

Continuous Femoral Nerve Blocks

Varying Local Anesthetic Delivery Method (Bolus versus Basal) to Minimize Quadriceps Motor Block while Maintaining Sensory Block

Matthew T. Charous, M.D.,* Sarah J. Madison, M.D.,† Preetham J. Suresh, M.D.,† NavParkash S. Sandhu, M.D.,‡ Vanessa J. Loland, M.D.,† Edward R. Mariano, M.D., M.A.S.,§ Michael C. Donohue, Ph.D.,|| Pascual H. Dutton, B.A.,# Eliza J. Ferguson, B.S.,** Brian M. Ilfeld, M.D., M.S.††

ABSTRACT

Background: Whether the method of local anesthetic administration for continuous femoral nerve blocks—basal infusion *versus* repeated hourly bolus doses—influences block effects remains unknown.

Methods: Bilateral femoral perineural catheters were inserted in volunteers (n = 11). Ropivacaine 0.1% was concurrently administered through both catheters: a 6-h continuous 5 ml/h basal infusion on one side and 6 hourly bolus doses on the contralateral side. The primary endpoint was

What We Already Know about This Topic

- Whether the method of local anesthetic administration (repeated bolus or continuous infusion) alters safety and efficacy of continuous femoral nerve blocks after surgery is not clear

What This Article Tells Us That Is New

- In 11 healthy volunteers receiving femoral nerve block with ropivacaine continuously or by hourly boluses, there was no difference in the degree of motor block of the quadriceps, suggesting no advantage of one method over the other for this unwanted effect

* Fellow (Regional Anesthesia), † Assistant Clinical Professor, ‡ Associate Clinical Professor, ** Research Coordinator, †† Associate Professor (In Residence), Department of Anesthesiology, || Assistant Project Scientist, Division of Biostatistics and Bioinformatics, University of California San Diego, San Diego, California. § Associate Clinical Professor, Department of Anesthesiology, University of California San Diego. Current affiliation: Stanford University School of Medicine, Palo Alto, California. # Medical Student, University of California San Diego School of Medicine, San Diego, California.

Received from the Department of Anesthesiology, University of California San Diego, San Diego, California. Submitted for publication October 8, 2010. Accepted for publication January 6, 2011. Supported by National Institutes of Health grant GM077026 from the National Institute of General Medical Sciences (Bethesda, Maryland) and by National Institutes of Health National Center for Research Resources grant UL1RR031980. Unrestricted research grant and the infusion pumps provided by Summit Medical (West Jordan, Utah). This company had no input into any aspect of study conceptualization, design, and implementation; data collection, analysis, and interpretation; or manuscript preparation. The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the funding entities.

One or more authors of this peer-reviewed article have been supported by FAER. In conjunction with the FAER 25th anniversary, articles and editorials in ANESTHESIOLOGY October 2011 issue celebrate the accomplishments of FAER. For additional information visit www.FAER.org.

Address correspondence to Dr. Ilfeld: Department of Anesthesiology, 200 West Arbor Drive, MC 8770, San Diego, California 92103-8770. bilfeld@ucsd.edu. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

Copyright © 2011, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins. Anesthesiology 2011; 115:774–81

the maximum voluntary isometric contraction (MVIC) of the quadriceps femoris muscle at hour 6. Secondary endpoints included quadriceps MVIC at other time points, hip adductor MVIC, and cutaneous sensation 2 cm medial to the distal quadriceps tendon in the 22 h after initiation of local anesthetic administration.

Results: Quadriceps MVIC for limbs receiving 0.1% ropivacaine as a basal infusion declined by a mean (SD) of 84% (19) compared with 83% (24) for those receiving 0.1% ropivacaine as repeated bolus doses between baseline and hour 6 (paired *t* test *P* = 0.91). Intrasubject comparisons (left *vs.* right) also reflected a lack of difference: the mean basal-bolus difference in quadriceps MVIC at hour 6 was −1.1% (95% CI −22.0–19.8%). The similarity did not reach the *a priori* threshold for concluding equivalence, which was the 95% CI decreasing within ± 20%. There were similar minimal differences in the secondary endpoints during local anesthetic administration.

Conclusions: This study did not find evidence to support the hypothesis that varying the method of local anesthetic administration—basal infusion *versus* repeated bolus doses—influences continuous femoral nerve block effects to a clinically significant degree.

A CONTINUOUS femoral nerve block (cFNB)—also termed “perineural local anesthetic infusion”—is frequently used to provide analgesia after major knee surgery.¹ Although inhibition of pain fibers is the primary goal of cFNB, currently available local anesthetics approved for clin-

ical use also influence other afferent (*e.g.*, non-pain-related sensory and proprioception) and efferent (*e.g.*, motor) nerve fibers.² Consequently, one well-recognized side effect of perineural infusion is muscle weakness,³ which is particularly undesirable during cFNB because the femoral nerve innervates the quadriceps femoris muscle required for ambulation, in itself a critical component of postoperative rehabilitation of the knee. Recently published data suggest that perineural infusion involving the femoral nerve increases the risk of falling.⁴ Because perineural infusions are often provided for analgesia after major surgical procedures in elderly patients, and a fall in this patient population may prove catastrophic,^{5,6} it is imperative that any fall risks be minimized. The potential gravity of the issue is suggested in the more than 500,000 knee arthroplasties performed every year in the United States alone, with that number expected to increase to 3.5 million annually within the next 20 yr.⁷

