

Comparison of Three Techniques for Ultrasound-guided Femoral Nerve Catheter Insertion

A Randomized, Blinded Trial

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ABSTRACT

Background: Ultrasound guidance for continuous femoral perineural catheters may be supplemented by electrical stimulation through a needle or through a stimulating catheter. The authors tested the primary hypothesis that ultrasound guidance alone is noninferior on both postoperative pain scores and opioid requirement and superior on at least one of the two. Second, the authors compared all interventions on insertion time and incremental cost.

Methods: Patients having knee arthroplasty with femoral nerve catheters were randomly assigned to catheter insertion guided by: (1) ultrasound alone (n = 147); (2) ultrasound and electrical stimulation through the needle (n = 152); or (3) ultrasound and electrical stimulation through both the needle and catheter (n = 138). Noninferiority between any two interventions was defined for pain as not more than 0.5 points worse on a 0 to 10 verbal response scale and for opioid consumption as not more than 25% greater than the mean.

Results: The stimulating needle group was significantly noninferior to the stimulating catheter group (difference [95% CI] in mean verbal response scale pain score [stimulating needle *vs.* stimulating catheter] of -0.16 [-0.61 to 0.29], $P < 0.001$; percentage difference in mean IV morphine equivalent dose of -5% [-25 to 21%], $P = 0.002$) and to ultrasound-only group (difference in mean verbal response scale pain score of -0.28 [-0.72 to 0.16], $P < 0.001$; percentage difference in mean IV morphine equivalent dose of -2% [-22 to 25%], $P = 0.006$). In addition, the use of ultrasound alone for femoral nerve catheter insertion was faster and cheaper than the other two methods.

Conclusion: Ultrasound guidance alone without adding either stimulating needle or needle/catheter combination thus seems to be the best approach to femoral perineural catheters. (ANESTHESIOLOGY 2014; 121:239-48)

TOTAL knee arthroplasties are common. They cause severe postoperative pain in most patients and moderate pain in the remainder.¹ Postoperative pain delays early intensive physical therapy, thereby prolonging rehabilitation.² Continuous femoral perineural catheters provide excellent postoperative analgesia and are now routinely used after knee arthroplasties.^{3,4}

Continuous femoral perineural catheters often fail,^{5,6} apparently because the catheter tip is not well positioned adjacent to the femoral nerve.⁷ Nerve stimulation is the classical method for confirming appropriate catheter or needle placement.⁶ However, it is now established that ultrasound guidance improves positioning success, speeds catheter insertion, and enhances patient satisfaction.^{3,8} Whether nerve stimulation improves ultrasound-guided catheter placement and block success remains unclear. In addition to its obvious

What We Already Know about This Topic

- Ultrasound-guided placement of femoral perineural catheters is sometimes supplemented with the use of electrical stimulation through the needle or catheter, but whether this improves catheter function is not known

What This Article Tells Us That Is New

- In a controlled study of 450 patients, neither supplemental electrical stimulation through the needle nor through needle and catheter was superior to ultrasound guidance alone in terms of pain score and IV opioid requirement
- Additionally, the use of ultrasound alone was both faster and less expensive

clinical importance, the question is of economic interest because stimulating needles and stimulating catheters have

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higher acquisition costs than routine block needles or catheters. Use of stimulation may also affect catheter insertion time.

We therefore compared ultrasound guidance alone with either ultrasound guidance plus needle stimulation or ultrasound guidance plus catheter stimulation for insertion of femoral nerve catheters for total knee arthroplasty under mainly neuraxial anesthesia or general anesthesia. Specifically, we tested the primary hypothesis that ultrasound guidance alone is noninferior on postoperative pain (as characterized by both pain scores and opioid requirements). Our secondary hypotheses were that ultrasound guidance alone is: (1) noninferior on block performance time and block failure rate and (2) less expensive than either stimulation approach.

