Continuous Femoral Nerve Blocks

Decreasing Local Anesthetic Concentration to Minimize Quadriceps Femoris Weakness

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ABSTRACT

Background: Whether decreasing the local anesthetic concentration during a continuous femoral nerve block results in less quadriceps weakness remains unknown.

Methods: Preoperatively, bilateral femoral perineural catheters were inserted in subjects undergoing bilateral knee arthroplasty (n = 36) at a single clinical center. Postoperatively, right-sided catheters were randomly assigned to receive perineural ropivacaine of either 0.1% (basal 12 ml/h; bolus 4 ml) or 0.4% (basal 3 ml/h; bolus 1 ml), with the left catheter receiving the alterna-

What We Already Know about This Topic

- There is concern that weakness during local anesthetic infusions in nerve blocks contributes to falls in patients after lower extremity surgery
- Whether or not local anesthetic concentration and volume infused around the femoral nerve influences muscle weakness in patients undergoing knee replacement is not known

What This Article Tells Us That Is New

- Reducing local anesthetic concentration and increasing volume did not influence weakness, pain or other endpoints in surgical patients; thus, total local anesthetic dosage influenced sensory and motor characteristics of the infusion

tive concentration/rate in an observer- and subject-masked fashion. The primary endpoint was the maximum voluntary isometric contraction of the quadriceps femoris muscles the morning of postoperative day 2. Equivalence of treatments would be concluded if the 95% CI for the difference fell within the interval −20%–20%. Secondary endpoints included active knee extension, passive knee flexion, tolerance to cutaneous electrical current applied over the distal quadriceps tendon, dynamic pain scores, opioid requirements, and ropivacaine consumption.

Results: Quadriceps maximum voluntary isometric contraction for limbs receiving 0.1% ropivacaine was a mean (SD) of 13 (8) N · m, *versus* 12 (8) N · m for limbs receiving 0.4% [intrasubject difference of 3 (40) percentage points; 95% CI −10–17; $P = 0.63$]. Because the 95% CI fell within prespecified tolerances, we conclude that the effect of the two concentrations were equivalent. Similarly, there were no statistically significant differences in secondary endpoints.

Conclusions: For continuous femoral nerve blocks, we found no evidence that local anesthetic concentration and volume influence block characteristics, suggesting that local anesthetic dose (mass) is the primary determinant of perineural infusion effects.

S URGICAL procedures involving the knee joint often result in significant postoperative pain that is frequently treated with a continuous femoral nerve block (cFNB).[1] However, these perineural infusions also induce undesired

sensory deficits and quadriceps femoris muscle weakness.[2] Minimizing motor effects is imperative because quadriceps weakness is associated with both functional disability[3] limiting ambulation/rehabilitation[4] and an increased risk of falling in elderly patients.[5] Unfortunately, optimizing infusion characteristics is problematic, given that it remains unknown whether the primary determinant of cFNB effects is solely local anesthetic dose (mass), or whether concentration and/or volume exert additional influence.[6–9] Currently, low local anesthetic concentrations are often used in an effort to minimize quadriceps weakness during cFNB.[10] Although for single-injection nerve blocks, concentration and volume do determine efficacy when dose is held constant,[11,12] this relationship does not necessarily hold true for continuous peripheral nerve blocks.

In fact, data from the only study of perineural infusion that varied both the infusion rate and concentration in a static ratio so that the total dose was comparable in each treatment group suggests that local anesthetic concentration and volume (rate) do not influence block effects as long as the total dose remains constant.[13] These results, though, were based exclusively on continuous posterior lumbar plexus catheters, and therefore may not be applicable to femoral infusion because local anesthetic pharmacodynamics vary considerably among anatomic catheter sites. For example, increasing local anesthetic concentration has differing effects on the incidence of an insensate extremity depending upon catheter site location: increased for infraclavicular,[14] decreased for popliteal,[15] no difference for axillary,[16] and variable for interscalene.[8,17,18] Considering cFNB is often provided for analgesia following major surgical procedures of the knee in elderly patients, and a fall in this patient population may prove catastrophic, it is imperative that the cFNB-related factors inducing quadriceps weakness be identified. The potential gravity of the issue is suggested in the more than 650,000 total knee arthroplasty (TKA) procedures performed every year in the United States alone,‡‡ with that number expected to grow to 3.5 million annually within the next 20 yr.[19]