Because quadriceps femoris weakness is associated with significant functional disability⁸ and an increased risk of falls in elderly patients,⁹ it is postulated that any nerve block-induced muscle weakness is best minimized during perineural local anesthetic infusion.⁴⁻⁶ Various femoral perineural infusion strategies have failed to decrease muscle weakness while still providing adequate analgesia. For example, decreasing the local anesthetic dose results in decreased muscle weakness, yet also reduces analgesia.¹⁰ Alternatively, decreasing the concentration of local anesthetic and increasing the delivered volume—to retain total delivered dose—has demonstrated little effect on either sensory or motor block.¹¹ However, one recent study involving continuous popliteal-sciatic nerve blocks after hallux valgus repair reported increased analgesia without a concurrent increase in motor block *via* administration of local anesthetic in repeated 5-ml hourly boluses compared with a 5 ml/h continuous infusion.¹² These results raise the exciting possibility of decreasing the fall risk during cFNB by decreasing muscle weakness while maintaining analgesia.

We therefore tested the hypothesis that changing the local anesthetic delivery method (continuous basal infusion *vs.* repeated bolus doses)—while providing an equal total local anesthetic dose—produces relatively equivalent effects when used for cFNB. The primary endpoint was the difference in maximum voluntary isometric contraction (MVIC) of the quadriceps femoris muscle expressed as a percentage of the baseline measurement 6 h after initiation of local anesthetic administration. Secondary endpoints included quadriceps femoris MVIC at other time points, hip adductor MVIC, and cutaneous sensation 2 cm medial to the distal quadriceps tendon in the 22 h after initiation of local anesthetic administration.

Materials and Methods

Enrollment

Our local institutional review board (University of California San Diego, San Diego, CA) approved all study procedures.

The trial was prospectively registered at clinicaltrials.gov (NCT01144559). Enrollment included a convenience sample of relatively healthy adult (≥ 18 yr) volunteers of both sexes. Exclusion criteria included current daily analgesic use, any opioid use within the previous 4 weeks, any neuromuscular deficit of either femoral nerves and/or thigh musculature, body mass index greater than 35 kg/m², pregnancy, and incarceration. Any individual (*e.g.*, medical trainees or study coordinators) whose nonstudy performance was potentially evaluated by the principal investigator (B.I.) was considered part of a “vulnerable population” and excluded from volunteering as a study subject as mandated by current United States ethical guidelines.¹³ All participants provided written, informed consent before any study procedures. This study was undertaken in a Clinical and Translational Research Institute (University of California, San Diego, CA).

Perineural Catheter Insertion

While in the supine position, subjects had an intravenous line placed in the upper extremity, standard American Society of Anesthesiologists-recommended external monitors applied, and oxygen administered by nasal cannula (3 l/min). Intravenous midazolam (1 mg) and fentanyl (50 μ g) were administered, while ensuring that patients remained responsive to verbal cues. Any hair in the area that would be subsequently covered by the catheter dressings was removed with a surgical hair clipper. After sterile preparation (chlorhexidine gluconate and isopropyl alcohol) and draping, bilateral femoral perineural catheters were inserted by use of the identical insertion protocol. Catheters on the dominant side (right *vs.* left) were always inserted first.

With a 13–6 MHz 38-mm linear array transducer (HFL 38x, SonoSite M-Turbo, Bothell, WA) in a sterile sleeve, the femoral nerve was identified in a transverse cross-sectional (short axis) view at the inguinal crease. A local anesthetic skin wheal was raised lateral to the ultrasound transducer. An uninsulated, 8.9-cm, 17-gauge, Tuohy-tip needle (FlexTip, Arrow International, Reading, PA) was inserted through the skin wheal and directed medially in-plane beneath the ultrasound transducer toward the femoral nerve with an anterior bevel direction. Normal saline (5 ml) was injected as the needle tip approached the lateral edge of the femoral nerve to open the space between the nerve and underlying muscle to avoid needle-nerve contact. A 19-gauge flexible epidural-type catheter (FlexTip) was then placed through the length of the needle and advanced 0.5 cm beyond the needle tip posterolateral to the nerve. With the catheter tip remaining visible by ultrasound to ensure that its position remains fixed, the needle was withdrawn over the catheter until the needle tip was superficial to the iliac fascia. The needle was then held in place and 2 cm of catheter inserted above the iliac fascia while ensuring that the catheter tip remained stationary; the needle was withdrawn over the remaining catheter. The injection port was attached to the catheter and the catheter

secured with sterile liquid adhesive, an occlusive dressing, and an anchoring device.

Randomization

The dominant side (right or left) was randomized to one of two treatment groups: ropivacaine 0.1% was administered as either a basal-only infusion (5 ml/h) or bolus-only doses (5 ml administered once hourly). The nondominant, contralateral side received the other possible treatment. In this way, subjects acted as their own controls. Randomization was based on computer-generated codes in blocks of two, stratified by sex. The Investigational Drug Service prepared the randomization list and all ropivacaine infusions. Two 100-ml sterile bags were filled with ropivacaine 0.1% and connected to disposable infusion pump cassettes and integrated tubing (fig. 1). One bag was labeled “Basal,” and the opposite end of its tubing was labeled either “dominant” or “other,” depending on the randomization for each subject. The other bag was labeled “Bolus,” and the opposite end of its tubing was labeled either “dominant” or “other.” The two pieces of tubing were then gently wound at least five rotations and covered with opaque tape, masking from all but the Investigational Drug Service pharmacists which tubing delivered the basal and bolus dosing (ropivacaine is clear, so the flow through the clear tubing from the tape to the perineural catheters was not visually distinguishable). The Investigational Drug Service delivered this apparatus to the investigators.



