The Effects of Perineural Versus Intravenous Dexamethasone on Sciatic Nerve Blockade Outcomes: A Randomized, Double-Blind, Placebo-Controlled Study

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BACKGROUND: Perineural dexamethasone has been investigated as an adjuvant for brachial plexus nerve blocks, but it is not known whether the beneficial effect of perineural dexamethasone on analgesia duration leads to a better quality of surgical recovery. We hypothesized that patients receiving dexamethasone would have a better quality of recovery than patients not receiving dexamethasone. We also sought to compare the effect of perineural with that of IV dexamethasone on block characteristics.

METHODS: Patients undergoing elective ankle and foot surgery were recruited over a 9-month period. Patients received ultrasound-guided sciatic nerve blocks by using 0.5% bupivacaine with epinephrine 1:300,000 (0.45 mL/kg) and were randomized into 3 groups: group 1 = perineural dexamethasone 8 mg/2 mL with 50 mL IV normal saline, group 2 = perineural saline/2 mL with IV 8 mg dexamethasone in 50 mL normal saline, and group 3 = perineural saline/2 mL with 50 mL normal saline. The primary outcome was the global score in the quality of recovery (QoR-40). The secondary outcomes included analgesia duration, opioid consumption, patient satisfaction, numeric pain rating scores, and postoperative neurologic symptoms.

RESULTS: Eighty patients were randomized, and 78 patients completed the study protocol. There was no improvement in the global QoR-40 score at 24 hours between the perineural dexamethasone and saline, median (97.5% CI) difference of ~3 (~7 to 3); IV dexamethasone and saline, median difference of ~1 (~8 to 5); or perineural dexamethasone and IV dexamethasone median difference of ~2 (~6 to 5). Analgesia duration (P < 0.001) and time to first toe movement (P < 0.001) were prolonged by perineural dexamethasone compared with saline. IV dexamethasone prolonged time to first toe movement compared with saline (P = 0.008) but not analgesia duration (P = 0.18). There was no significant difference in the time to first toe movement or analgesia duration between the perineural and IV dexamethasone groups. Postoperative opioid consumption was not different among study groups. Self-reported neurologic symptoms at 24 hours were not different among perinerveal dexamethasone (17, 63%), IV dexamethasone (10, 42%), or normal saline (8, 30%) (P = 0.31). All postoperative neurologic sequelae were resolved by 8 weeks.

CONCLUSIONS: Preoperative administration of IV and perineural dexamethasone compared with saline did not improve overall QoR-40 or decrease opioid consumption but did prolong analgesic duration in patients undergoing elective foot and ankle surgery and receiving sciatic nerve block. Given the lack of clinical benefit and the concern of dexamethasone neurotoxicity as demonstrated in animal studies, the practice of perineural dexamethasone administration needs to be further evaluated. (Anesth Analg 2014;118:1113–9)
on recovery outcomes when compared with IV dexamethasone for patients receiving a lower extremity nerve block.

The primary objective of the current investigation was to determine whether perineural dexamethasone provides a better quality of postsurgical recovery than IV dexamethasone or a saline control in patients receiving a local anesthetic sciatic nerve block. We hypothesized that patients receiving dexamethasone would have a better quality of recovery than patients not receiving dexamethasone. A secondary objective of the study was to compare the effect of perineural with IV dexamethasone on sciatic nerve block duration and postoperative analgesic use.

METHODS
This study was a randomized, double-blind, placebo-controlled trial. Clinical trial registration for this study can be found at ClinicalTrials.gov, NCT01616173. Study approval was obtained from the Northwestern University IRB, Chicago, IL, and written informed consent was obtained from all the study participants. An investigational new drug exemption (PIND #114062) was granted by the Food and Drug Administration. Healthy adults, aged between 18 and 70 years, undergoing elective ankle and foot surgery were recruited to participate. Patients with contraindications to regional anesthesia, history of allergy to local anesthetics, presence of a progressive neurological deficit, coagulopathy, infection, types 1 and 2 diabetes mellitus, systemic use of corticosteroids within 6 months of surgery, chronic use of an opioid analgesic (>3 months), midfoot and forehead surgery or pregnancy were not enrolled.