We therefore tested the hypothesis that providing ropivacaine at different concentrations and rates (0.1% at 12 ml/h *vs.* 0.4% at 3 ml/h), but at an equivalent total basal (12 mg/h) and patient-controlled bolus doses (4 mg), produces comparable effects when used in cFNB following TKA. The primary endpoint was the maximum voluntary isometric contraction (MVIC) of the quadriceps femoris muscles the morning of postoperative day 2. Secondary endpoints included quadriceps MVIC at other time points, active knee extension, passive knee flexion, tolerance to cutaneous electrical current applied 0 to 1 cm medial to the distal quadri-

ceps tendon, dynamic pain scores, opioid requirements, and ropivacaine consumption.

Materials and Methods

Enrollment

The local Institutional Review Board (Cleveland Clinic, Cleveland, Ohio) approved all study procedures for this single-center clinical trial, and all participants provided written, informed consent. The trial was prospectively registered at clinicaltrials.gov (NCT00923598). Patients offered enrollment included adults (18 yr or older) scheduled for primary, bilateral, tricompartment knee arthroplasty with bilateral cFNB. Exclusion criteria included a history of opioid dependence, abuse, or current chronic analgesic therapy (daily use more than 20 mg oxycodone, equivalent opioid use within the 2 weeks before surgery and duration of use more than 4 weeks); a neuromuscular deficit of either femoral nerves and/or quadriceps muscles; pregnancy; or incarceration.

Preoperative Management

Bilateral femoral perineural catheters (StimuCath, Teleflex Medical, Research Triangle Park, NC) were inserted in all subjects using a nerve stimulator initially set at 1.2 mA, 0.1 ms, and 2 Hz, using a technique similar to one previously described with a muscle contraction endpoint of the quadriceps at 0.20–0.50 mA *via* the insulated needle and less than 80 mA *via* the stimulating catheter.[20] Twenty-five milliliters of mepivacaine 1.5%, with epinephrine, 2.5 μg/ml, was injected *via* the catheter with gentle aspiration every 3 ml. The femoral nerve block was evaluated 20 min later and considered successful when subjects had increased difficulty extending at the ipsilateral knee joint. Subjects with catheter placements per protocol and nerve block onset were retained in the study.

Randomization

Remaining subjects had the right-sided catheter randomly assigned to one of two treatment groups: a ropivacaine concentration of 0.1% or 0.4%. Subjects acted as their own controls, with the contralateral side receiving the alternative concentration. Randomization was based on computer-generated codes in blocks of four and stratified by surgeon. The Investigational Drug Service prepared the ropivacaine reservoirs, and one investigator uninvolved with endpoint measurement programmed two portable, electronic infusion pumps (ambIT PCA, Summit Medical, West Jordan, UT), with the basal rate and patient-controlled bolus volume determined by the ropivacaine concentration in each pump reservoir (table 1). Although the basal rate and bolus volume differed for each concentration, the total dose of local anesthetic was the same for both treatments (table 1). The infusion pumps were labeled as either "left" or "right" so that subjects could self-administer a bolus to the necessary side. The electronic display was covered with opaque medical tape to mask treatment assignments.

‡‡ Health Care Cost and Utilization Project. (2008). "HCUP Facts and Figures: Statistics on Hospital-Based Care in the United States." http://www.hcup-us.ahrq.gov/reports/factsandfigures/2008/exhibit3_1.jsp. Accessed June 29, 2011.

Table 1. Perineural Ropivacaine Infusion Profile by Treatment Group

Ropivacaine Concentration	Basal Rate (mL/h)	Basal Dose (mg/h)	Bolus Volume (mL)	Bolus Dose (mg)	Lockout Duration (min)	Maximum Dose (mg/h)
0.1% (1 mg/mL)	12	12	4	4	30	20
0.4% (4 mg/mL)	3	12	1	4	30	20

Intraoperative Management

Subjects received either a standardized general anesthetic with an inhaled anesthetic with or without nitrous oxide; a standardized spinal anesthetic (isobaric bupivacaine 15 mg with epinephrine 200 μg and fentanyl 25 μg); or a combined spinal/epidural with the spinal anesthetic just described and optional lidocaine/mepivacaine 1.5% epidural boluses combined with epinephrine. Epidurals were discontinued in the recovery room; they were only used intraoperatively to prolong the surgical anesthetic, when necessary. Opioids were administered, when necessary (fentanyl in 25 μg increments). The two infusion pumps were attached to each of the perineural catheters, and the local anesthetic infusions initiated within the operating room. Shortly before anesthetic emergence, intravenous morphine was titrated for a respiratory rate of 12–14. Upon emergence, subjects were taken to the recovery room and then to the surgical ward.