Fig. 1. Infusion apparatus allowing randomized, double-masked local anesthetic administration.

The investigators programmed two electronic, portable infusion pumps (ambi-T PCA, Summit Medical, West Jordan, UT), one delivering a continuous basal infusion (5 ml/h) and the other on-demand bolus doses (5 ml). These infusion pumps were attached to the appropriate cassettes connected to the ropivacaine reservoirs labeled either “Basal” or “Bolus” by the Investigational Drug Service. The remaining tubing ends were connected to the femoral catheters, as they were labeled either “Dominant” or “Other.” In this manner, all investigators, nursing staff, and subjects remained masked to treatment group assignment: all subjects received both a basal-only infusion and repeated bolus doses, but which femoral catheter received which treatment remained unknown.

Perineural Infusion

At hour 0, both infusion pumps were turned on. The infusion pump providing a basal infusion of 5 ml/h remained active for 6 h (30 ml = 30 mg). The infusion pump providing bolus doses of 5 ml was activated by one of the investigators at hour 0, and every hour afterward for a total of six delivered bolus doses (30 ml = 30 mg); the final dose was at hour 5. Infusion pumps were turned off at hour 6, and the perineural catheters removed.

Subjects remained in the Clinical and Translational Research Institute for 23 h, or until quadriceps femoris strength had returned to baseline concentrations, whichever was longer.

Outcome Measurements

We selected measures that have established reliability and validity^{9,14–17} and minimal interrater discordance.¹⁶ Measurements were performed at hour 0 (baseline) and hourly until hour 14, as well as the following morning at approximately hour 22. In addition, measurements were performed every 10 min from hour 0–1 and 5–6. In all cases, measurements were taken in the seated position with the dominant side measured before the nondominant side. Initially, quadriceps femoris strength was evaluated, followed by hip adductor strength, and then tolerance of transcutaneous electrical stimulation slightly medial to the distal quadriceps tendon.

Muscle Strength

We evaluated muscle strength with an isometric force electromechanical dynamometer (MicroFET2, Lafayette Instrument Company, Lafayette, IN) to measure the force produced during a MVIC in a seated position with the knees flexed at 90°. For quadriceps femoris evaluation, the dynamometer was placed on the ipsilateral anterior tibia perpendicular to the tibial crest just proximal to the medial malleolus.^{15–17} For hip adductor evaluation, the femoral shaft was held at 30° off midline and the dynamometer placed over the medial femoral epicondyle (adductor tubercle). For all measurements, subjects were asked to take 2 s to reach maximum effort contracting the target muscle(s), maintain this effort for 5 s, and then relax.^{9,17} The measurements immediately before

perineural ropivacaine administration were designated as baseline measurements, and all subsequent measurements are expressed as a percentage of the preinfusion baseline.⁹

Sensory Effect

We evaluated tolerance of transcutaneous electrical stimulation with the same quantitative procedure as described previously.^{11,14} Electrocardiogram pads were placed 2 cm medial to the distal quadriceps tendon and attached to a nerve stimulator (EZstimII, Model ES400; Life-Tech, Stafford, TX). The current was increased from 0 mA until subjects described mild discomfort, at which time the current was recorded as the tolerated level and the nerve stimulator turned off. All sensory measurements are expressed as a percentage of each patient's preinfusion baseline.

Statistical Analysis

Sample size calculations were based on our primary hypothesis that differing the method of perineural local anesthetic administration (continuous basal infusion *vs.* repeated bolus doses)—while providing an equal total dose—produces comparable effects when used in cFNBS. The primary endpoint was the quadriceps femoris MVIC, expressed as a percentage of the baseline MVIC at hour 6. We consider a difference of 20 percentage points to be clinically relevant because a 10% side-to-side strength difference is common, yet functionally unnoticeable in healthy individuals.^{18,19} We used the method described by Armitage *et al.*²⁰ whereby we would conclude equivalence if the 95% CI for the difference falls within a prespecified tolerated interval (−20%–20%). Based on previously published data, we assumed that the SD of the percent change from baseline in MVIC would be 16%.¹⁴ Assuming a within-subject correlation of percent change from baseline in MVIC of 0.4, this value yields a SD of the treatment difference of 17.5% = $[16\%^2 \times 2 \times (1 - 0.4)]^{1/2}$. Under these assumptions, a trial with $n = 11$ subjects would correctly conclude there is no treatment difference with probability 85% (power), and incorrectly conclude equivalence when there is a difference of 18% with probability 5% (α). Subjects were deemed nonresponders if one or both extremities failed to exhibit more than 20% change from baseline in quadriceps femoris MVIC or sensory effect at hour 4. Nonresponders were not included in the primary analyses, but were included in *post hoc* intent-to-treat analyses.