All subjects received an ultrasound-guided sciatic nerve block by using the infragluteal-parabiceps approach with 0.5% bupivacaine with epinephrine 1:300,000 (0.45 mL/kg). Subjects were randomized using a computer-generated table of random numbers into the following 3 groups: group 1 = perineural dexamethasone 8 mg/2 mL with 50 mL IV normal saline, group 2 = perineural saline/2 mL with IV 8 mg dexamethasone diluted in 50 mL normal saline, and group 3 = perineural saline/2 mL with 50 mL normal saline infusion. Group assignments were sealed in sequentially numbered opaque envelopes that were not opened until informed consent was obtained. Study drug medications were identical and were prepared by an investigator not involved with patient care or data collection.

After placement of standard American Society of Anesthesiologists monitors and peripheral IV access, patients were sedated with midazolam 2 to 5 mg IV, and if necessary, fentanyl 25 to 50 mcg IV was administered incrementally. All sciatic nerve blocks were performed by resident trainees supervised by the primary investigator. After a sterile prepping procedure, a 21-gauge echogenic, stimulating needle (Pajunk, Medizintechnologie, Geisingen, Germany) was directed under real-time ultrasound guidance toward the sciatic nerve. The local anesthetic and study drug were injected incrementally in 3 mL aliquots to a total volume of 0.45 mL/kg to a maximum of 40 mL until uniform distribution of local anesthetic was seen encircling the entire sciatic nerve. A midtibial or supramalleolar saphenous nerve block was also administered in all subjects. Sensory and motor blockade on the operative limb were evaluated at 30 minutes. Complete sensory analgesia was defined as analgesia to pinprick in all the terminal nerve distributions of the sciatic nerve. Complete motor block was defined as inability to move the ankle and toes at 30 minutes. Propofol was administered intraoperatively (25–75 μg/kg/min) to provide sedation while maintaining responsiveness to tactile or verbal stimulation. As per study protocol, no patient received ketamine, narcotics, additional local anesthetic, or dexamethasone intraoperatively. At discharge, patients were instructed by study personnel to record first initial toe movement, first experience of pain not in the saphenous distribution, and pain medications consumed. Postoperative analgesic medication consisted of 10 mg hydrocodone plus 325 mg acetaminophen at 4-hour intervals as needed.

Perioperative data collected included patient’s characteristics (age, body mass index, and sex), block variables (side of surgery, type of surgery, and needle attempts), time to complete block (needle insertion to needle withdrawal), paresthesias during block placement, time to first reported pain, and global 24-hour pain scores at rest and during movement (activity). Patients were contacted by telephone by an investigator unaware of group allocation and were administered the quality of recovery (QoR-40) questionnaire.

The questionnaire consists of 40 questions that examine 5 domains of patient recovery by using a 5-point Likert scale: none of the time, some of the time, usually most of the time, and all the time. The 5 domains include physical comfort, pain, physical independence, psychological support, and emotional state. In addition, all patients were asked on postoperative day 1, postoperative day 2, and at 2 weeks to answer questions regarding time to first toe movement, time to first pain not in the saphenous distribution (analgesic duration), pain score at rest and during activity/movement, analgesic use, symptoms of residual anesthesia, dysesthesias, paresthesia, or motor weakness in the operated limb. Patients were asked to rate their satisfaction with anesthesia care and postoperative pain control on a 10-point scale (0 = not satisfied to 10 = highly satisfied). They were also asked if they would recommend this method of pain management. Postoperative opioid consumption was converted to equivalent dosage of oral morphine at 24, 48 hours, and 2 weeks after surgery.

Physical examination of the patients was done for motor and sensory deficits by the surgeon at 1-month postoperatively. All cases of persistent sensory or motor deficits were referred to the anesthesiology pain clinic and neurology clinic for further evaluation and additional testing. Patients reporting any postoperative neurologic sequelae were contacted biweekly by a single investigator until resolution of symptoms.