Postoperative Management

In addition to the ropivacaine perineural infusion initiated in the operating room and continued through postoperative day 2, all subjects were provided oral acetaminophen (1,000 mg every 6 h), celecoxib (200 mg every 12 h), and a sustained-release synthetic opioid, oxycodone (OxyContin, 10 mg every 12 h; Purdue Pharma L.P., Stamford, CT). For breakthrough pain, subjects were instructed to depress the bolus buttons of the ipsilateral infusion pump and wait 15 min for the effect. When needed, rescue opioid and route of administration were titrated to pain severity: oral oxycodone 5–10 mg or intravenous morphine 2–4 mg.

Subjects underwent physical therapy twice daily beginning the morning following surgery and thereafter until discharge. If the physical therapist believed subject ambulation was limited because of quadriceps weakness, the perineural infusion basal rate and patient-controlled bolus volume of the affected side were reset by the unmasked investigator at half the previous values. The investigator who initially programmed the infusion pumps subsequently interrogated each pump's memory following the afternoon physical therapy session on postoperative day 2.

Outcome Measurements

Postoperative measurements were performed the 2 days following surgery in both the morning and afternoon. Staff masked to treatment group assignment performed all measures and assessments. We selected measures that have established reliability and validity,[5,21–23] and the right side was always assessed first.

Quadriceps Femoris Muscle Strength. Evaluated with an isometric force electromechanical dynamometer (BEP IIId Cable Tensiometer; Human Performance Measurement, Arlington, TX) to measure the force produced during a MVIC.[22,23] Subjects were placed in a seated position and the knee flexed at 90 degrees. The dynamometer was placed on the ipsilateral anterior tibia perpendicular to the tibial crest, just proximal to the medial malleolus. Subjects were asked to take 2 s to come to maximum effort contracting the quadriceps, maintain this effort for 5 s, and then relax.[22,23]

Sensory Effect. Evaluated with subjects in the seated position using tolerance to transcutaneous electrical stimulation, measured using the same quantitative procedure described previously.[21] Electrocardiogram pads were placed 0 to 1 cm medial to the proximal patella and quadriceps tendon and attached to a nerve stimulator (Model NS252; Fisher & Paykel, Auckland, New Zealand). 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. This endpoint was measured only on postoperative day 2 after the knee bandages were removed early that morning.

Knee Range-of-motion. Evaluated using standard goniometry for passive flexion and active extension.

Pain. Evaluated using a standard Visual Analog Scale, with scores recorded immediately following the above assessments for each side.

Statistical Analysis

Sample size calculations were based on our primary aim of determining the relationship between perineural ropivacaine concentration and cFNB effects. To this end, the primary endpoint was designated as the MVIC of the quadriceps femoris the morning of postoperative day 2. The primary alternative hypothesis was that differing the concentration (0.1% vs. 0.4%) but providing an equal total dose of ropivacaine through a femoral perineural catheter following TKA results in a change in MVIC (in either direction) between −20–20%. A difference of 20% points was considered clinically relevant because a 10% side-to-side strength difference is common, yet functionally unnoticeable, in healthy individuals.[24,25] Based on unpublished data, the MVIC SD was estimated to be 30, which also implies a SD for the difference in MVIC between the two treated legs of approximately 30 (assuming a correlation of 0.5 among repeated measurements). The percentage difference between treatments was calculated using the formula of (0.4% side − 0.1% side)/ 0.1% side × 100.[5]

The method described by Armitage *et al.* was used,[26] whereby equivalence of treatments would be concluded if the 95% CI for the difference fell within the prespecified tolerated interval (−20–20%). Under these assumptions, a trial with n = 36 subjects (72 limbs) would correctly conclude there is no treatment difference with probability 80% ("power"), and incorrectly conclude equivalence when there is a difference of 20% with probability 5% ("α"). Because this was a pharmacodynamics study, as opposed to an outcomes trial, we prospectively elected to exclude from the primary analyses subjects who did not provide assessments for the primary endpoint. However, all subjects with bilateral successfully inserted catheters/blocks were included in *post hoc* intent-to-treat secondary analyses.