We applied the same analysis of percent change from baseline at hour 6 to the secondary outcome measures. In addition, we examined the time profiles of the responses over time with spaghetti and mean plots. Further secondary analyses included mixed-effects modeling of the repeated hourly measures to confirm the analysis of percent change at hour 6. These models accounted for the hierarchical correlation of

paired measures from each subject over time. We adjusted the *P* values for each of the 25 time points considered using the Holm method.²¹ These analyses were executed using R version 2.12 (2010).^{‡‡} Additional analyses included the Mann–Whitney *U* test for nonparametric comparisons and chi-square test for categorical variables (GraphPadInStat, GraphPad Software, San Diego, CA).

Results

Fifteen subjects were enrolled during a 3-month period beginning July 2010. All had bilateral femoral perineural catheters successfully inserted per protocol. Each subject's dominant side was randomized to either one of the two ropivacaine 0.1% treatments—a continuous 5 ml/h basal infusion for 6 h or 6 hourly 5-ml bolus doses—and the nondominant side received the opposite treatment. Four subjects did not exhibit at least a 20% change from baseline in either their quadriceps MVIC or sensory effects (table 1). Although only the remaining 11 subjects were included in the primary analyses, all 15 subjects were included in the intent-to-treat analyses (table 1).

Quadriceps femoris MVIC for limbs receiving 0.1% ropivacaine as a basal infusion declined by a mean (SD) of 84% (19) compared with 83% (24) for limbs receiving 0.1% ropivacaine as repeated bolus doses between baseline and hour 6 (paired *t* test *P* = 0.91). Intrasubject comparisons (left *vs.* right) also reflected this lack of difference: the mean basal-bolus difference in quadriceps MVIC at hour 6 was −1.1% (95% CI −22.0–19.8%). The similarity did not reach our *a priori* threshold for concluding equivalence, which was the 95% CI decreasing within $\pm 20\%$. The mixed-effects model of the repeated measures of basal-bolus differences over time resulted in a tighter CI for quadriceps femoris MVIC at 6 h (95% CI −20.8–18.6%), but the CIs were still not within −20–20% at any observed time point. On the contrary, at hours 10 through 14, the basal-bolus difference in MVIC was statistically significant (*P* < 0.05), and the difference at hours 12 and 13 retained significance (*P* < 0.01) after the Holm adjustment.

There were similar minimal differences between treat-

Table 1. Anthropometric Subject Characteristics

	Included in Primary Analyses (n = 11)	Excluded from Primary Analyses (n = 4)	<i>P</i> Value
Age (yr)	26 (4)	26 (3)	0.85
Sex (female/male)	4/7	3/1	0.19
Height (cm)	175 (8)	171 (14)	0.57
Weight (kg)	69 (11)	66 (13)	0.64
Body mass index (kg/m ²)	22 (2)	22 (2)	0.91
Dominant side (left)	0	0	

Values are reported as mean (SD) or number of subjects.

‡‡ R Software Environment for Statistical Computing, R Foundation for Statistical Computing (version 2.12), Vienna, Austria. Available at: <http://www.r-project.org>. Accessed October 15, 2010.

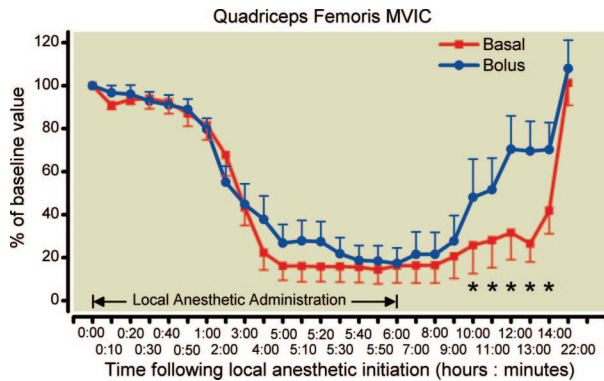


Fig. 2. Effects of femoral perineural local anesthetic administration method (basal-only vs. repeated boluses) on *quadriceps femoris strength* (mean [SE] illustrated). Statistically significant differences between treatments at 95% CI are designated with an asterisk.

ment groups in the secondary endpoints during local anesthetic administration (figs. 2–4). The estimated difference in hip adductor strength at hour 6 was -6% (95% CI -14% – 2%), which allows a formal conclusion of equivalence (fig. 3). There was a great degree of variability in the measurement of sensory effect, resulting in very wide CIs. The mean difference in sensory effect at hour 6 was -7% (95% CI -127% – 112% ; fig. 4).

Results were similar in the intent-to-treat population. The hour 6 basal-bolus difference in quadriceps MVIC was -0.6% (95% CI -24.7% – 23.5%). For hip adductor strength, the basal-bolus was equivalent: -6.0% (95% CI -13.7% – 1.7%). The difference in sensory effect was again highly variable, with a mean of 15.2% (95% CI -99.2% – 68.7%).