The primary outcome measure was the global QoR-40 score. The QoR-40 questionnaire has been used by our group and several other investigators to examine outcomes after regional anesthesia, neuraxial anesthesia, or both. Specifically for ambulatory surgery, Idvall et al. confirmed validity, reliability, and responsiveness of the QoR-40 in 176 patients receiving regional or local anesthesia. Global QoR-40 scores range from 40 to 200 for representing, respectively, very poor to outstanding quality of recovery. A sample size of 23 patients per group was estimated to achieve 80%
power to detect a 10-point difference in the aggregated QoR-40 score for the 3 study groups to be compared assuming an overall standard deviation (SD) of 12. A 10-point difference represents a clinically relevant improvement in quality of recovery based on previously reported values on the mean and range of the QoR-40 score in patients after anesthesia and surgery.\textsuperscript{23} To account for losses to follow-up, 80 patients were recruited. The sample size calculation was made by using PASS version 8.0.15 release date January 14, 2010 (NCSS, LLC, Kaysville, UT).

Non-normally distributed interval and ordinal data are reported as median (interquartile range) and compared among groups by using the Kruskal-Wallis H test. Post hoc comparisons were made by using the Dunn test and corrected for multiple comparisons \((n = 3)\) by using the Bonferroni method. Categorical variables were evaluated by using a \(\chi^2\) statistic. Estimates of exact \(P\) values were determined for the \(\chi^2\) and the Kruskal-Wallis test by using a Monte Carlo method with 10,000 samples and confidence limits of 97.5%. Time to first reported toe movement and time to first reported pain were evaluated by constructing Kaplan–Meier plots and by using the log rank test with Bonferroni correction for multiple comparisons. All reported \(P\) values are 2-tailed. Statistical analysis was performed by using NCSS 8 version 8.0.13, release date October 26, 2012 (NCSS, LLC, Kaysville, UT) and R version 3.0.0, release date April 3, 2013 (The R Foundation for Statistical Computing, Vienna, Austria).

**RESULTS**

The details of the conduct of the study are shown in Figure 1. Of 100 who were approached to participate in the study, 80 patients were randomized, and 78 patients completed the study protocol. Patients were enrolled consecutively from June 2012 through February 2013. Baseline characteristics and surgical factors were not different among groups (Table 1).

QoR-40 scores were similar among groups before surgery (Table 2). There was no significant difference in the global QoR-40 score at 24 hours among the perineural dexamethasone and saline control groups, median (97.5% CI) difference of \(-3 (-7 to 3)\); IV dexamethasone and saline control, median difference of \(-1 (-8 to 5)\); or perineural dexamethasone and IV dexamethasone median difference of \(-2 (-6 to 5)\). QoR-40 values irrespective of randomization group were increased at 2 weeks compared with baseline, median difference 7 (4–11) compared with preoperative values \((P < 0.001)\).

In contrast, analgesia duration (Fig. 2) and time to first toe movement (Fig. 3) were prolonged by perineural dexamethasone compared with saline. IV dexamethasone prolonged
time to first toe movement compared with saline control ($P = 0.008$) but not analgesia duration ($P = 0.18$). There was no significant difference in the time to first toe movement or analgesia duration between the perineural and IV dexamethasone groups. Numerical pain scores on postoperative day 1 were lower in the perineural dexamethasone group compared with saline, but opioid consumption was not different among groups (Table 2). At 2 weeks, pain scores, opioid consumption, and quality of recovery were not different among the study groups.

Postoperative neurological symptoms were reported by patients in each study group (Table 3). Follow-up evaluation
identified postoperative neurologic symptoms in 35 patients. Self-reported symptoms at 24, 48 hours, and 2 weeks were 42, 23, and 9, respectively. There was no difference in the incidence of postoperative neurologic symptoms after perineural dexamethasone (17, 63%) or IV dexamethasone (10, 42%), when compared with normal saline ($P = 0.31$). In both dexamethasone groups, there may have been more numbness and paresthesia reported at 48 hours. At 2 weeks, 9 patients (11.5%) had self-reported symptoms or concerns.