The same analyses were applied to the secondary endpoints. Profiles of the responses over time were examined with spaghetti and mean plots. Further secondary analyses included mixed-effects modeling of the repeated measures. These models account for the hierarchical correlation of paired measures from each subject over time, and were used to test the effects of subject characteristics, including sex, height, weight, body mass index, and age. The model also allowed simultaneous analysis of all observations while accounting for within-subject correlation, which can improve the standard errors of the estimated differential at each time point.

Analyses were executed using R version 2.12 (2010).§§ Additional analyses included the Mann–Whitney U test for nonparametric comparisons and Fisher exact test for categorical variables (InStat, GraphPad Software, San Diego, CA).

Results

During a 20-month period between July 2009 and February 2011, 48 subjects enrolled and all but three had successful bilateral perineural catheters inserted with subsequent femoral nerve blockade, per protocol (table 2). Of these, nine did not have the primary endpoint assessed because of inability to reach a sitting position (n = 2), physical therapist unavailability (n = 4), subject refusal (n = 2), and subject confusion (n = 1). Although only the remaining 36 subjects were included in the primary analyses as prospectively intended, all 45 subjects with bilateral successfully inserted catheters/blocks were included in the intent-to-treat analyses (fig. 1).

Primary Endpoint

Quadriceps MVIC for limbs receiving 0.1% ropivacaine was a mean (SD) of 13 (8) N · m, *versus* 12 (8) N · m for limbs receiving 0.4% [intrasubject difference of 3 (40) percentage points; 95% CI −10–17; *P* = 0.63]. Because the CI falls within the prespecified −20–20% range, we conclude that the effect of the two concentrations on quadriceps MVIC were equivalent.

§§ R Software Environment for Statistical Computing, R Foundation for Statistical Computing (version 2.12), Vienna, Austria. http://www.r-project.org. Accessed June 13, 2011.

Table 2. Anthropomorphic Characteristics and Supplemental Opioid Requirements

	All Analyses (n = 36)	Exclusively Intent-to-treat Analyses (n = 9)	*P* Value
Age (yr)	60 (9)	65 (9)	0.14
Sex (female/male)	21/15	7/2	0.45
Height (cm)	171 (11)	164 (10)	0.08
Weight (kg)	90 (19)	97 (21)	0.38
Body mass index (kg/m^2)	30 (5)	36 (8)	0.08
Morphine equivalents, intraoperative (mg)	2 (2–2)	2 (1–2)	0.89
Morphine equivalents, recovery room (mg)	7 (5–14)	8 (1–11)	0.37
Morphine equivalents, postrecovery room through postoperative day 2 (mg)	42 (33–60)	28 (27–37)	0.04

Values are reported as number of subjects; mean (SD) for parametric data; or median (interquartile) for nonparametric data. Because this was a pharmacodynamics study, as opposed to an outcomes trial, we prospectively elected to exclude from the primary analyses subjects who did not provide assessments for the primary endpoint. However, all subjects with bilateral successfully inserted catheters/blocks were included in *post hoc* intent-to-treat secondary analyses.

Secondary Endpoints

Similarly, there were no statistically significant differences in any secondary endpoints, including analgesia, based upon pain scores and local anesthetic requirements (table 3, fig. 2). Ropivacaine consumption between the catheters with 0.1% and 0.4% were nearly identical, with patient-controlled bolus dose requests of 43 (35) and 42 (39), and delivered bolus doses of 23 (11) and 23 (12), respectively. Supplemental opioid requirements from recovery room discharge through postoperative day 2 were 57 (60) mg morphine equivalents. Of the 72 infusions, only 1 (receiving 0.4%) resulted in enough quadriceps weakness to warrant a decrease in the basal infusion rate. Results were similar in the intent-to-treat population, with no statistically significant differences between treatments for any endpoint.