Discussion

This randomized, double-masked, controlled investigation did not find evidence to support the hypothesis that varying the method of local anesthetic administration—basal infu-

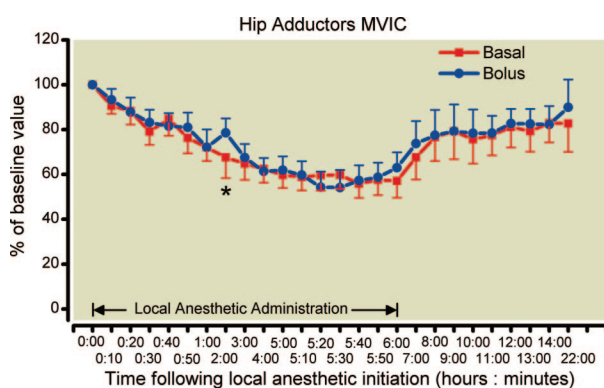


Fig. 3. Effects of femoral perineural local anesthetic administration method (basal-only vs. repeated boluses) on *hip adductor strength* (mean [SE] illustrated). The one statistically significant difference between treatments at 95% CI is designated with an asterisk.

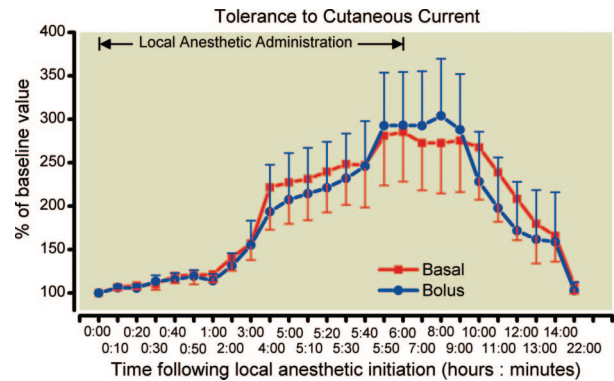


Fig. 4. Effects of femoral perineural local anesthetic administration method (basal-only vs. repeated boluses) on *tolerance of transcutaneous electrical stimulation in the cutaneous distribution of the femoral nerve* (mean [SE] illustrated). There were no statistically significant differences between treatments at 95% CI.

sion versus repeated bolus doses—influences cFNB effects to a clinically significant degree. However, because of a larger SD than anticipated, the 95% CI at hour 6 (-22.0% – 19.8%) did not decrease within our prespecified tolerance interval of -20% – 20% . To conclude equivalence would require a larger independent cohort. Conversely, we detected little difference between treatments at any time point during local anesthetic administration (figs. 2–4). This might be viewed as a positive finding if the sensory block—and, therefore, possibly analgesia—was greatly increased in the bolus-only group, in line with previous reports of continuous popliteal-sciatic nerve blocks.^{12,22} Unfortunately, this was not the case: tolerance to cutaneous electrical current was virtually indistinguishable at hour 6 between the two groups (fig. 4).

Previously Published Evidence

The differences between our findings for femoral infusion and the previous reports for popliteal-sciatic infusion may be explained in several ways. The first is in catheter-insertion methodology: the previous studies used nerve stimulation to guide needle placement, but then “blindly” advanced non-stimulating catheters 4–5 cm past the needle tip.^{12,22} As the previous investigators noted,

the final location of the catheter tip... may have actually been located distant from the targeted nerve... This may render it difficult, or even impossible, for the local anesthetic to traverse the distance between the tip and the two sciatic nerve trunks when a slow continuous infusion with an overall small volume is used... In contrast, the use of an intermittent bolus is accompanied by higher pressure and more volume per time, which may increase the spread of local anesthetic...¹²

In contrast, our current study used ultrasound to allow positioning of the catheter tips at a precise (and bilaterally equivalent) location immediately posterolateral to the femoral nerve, resulting in very accurate perineural local anes-

thetic deposition and possibly improved nerve-anesthetic contact.

A second possible explanation for the differing results among studies is the anatomic location of the catheters: local anesthetic deposited in the popliteal fossa in previous studies may have been absorbed by perineural tissue, including blood vessels and the lymphatic system.^{12,22} Conversely, in the femoral region, the local anesthetic may pool better between the iliac fascia and underlying muscle, providing a conduit and/or reservoir keeping the medication in contact with the femoral nerve.

Regardless of which—or either—supposition is accurate, the results of the current study suggest that the “novel” repeated-bolus application will not be clinically useful to decrease the motor-induced weakness (and possible increased risk of falling) of cFNB after knee surgery. Our intention is not to suggest that repeated boluses are unhelpful for all continuous peripheral nerve blocks: there is high-quality evidence they improve analgesia for continuous popliteal-sciatic blocks.^{12,22} However, the current study suggests that the increased analgesia previously reported with repeated boluses may result not from a more favorable motor-sensory block ratio—as suggested recently²²—but rather simply from additional local anesthetic reaching the target nerves, increasing both the motor and sensory blocks concurrently.

If this latter supposition is accurate, then previous investigations involving the sciatic nerve in the popliteal fossa should have detected an increased motor block accompanying the improved analgesia in the bolus-only group.^{12,22} Although the investigators did not describe the technique used to evaluate motor block,^{12,22} they did find in their second publication that 20% of the bolus-only group experienced “motor block” (undefined) at 6 h, compared with only 8% of patients receiving a basal-only infusion (specific *P* value not provided, but reported as greater than 0.05).²² Given that the study was powered for postoperative pain, it is very possible—even probable—that a true difference in motor block was not detected in this secondary endpoint that appears to have been evaluated as a binary variable (motor block *vs.* no motor block) without a sensitive instrument. Therefore, the repeat-bolus administration method may be superior to an infusion-only method for catheter locations in which increased motor weakness is acceptable (such as in patients ambulating with crutches after foot surgery), but it does not appear to be a promising technique to decrease the risk of quadriceps weakness and possibly falls during cFNB.