At 4 weeks, 4 patients self-reported symptoms of numbness. Two patients in the IV dexamethasone group reported concerns of numbness, 1 patient reported numbness in second, third, and fourth toes that resolved by 6 weeks after open reduction internal fixation procedure, and the other patient reported numbness on the top of the big toe, second, third, and fourth toes that resolved by 8 weeks after an ankle arthroscopy procedure. One patient who underwent an open reduction internal fixation ankle procedure in the perineural dexamethasone group (1.2%) self-reported symptoms of numbness in the distribution of the sciatic nerve, but these symptoms resolved by 6 weeks. In the saline group, 1 patient who had a Brostrom procedure self-reported symptom of numbness in the distribution of the sciatic nerve that resolved by 6 weeks. All symptoms resolved without intervention, and none were persistent beyond 8 weeks postoperatively.

**DISCUSSION**

The most important finding of the current investigation was the lack of benefit of perineural and IV dexamethasone compared with saline on quality of postsurgical recovery.

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**Table 3. Reported Neurological Sequela at Study Time Intervals**

<table>
<thead>
<tr>
<th>Group 1, perineural dexamethasone, $n = 27$</th>
<th>Group 2, IV dexamethasone, $n = 24$</th>
<th>Group 3, normal saline, $n = 27$</th>
<th>$P$</th>
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<tr>
<td>POD 1 (N)</td>
<td>17</td>
<td>10</td>
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<td>Paraesthesia</td>
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<td>6</td>
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<tr>
<td>Numbness</td>
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<td>Pain in any other area</td>
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<td>Discoloration</td>
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<td>POD 2 (N)</td>
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<td>2</td>
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<tr>
<td>Paraesthesia</td>
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<tr>
<td>Muscle weakness</td>
<td>0</td>
<td>0</td>
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<td>Dysesthesia</td>
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<td>Numbness</td>
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Number of self-reported symptoms during follow-up. Subjects may have reported >1 symptom. All reported $P$ values are 2-tailed. Relative risk (97.5% CI) of numbness reported on POD2 with perineural dexamethasone are 20 (1–144) and with IV dexamethasone 16 (1–107) compared with saline. $N =$ number of subjects reporting symptoms; POD = postoperative day.
among patients undergoing ankle and foot surgery with a sciatic nerve block. Despite a reduction in pain scores, patients receiving perineural dexamethasone had comparable postoperative opioid consumption with those patients receiving IV dexamethasone or saline. Taken together, our results do not suggest that either route (perineural or IV) of dexamethasone administration improves overall quality of recovery in ankle and foot surgery under sciatic blocks.

Another important finding of the current investigation was the detection of prolonged analgesic duration of IV or perineural dexamethasone compared with saline. Even more importantly, we did not observe a clinically significant difference relative to a large confidence interval between IV and perineural dexamethasone on analgesic duration. Our results are similar to the findings of Desmet et al.24 who reported an equivalent effect of IV compared with perineural dexamethasone on analgesic duration for interscalene blocks.

Recently, Fredrickson et al.13 compared the addition of 8 mg dexamethasone with 30 mL 0.5% bupivacaine, with bupivacaine only in subjects receiving popliteal sciatic nerve blocks for ankle and foot surgery. The addition of the perineural dexamethasone reduced the proportion of patients reporting time to first analgesic request. IV dexamethasone 8 mg was administered to all patients, which may have contributed to the high number of patients who did not report pain at the end of the 48-hour follow-up period.13 In the present study, patients either received perineural dexamethasone or IV dexamethasone but not both. In the aforementioned study and in the current study, systemic dexamethasone had comparable effects on analgesia duration as perineural dexamethasone. Future studies investigating the dosage response of dexamethasone are warranted.

Animal studies have suggested a possible neuronal toxicity of dexamethasone and other adjuvants.25 In rats, an increase in neurotoxicity was observed when the dexamethasone concentration was increased from 66 to 133 μg/mL; when combined with ropivacaine. This finding suggests that even “subclinical” concentrations of dexamethasone may enhance neurotoxicity of local anesthetics. In the present study, we did observe higher median pain scores on postoperative day 2 at rest and with activity in the perineural dexamethasone group compared with saline controls, which may suggest inflammation by dexamethasone. We also observed more frequent numbness and paresthesia in the dexamethasone groups, compared with saline, although this likely reflects the prolonged duration of sensory and motor analgesia of the combination. Although we did not observe a difference in the frequency or duration of reported clinically evident neurologic sequelae among the groups, we cannot exclude the potential for increased neurotoxicity from the combination of dexamethasone with amide-type local anesthetics.