Discussion

This randomized, controlled investigation provides evidence that local anesthetic concentration and volume do not influence cFNB characteristics, including quadriceps muscle weakness and physical therapy goals such as knee flexion/extension, indicating that local anesthetic dose (mass) is the primary determinant of femoral infusion effects. These results are important because they suggest that lowering the concentration of local anesthetic is not an effective component of a strategy to minimize undesired motor weakness during cFNB. In contrast, decreasing local anesthetic concentration at a given infusion rate, resulting in a lower total
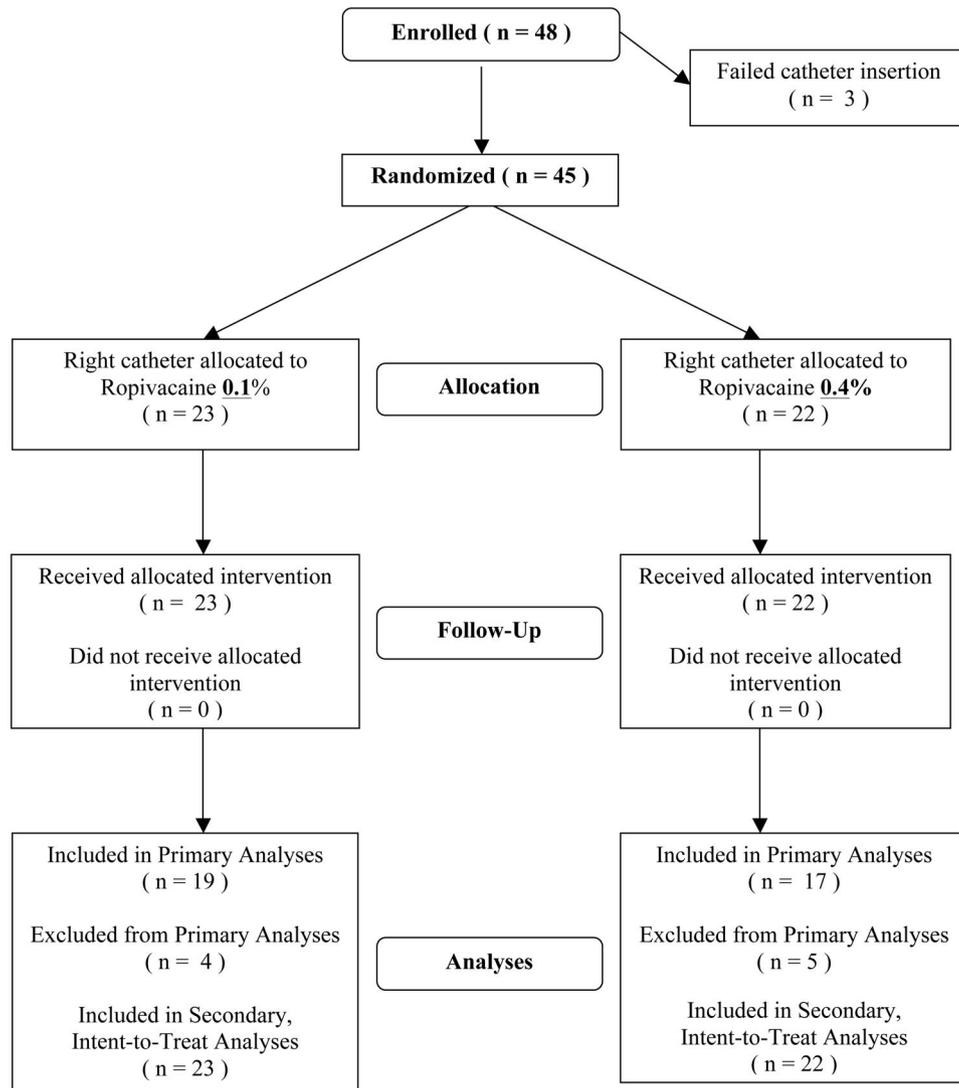
Fig. 1. Consort flowchart.

dose, will decrease muscle weakness during cFNB, but at the expense of reduced analgesia.[27]

The findings of the current study are somewhat disappointing in that it appears practitioners have one fewer potential tool for decreasing cFNB-induced quadriceps weakness while retaining equivalent analgesia. However, this new data may diminish an apparently false sense of security among healthcare providers who currently decrease concentration while increasing rate/volume during cFNB in the belief that quadriceps function will be spared. In addition, the new information allows investigators to invest time and resources in other strategies to maximize the benefits of cFNB while concurrently minimizing the associated risks.[2,13] Although the results of the current study are the most definitive to date regarding the issue of the relative importance of local anesthetic dose *versus* concentration/volume during cFNB, these data should be viewed as a reference point to help design future clinical trials. The current study is one step in this endeavor.