Of note is that a statistically significant difference between treatments was detected by mixed-effects models of the repeated measures 4–8 h following catheter removal: those in the bolus-only group experienced a faster resolution of quadriceps femoris weakness compared with patients receiving a basal infusion only (fig. 2). The clinical relevance of this finding is unclear. It is also noteworthy that for continuous iliac fascia blocks—very similar to cFNB—bolus-only administration of 10 ml ropivacaine 0.2% (60-min lockout)

resulted in similar analgesia to a continuous 10 ml/h infusion of the same medication.²³ However, in this investigation, the bolus doses were not repeated hourly, but were patient-controlled, resulting in a decreased consumption of local anesthetic in the bolus-only group. This study reported a lack of motor block in all patients of both treatment groups, but the methods of evaluation were not reported, and it is therefore impossible to compare and contrast their results with those of the current study.

Safety of Large Bolus Doses

Because quadriceps femoris weakness is associated with significant functional disability⁸ and an increased risk of falls in elderly patients,⁹ perineural infusion induces motor block,³ and cFNB is associated with postarthroplasty falls,⁴ it is postulated that any local anesthetic-induced muscle weakness is best minimized during cFNB.^{4–6} It is therefore disappointing that we did not detect clinically relevant muscle-sparing by varying the technique of local anesthetic administration (basal *vs.* bolus). However, our results may be viewed as reassuring when providing relatively large-volume, patient-controlled bolus doses during cFNB. Of previous concern was the scenario of a patient who had recent knee surgery. While standing in preparation for therapy, the patient experienced pain and self-administered a local anesthetic bolus; 15 to 20 min after ambulating, the patient subsequently experienced abrupt-onset bolus-induced quadriceps weakness, which leads to a high risk of falling.^{1,4,24} It is for this reason that we evaluated quadriceps MVIC every 10 min during two 1-h periods: from hour 0–1 to observe the initial effect of a bolus; and from hour 5–6 to observe the effect of a bolus after 5 previous hours of administration (figs. 2–4). Although progressive infusion effects were observed at all time periods, as anticipated, no subject exhibited dramatic bolus-induced abrupt-onset quadriceps weakness. Our results suggest that a relatively large bolus dose retains an acceptable margin of safety.²⁵

Adductor Strength

Multiple investigations have suggested that local anesthetic deposition near the femoral nerve at the level of the inguinal crease results in a low (less than 20%) incidence of obturator nerve block.^{26–30} Because the obturator nerve innervates most of the hip adductor muscles, it may appear confusing that our study found a greater than 40% decrease in adductor MVIC after 6 h of local anesthetic administration. However, we do not believe that our results contrast with previous reports.^{26–28} Rather, the pectineus muscle is innervated by the femoral nerve and adducts the femur.³¹ Therefore, the adduction weakness found in our study most likely reflects a block of the femoral—as opposed to the obturator—nerve, with resulting motor block in the pectineus muscle and, consequently, weakness in hip adduction.

Study Limitations

The current findings regarding cFNB with 0.1% ropivacaine may not be applicable to other anatomic catheter locations,^{12,22,32–34} local anesthetics,³ infusion durations, or ropivacaine concentrations/dosages.^{10,11} Previous findings,¹¹ along with the results of the current study, suggest that local anesthetic dose (mass) is the primary determinant of perineural infusion effects; however, that is not to suggest that in *clinical use*, delivery method,^{12,22} concentration, and volume are irrelevant.¹⁰ Related to this issue, our study measured cutaneous sensation just medial to the distal quadriceps tendon in nonsurgical volunteers. Whether cutaneous sensation correlates well with postoperative pain after various knee procedures remains unknown, as the anterior branch of the femoral nerve contains afferent nerve fibers providing cutaneous sensation, whereas the posterior branch contains both afferent (muscle and bone innervation) as well as efferent (muscle innervation) nerve fibers. Answering this question will require a clinical trial involving patients undergoing multiple types of surgical procedures. However, our study did not find evidence to support the hypothesis that varying the method of local anesthetic administration—basal infusion versus repeated bolus doses—influences cFNB effects to a clinically significant degree. However, because of a larger SD than anticipated, the 95% CI at hour 6 did not decrease within our prespecified tolerance interval of –20–20%. To conclude equivalence would require a larger independent cohort. Because each comparison dilutes all other *P* values, findings in secondary outcomes should be viewed as suggestive, requiring confirmation in a future trial before considering them as definitive.

Study Model

By including only nonsurgical volunteers, we were able to exclude postoperative pain as a confounding variable, allowing isolation of the variable local anesthetic administration method effects on muscle strength and cutaneous sensation. For example, in postsurgical patients, inadequate analgesia is often (best?) treated with patient-controlled bolus doses, adding a confounding variable to the study design.^{22,23} In addition, by having each subject concurrently receive both study treatments (basal and bolus) and analyzing the intra-subject differences, the study model provided equivalent power with fewer subjects compared with a parallel-group design. Of course, the inclusion of nonsurgical volunteers also makes extrapolation to clinical practice more difficult.

