–2 h of reaching the recovery room. We relied upon telephone follow-up interviews as our outpatient surgery center does not provide for 23-h observation admissions. Second, we were also unable to completely control the use of opioid analgesics in the postoperative period. It has been our experience that patients will often use opioid analgesics for any pain after surgery (general position-induced body aches or sore throats from airway instrumentation), or they may use opioids before sleeping to prevent pain during the nighttime. Larger study groups and the use of a patient-controlled analgesia regimen may detect a greater difference between groups.

This is the first clinical study demonstrating an analgesic effect from the addition of an opioid to a LA administered as an adjuvant during sciatic nerve block. The results of the current study demonstrate that buprenorphine may enhance and prolong the analgesic effect of bupivacaine when used for sciatic nerve blocks in patients undergoing general anesthesia for elective foot and ankle surgery but does not do so to the extent shown in previous studies using brachial plexus models.

Before determining whether buprenorphine should be added to bupivacaine for sciatic nerve block, one should consider the benefits *versus* the downside of proceeding with this additive. Benefits include lower pain scores and less opioid analgesic use in the first 12 h at home, 6-h prolonged duration of analgesia, and the reasonable cost of buprenorphine. The cost-per-unit dose of buprenorphine ($3.25 for not-for-profit hospitals through Hospira Inc, Lake Forest, IL) likely favors this adjunctive therapy compared with the costs of a disposable infusion system and catheter for at-home use ($478.80 for not-for-profit hospitals: $285 for Pain Pump 2 through Stryker, Kalamazoo, MI; $61.80 for a continuous catheter using Arrow International, Reading, PA; and $132 for 400 ml ropivacaine from AstraZeneca Pharmaceuticals, Wilmington, ME; plus the cost of ultrasound machine use). In contemporary medical practices wherein cost containment has become a stark reality, adjunctive therapies may become optional methods of providing sustained analgesia. Downsides include an increased use of opioid medications after 12 h at home and an inability to control or titrate postoperative perineural analgesia compared with continuous at-home infusions (36–48 h).

Buprenorphine added to bupivacaine for sciatic nerve block is not intended to be a substitute for the demonstrated efficacy of at-home patient controlled regional analgesia; merely it offers an economically affordable extended bridge for certain patients transitioning from single-shot nerve blocks to oral analgesics. The patient population likely to benefit from this technique would be those patients for whom a continuous peripheral block catheter is deemed not to be indicated as a result of lack of sufficient home support; possible compliance issues including language, education, or cultural constraints; a failure to successfully place catheters in a timely fashion; or practice in an environment not trained in the implementation of such devices.

Nevertheless, as multimodal regimens of providing perioperative analgesia continue to evolve, and as the economical advantages of minimizing reliance upon expensive technology becomes a reality, adjuvants to LA peripheral nerve blocks may assume a more prominent role in acute pain control.

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