Quadriceps Weakness

Until additional data are available, practitioners may want to consider steps that may minimize the risk of falls during cFNB,[13,28] including minimizing the dose/mass of local anesthetic; providing limited-volume patient-controlled bolus doses that allow for a decreased basal dose without compromising analgesia in some cases[29,30], although not all[31]; using a knee immobilizer and walker/crutches during ambulation,[32] and educating physical therapists, nurses, and surgeons of possible muscle weakness induced by continuous peripheral nerve blocks and the importance of fall precautions. Unless a single optimal dose may be accurately and prospectively predicted for each individual patient, it is probable that fixed-rate basal infusions without bolus capability will fail to both optimize postoperative analgesia and minimize muscle weakness (and probably sensory perception and proprioception).[13] In contrast, infusion pumps with an adjustable basal rate will permit titration to the minimum effective analgesic dose, and pumps providing for patient-con-

Table 3. Primary* and Secondary Endpoints (Primary Analyses)

	Time Point		Limbs Receiving Ropivacaine		Intrasubject (Left *vs.* Right Limb)		
Endpoint	Postoperative Day	Therapy Session	0.1% (n = 36)	0.4% (n = 36)	Difference† (Percentage Points)	95% CI	P Value
Quadriceps Femoris MVIC (N · m)*	1	Morning	9 (3)	9 (3)	14 (52)	−6–33	0.18
		Afternoon	10 (5)	8 (2)	−6 (37)	−19–7	0.35
	2	Morning*	13 (8)	12 (8)	3 (40)*	−10–17	0.63*
		Afternoon	14 (8)	14 (10)	12 (69)	−12–35	0.31
Cutaneous current tolerance (mA)	2†	Morning	72 (13)	66 (18)	−7 (35)	−19–5	0.24
		Afternoon	73 (13)	65 (18)	−8 (34)	−19–4	0.18
Passive flexion (degrees)	1	Morning	80 (11)	79 (14)	1 (20)	−6–8	0.85
		Afternoon	85 (9)	84 (10)	0 (12)	−5–4	0.83
	2	Morning	90 (9)	87 (10)	−2 (10)	−6–1	0.17
		Afternoon	91 (8)	89 (10)	−1 (9)	−5–2	0.43
Active extension (degrees)	1	Morning	−52 (11)	−51 (12)	3 (31)	−9–14	0.63
		Afternoon	−50 (12)	−53 (10)	14 (49)	−4–32	0.11
	2	Morning	−43 (14)	−43 (15)	7 (35)	−5–19	0.27
		Afternoon	−41 (16)	−39 (15)	16 (60)	−5–36	0.13
Maximum VAS during therapy	1	Morning	7 (2)	7 (1)	11 (36)	−2–25	0.10
		Afternoon	6 (2)	6 (3)	1 (27)	−5–4	0.83
	2	Morning	6 (3)	6 (2)	8 (36)	−4–21	0.17
		Afternoon	5 (3)	5 (2)	15 (74)	−8–39	0.19
Average VAS during therapy	1	Morning	5 (2)	5 (2)	15 (49)	−3–33	0.10
		Afternoon	5 (2)	5 (2)	9 (36)	−4–21	0.19
	2	Morning	4 (3)	4 (3)	12 (38)	−1–24	0.08
		Afternoon	4 (2)	4 (2)	13 (60)	−6–32	0.19

Values expressed as mean (SD).

* Primary endpoint: quadriceps femoris maximum voluntary isometric contraction the morning of postoperative day 2. † (Ropivacaine 0.4% limb − Ropivacaine 0.1% limb)/Ropivacaine 0.1% limb · 100. ‡ Tolerance to cutaneous current evaluated only on postoperative day 2 after bandage removal.