However, there is evidence that perineural catheter tip location must be equivalent bilaterally for the study model to retain the desired power to detect either equivalency or treatment differences.¹⁴ Therefore, we used ultrasound to precisely place the tip of each catheter immediately posterolateral relative to the femoral nerve, confirmed by sonographic visualization. This required that no catheter “slack” be placed between where the catheter penetrated the iliac fascia and the catheter tip itself; resulting in what we had theorized might

be a high risk of catheter tip retraction above the iliac fascia. Because this was not an outcomes trial—but rather a pharmacodynamics study—we elected to exclude from the primary analyses subjects in whom catheter tip dislodgement was a probability (as opposed to intention-to-treat analysis optimally used in outcomes trials). We defined probable dislodgement as exhibiting less than a 20% change from baseline in quadriceps femoris MVIC or sensory effect at hour 4. Using this definition, we may have excluded subjects who were simply very resistant to local anesthetic effects, as opposed to subjects who had a dislodged catheter tip. Of 15 total subjects, four failed to exhibit at least a 20% change from baseline: one limb received bolus doses in one subject; one limb received basal doses in two different subjects; and there was a complete lack of changes in one subject bilaterally. There were minimal differences in subject characteristics between included and excluded subjects (table 1).

In summary, this study did not find evidence to support the hypothesis that varying the method of local anesthetic administration—basal infusion versus repeated bolus doses—influences cFNB effects to a clinically significant degree. Thus, it is doubtful that, when using a cFNB, varying the method of local anesthetic administration will provide an increased sensory-to-motor block ratio and minimize motor block and the risk of falling while optimizing cutaneous analgesia. However, additional study within a surgical population is warranted owing to the limitations of the volunteer subject model of the current investigation.

The authors gratefully acknowledge the invaluable assistance of the nursing staff of the University of California San Diego Clinical and Translational Research Institute and the University of California San Diego Investigational Drug Service (both San Diego, California).

References

- Ilfeld BM, Mariano ER, Girard PJ, Loland VJ, Meyer RS, Donovan JF, Pugh GA, Le LT, Sessler DI, Shuster JJ, Theriaque DW, Ball ST: A multicenter, randomized, triple-masked, placebo-controlled trial of the effect of ambulatory continuous femoral nerve blocks on discharge-readiness following total knee arthroplasty in patients on general orthopaedic wards. *Pain* 2010; 150:477–84
- Ilfeld BM, Yaksh TL: The end of postoperative pain—a fast-approaching possibility? And, if so, will we be ready? *Reg Anesth Pain Med* 2009; 34:85–7
- Borgeat A, Kalberer F, Jacob H, Ruetsch YA, Gerber C: Patient-controlled interscalene analgesia with ropivacaine 0.2% versus bupivacaine 0.15% after major open shoulder surgery: The effects on hand motor function. *Anesth Analg* 2001; 92:218–23
- Ilfeld BM, Duke KB, Donohue MC: The association between lower extremity continuous peripheral nerve blocks and patient falls following knee and hip arthroplasty. *Anesth Analg* 2010; 111:1552–4
- Kandasami M, Kinninmonth AW, Sarungi M, Baines J, Scott NB: Femoral nerve block for total knee replacement - a word of caution. *Knee* 2009; 16:98–100
- Feibel RJ, Dervin GF, Kim PR, Beaulé PE: Major complications associated with femoral nerve catheters for knee arthroplasty: A word of caution. *J Arthroplasty* 2009; 24:132–7
- Kurtz S, Ong K, Lau E, Mowat F, Halpern M: Projections of

- primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am* 2007; 89:780-5
8. Mizner RL, Snyder-Mackler L: Altered loading during walking and sit-to-stand is affected by quadriceps weakness after total knee arthroplasty. *J Orthop Res* 2005; 23:1083-90
 9. Stevens JE, Mizner RL, Snyder-Mackler L: Quadriceps strength and volitional activation before and after total knee arthroplasty for osteoarthritis. *J Orthop Res* 2003; 21:775-9
 10. Brodner G, Buerkle H, Van Aken H, Lambert R, Schweppe-Hartenauer ML, Wempe C, Gogarten W: Postoperative analgesia after knee surgery: A comparison of three different concentrations of ropivacaine for continuous femoral nerve blockade. *Anesth Analg* 2007; 105:256-62
 11. Ilfeld BM, Moeller LK, Mariano ER, Loland VJ, Stevens-Lapsley JE, Fleisher AS, Girard PJ, Donohue MC, Ferguson EJ, Ball ST: Continuous peripheral nerve blocks: Is local anesthetic dose the only factor, or do concentration and volume influence infusion effects as well? *ANESTHESIOLOGY* 2010; 112:347-54
 12. Taboada M, Rodríguez J, Bermudez M, Valiño C, Ulloa B, Aneiros F, Gude F, Cortés J, Alvarez J, Atanassoff PG: A "new" automated bolus technique for continuous popliteal block: A prospective, randomized comparison with a continuous infusion technique. *Anesth Analg* 2008; 107:1433-7
 13. The Common Rule, Title 45 (Public Welfare), Code of Federal Regulations, Part 46 (Protection of Human Subjects). U.S. Department of Health and Human Services, National Institutes of Health, and Office for Human Research Protections, 2001:1-18
 14. Salinas FV, Neal JM, Sueda LA, Kopacz DJ, Liu SS: Prospective comparison of continuous femoral nerve block with non-stimulating catheter placement *versus* stimulating catheter-guided perineural placement in volunteers. *Reg Anesth Pain Med* 2004; 29:212-20
 15. Kwok CK, Patrick MA, Munin MC: Inter-rater reliability for function and strength measurements in the acute care hospital after elective hip and knee arthroplasty. *Arthritis Care Res* 1997; 10:128-34
 16. Roy MA, Doherty TJ: Reliability of hand-held dynamometry in assessment of knee extensor strength after hip fracture. *Am J Phys Med Rehabil* 2004; 83:813-8
 17. Bohannon RW: Measuring knee extensor muscle strength. *Am J Phys Med Rehabil* 2001; 80:13-8
 18. Krishnan C, Williams GN: Evoked tetanic torque and activation level explain strength differences by side. *Eur J Appl Physiol* 2009; 106:769-74
 19. Ostenberg A, Roos E, Ekdahl C, Roos H: Isokinetic knee extensor strength and functional performance in healthy female soccer players. *Scand J Med Sci Sports* 1998; 8:257-64
 20. Armitage P, Berry G, Matthews JNS: Statistical methods in medical research. Oxford, Blackwell Science, 2002
 21. Holm S: A simple sequentially rejective multiple test procedure. *Scand J Statistics* 1979; 6:65-70
 22. Taboada M, Rodríguez J, Bermudez M, Amor M, Ulloa B, Aneiros F, Sebaste S, Cortés J, Alvarez J, Atanassoff PG: Comparison of continuous infusion *versus* automated bolus for postoperative patient-controlled analgesia with popliteal sciatic nerve catheters. *ANESTHESIOLOGY* 2009; 110:150-4
 23. Eledjam JJ, Cuvillon P, Capdevila X, Macaire P, Serri S, Gaertner E, Jochum D, French study group: Postoperative analgesia by femoral nerve block with ropivacaine 0.2% after major knee surgery: Continuous *versus* patient-controlled techniques. *Reg Anesth Pain Med* 2002; 27:604-11
 24. Ilfeld BM, Le LT, Meyer RS, Mariano ER, Vandendorpe K, Duncan PW, Sessler DI, Enneking FK, Shuster JJ, Theriaque DW, Berry LF, Spadoni EH, Gearen PF: Ambulatory continuous femoral nerve blocks decrease time to discharge readiness after tricompartment total knee arthroplasty: A randomized, triple-masked, placebo-controlled study. *ANESTHESIOLOGY* 2008; 108:703-13
 25. Fredrickson MJ, Danesh-Clough TK: Ambulatory continuous femoral analgesia for major knee surgery: A randomised study of ultrasound-guided femoral catheter placement. *Anaesth Intensive Care* 2009; 37:758-66
 26. Bouaziz H, Vial F, Jochum D, Macalou D, Heck M, Meuret P, Braun M, Laxenaire MC: An evaluation of the cutaneous distribution after obturator nerve block. *Anesth Analg* 2002; 94:445-9
 27. Lang SA, Yip RW, Chang PC, Gerard MA: The femoral 3-in-1 block revisited. *J Clin Anesth* 1993; 5:292-6
 28. Atanassoff PG, Weiss BM, Brull SJ, Horst A, Külling D, Stein R, Theiler I: Electromyographic comparison of obturator nerve block to three-in-one block. *Anesth Analg* 1995; 81:529-33
 29. Cappelleri G, Aldegheri G, Ruggieri F, Carnelli F, Fanelli A, Casati A: Effects of using the posterior or anterior approaches to the lumbar plexus on the minimum effective anesthetic concentration (MEAC) of mepivacaine required to block the femoral nerve: A prospective, randomized, up-and-down study. *Reg Anesth Pain Med* 2008; 33:10-6
 30. Marhofer P, Nasel C, Sitzwohl C, Kapral S: Magnetic resonance imaging of the distribution of local anesthetic during the three-in-one block. *Anesth Analg* 2000; 90:119-24
 31. Snaith R, Dolan J: Ultrasound-guided interfascial injection for peripheral obturator nerve block in the thigh. *Reg Anesth Pain Med* 2010; 35:314-5
 32. Le LT, Loland VJ, Mariano ER, Gerancher JC, Wadhwa AN, Renehan EM, Sessler DI, Shuster JJ, Theriaque DW, Maldonado RC, Ilfeld BM, PAINfRE Investigators: Effects of local anesthetic concentration and dose on continuous interscalene nerve blocks: A dual-center, randomized, observer-masked, controlled study. *Reg Anesth Pain Med* 2008; 33:518-25
 33. Ilfeld BM, Le LT, Ramjohn J, Loland VJ, Wadhwa AN, Gerancher JC, Renehan EM, Sessler DI, Shuster JJ, Theriaque DW, Maldonado RC, Mariano ER, Horlocker TT, PAINfRETM Investigators: The effects of local anesthetic concentration and dose on continuous infraclavicular nerve blocks: A multicenter, randomized, observer-masked, controlled study. *Anesth Analg* 2009; 108:345-50
 34. Ilfeld BM, Loland VJ, Gerancher JC, Wadhwa AN, Renehan EM, Sessler DI, Shuster JJ, Theriaque DW, Maldonado RC, Mariano ER, PAINfRE Investigators: The effects of varying local anesthetic concentration and volume on continuous popliteal sciatic nerve blocks: A dual-center, randomized, controlled study. *Anesth Analg* 2008; 107:701-7