Other studies have examined the use of perineural dexamethasone as an adjunct for local anesthetics in brachial plexus blocks. Similar to our results, Cummings et al.13 demonstrated that perineural dexamethasone prolonged analgesia duration, but it did not decrease postoperative opioid consumption. A reduction in opioid consumption has been correlated to improved quality of recovery in subjects undergoing ambulatory surgery.23 It is likely, therefore, that the similar postoperative opioid consumption observed in the study groups explains the lack of differences on postoperative quality of recovery.

Our group has previously demonstrated a benefit of IV dexamethasone on postoperative quality of recovery after ambulatory gynecological surgery.14 Some of the beneficial effects of dexamethasone in postoperative nausea and vomiting and upper airway morbidity in patients undergoing general anesthesia are likely not translated to patients having procedures under regional anesthesia.26,27 Our results suggest the need to reevaluate the applicability of strategies that improve quality of recovery after general anesthesia in patients receiving regional anesthesia.

Our results should be interpreted within the context of several limitations. We enrolled a very specific surgical patient population, and the generalizability of our findings needs to be verified by future studies. All the surgical procedures required a saphenous nerve block, and the pain in the saphenous nerve distribution could have affected some of our results. We use a proximal sciatic nerve block because it provides more rapid onset of anesthesia than a popliteal sciatic block.26 In addition, some of those cases used a thigh tourniquet, and the proximal sciatic nerve blockade provides better analgesia from the vascular ischemic pain arising from the tourniquet inflation. Nonetheless, the proximal site used in this study may have impacted the frequency of reported neurologic sequelae. We used assessment tools modified after the McGill Pain Questionnaire and the self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale. We accepted all reported symptoms as an outcome and did not attempt to validate whether the symptoms arose from a neuropathic origin. A physical assessment was performed only at the 1-month follow-up surgeon visit and not at each follow-up interval.

In summary, we demonstrated that perineural dexamethasone compared with saline prolongs analgesia duration but does not offer improvements in overall recovery and opioid consumption for procedures under a sciatic nerve block. In addition, when added to the sciatic nerve block, systemic dexamethasone had comparable effects on analgesia duration as perineural dexamethasone. Given the lack of clinical benefit and the concern of dexamethasone’s neurotoxicity as demonstrated in animal studies, the practice of perineural dexamethasone administration needs to be further evaluated.

DISCLOSURES
Name: Rohit Rahangdale, MD.
Contribution: This author participated in design and conduct of the study and manuscript preparation.
Attestation: Rohit Rahangdale approved the final manuscript.

Name: Mark C. Kendall, MD.
Contribution: This author participated in design and conduct of the study, data collection, and manuscript preparation.
Attestation: Mark C. Kendall approved the final manuscript.

Name: Robert J. McCarthy, PharmD.
Contribution: This author participated in data analysis and manuscript preparation.
Attestation: Robert J. McCarthy approved the final manuscript.

Name: Antoun Nader, MD.
Contribution: This author participated in the manuscript preparation.
Attestation: Antoun Nader approved the final manuscript.
Name: Luminita Tureanu, MD.

Contribution: This author participated in the conduct of the study.
Attestation: Luminita Tureanu approved the final manuscript.

Name: Robert Doty Jr, MD.

Contribution: This author participated in conduct of the study.
Attestation: Robert Doty approved the final manuscript.

Name: Adam Weingart, MD.

Contribution: This author participated in conduct of the study.
Attestation: Adam Weingart approved the final manuscript.

Name: Gildasio S. De Oliveira Jr, MD, MSCI.

Contribution: This author participated in the study design, data analysis, and manuscript preparation. This author attests the integrity of the data and analysis.
Attestation: Gildasio S. De Oliveira approved the final manuscript.

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REFERENCES