MVIC = maximum voluntary isometric contraction; VAS = Visual Analog Score.

trolled boluses will permit rapid analgesia reinforcement with a minimized basal rate.

Ambulatory Infusion

The results of the current study are beneficial for patients provided with cFNB on an outpatient basis.[33] Ambulatory perineural infusion requires patients to carry the local anesthetic reservoir. Our new data suggest that providing a higher local anesthetic concentration and concurrent lower basal infusion rate for these patients will neither compromise analgesia nor increase quadriceps weakness. Minimizing the local anesthetic consumption rate (thus volume) allows for maximum infusion, and analgesic, duration.[34] For example, in the current study, limbs receiving 0.1% ropivacaine required a median (interquartile) of 649 (609–701) ml of ropivacaine, compared with only 161 (159–182) ml for limbs receiving a 0.4% concentration. For an ambulatory patient with a set local anesthetic reservoir volume,[35] this difference would markedly increase potential infusion duration.

Study Model

By including subjects undergoing TKA, we were able to adequately test the effect of varying concentration and rate

relative to dose for cFNB on analgesic endpoints (*e.g.*, pain scores), unlike related studies involving nonsurgical volunteers.[2] In addition, the bilateral cFNB split-body study model in which each subject simultaneously received both study treatments (0.1% and 0.4% ropivacaine) and intrasubject differences analyzed enabled exclusion of noninfusion analgesics as a confounding variable; any opioids consumed by subjects affected both treatments equally.

Study Limitations

The current findings involving stimulating catheters and 0.1% or 0.4% ropivacaine for cFNB may not be applicable to other catheter designs[36] or insertion techniques[37]; local anesthetic types,[38] concentrations, or doses[27]; infusion delivery methods[39] or durations[35]; and certainly anatomic catheter locations.[8,13–18,40] Importantly, although the current study suggests that local anesthetic dose (mass) is the primary determinant of cFNB effects, this does not suggest that concentration and volume are irrelevant if one of these factors is held constant (*e.g.*, basal rate) resulting in differing drug doses.[27] Although subjects, clinical staff, and nearly all investigators were masked to treatment assignment using opaque tape to cover the electronic display of each infusion pump, the tape
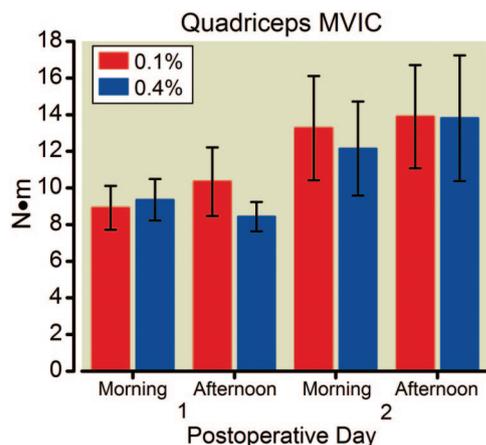
Quadriceps MVIC

Fig. 2. Effects of continuous femoral nerve block ropivacaine concentration on quadriceps femoris strength following bilateral tricompartment knee arthroplasty. Muscle strength was evaluated using a dynamometer to measure maximum voluntary isometric contractions. Data are expressed as mean (*horizontal bar*) with 95% CI of the mean (*whiskers*) for limbs randomly assigned to receive ropivacaine 0.1% (basal 12 ml/h, 4 ml bolus) or ropivacaine 0.4% (basal 3 ml/h, 1 ml bolus). There were no statistically significant differences between treatments. Furthermore, because the 95% CI for the primary endpoint (intrasubject differences the morning of postoperative day 2) fell within prespecified tolerances, we found that the effect of the two concentrations on quadriceps maximum voluntary isometric contractions were equivalent.

was technically removable and the reservoir volumes within the black pump cases accessible. Therefore, although this may be considered a double-masked study design, we chose a conservative approach and did not describe it as such. Yet, even if the masking was broken, it is unlikely that subjects had a bias toward one concentration.

In summary, we found no evidence that local anesthetic concentration and volume influence block characteristics, specifically quadriceps weakness, during cFNB. This suggests that local anesthetic dose (mass) is the primary determinant of perineural infusion effects.

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