Materials and Methods

With approval of the Institutional Review Board at the Cleveland Clinic (Cleveland, Ohio) and written consent, we enrolled 453 patients 18 to 80 yr old from August 13, 2009 to December 28, 2012, who were scheduled for total knee arthroplasty with either general or neuraxial anesthesia. We excluded patients who used illicit drugs within 6 months, were pregnant, or refused a femoral nerve catheter. The study was conducted at the Cleveland Clinic Main Campus and registered at ClinicalTrials.gov (NCT00927368).

Protocol

Femoral perineural catheters were inserted by staff anesthesiologists experienced in ultrasound or by experienced senior residents or fellows supervised by experienced staff. Most were inserted preoperatively. All catheters were inserted with ultrasound guidance, using a 13- to 6-MHz linear ultrasound probe (SonoSite, Bothell, WA or GE, Duluth, GA) to provide a short-axis view of the femoral nerve *via* an out-of-plane approach. Typically, the femoral nerve appeared as a hyperechoic structure ventrally to the iliopsoas hypoechoic muscle, lateral to the pulsating femoral artery.

For study purposes, we used insulated 17-gauge, 10-cm-long Tuohy needles in all patients. We similarly used 19-gauge StimuCath catheters designed for electrical stimulation in all patients (StimuCath; Arrow International, Reading, PA).

Participating patients were randomized to one of the three catheter insertion techniques: (1) ultrasound guidance alone (ultrasound alone); (2) ultrasound guidance and needle stimulation (needle stimulation); or (3) ultrasound guidance and catheter stimulation (catheter stimulation). Randomization (1:1:1 without stratification) was provided by a Web-based system that was accessed just before catheter insertion. Allocation was thus concealed until the last practical moment. Treatment assignments were generated in randomly sized blocks using SAS statistical software (SAS Institute, Cary, NC).

In the ultrasound-alone group, the Tuohy needle was inserted in an out-plane approach. Needle placement was considered adequate when the tip was visualized beneath the fascia iliaca; the catheter was then introduced 5 cm beyond the needle tip. Electrical stimulation was not used.

In the needle-stimulation group, the Tuohy needle was positioned with the tip beneath the fascia iliaca under ultrasound guidance. The needle tip was then adjusted as necessary to obtain a quadriceps muscle response with a stimulating current of 0.5 mA or less (2 Hz, pulse width 0.1 ms). Subsequently, the catheter was threaded 5 cm beyond the needle tip without additional electrical stimulation.

In the catheter-stimulation group, the Tuohy needle was positioned with the tip beneath the fascia iliaca under ultrasound guidance. The needle tip was then adjusted as necessary to obtain a quadriceps muscle response with a stimulating current of 0.5 mA or less. At that point, the peripheral nerve stimulator was then disconnected from the stimulating needle and connected to the proximal end of the catheter. The catheter was then advanced 5 cm beyond the needle tip. If the motor response disappeared during catheter advancement, the catheter was withdrawn slightly until the response returned. Needle orientation and catheter advancement were adjusted as necessary to elicit quadriceps contractions *via* the catheter with a stimulating current of 0.5 mA or less.

Once the femoral nerve catheter was positioned using the assigned technique, 20 ml of 0.1% ropivacaine was injected. Postoperatively, patients were given an infusion of 0.1% ropivacaine at a rate of 8 ml/h until the second postoperative day. If the anesthesiologist was unable to elicit nerve stimulation or to maintain quadriceps contractions using stimulating catheter, the catheter was inserted using ultrasound guidance alone.

Patients were given either general or neuraxial anesthesia. Neuraxial block is the preferred method of anesthetic management at the Clinic and usually performed with 3 ml bupivacaine 0.5%. General endotracheal anesthesia was usually induced with propofol and maintained with sevoflurane.

In the postoperative period, we tested the effectiveness of the femoral perineural catheter to provide the appropriate pain relief. Intravenous patient-controlled analgesia was provided as necessary if the block failed or was insufficient. Morphine sulfate was the default drug, but fentanyl or hydromorphone was substituted if necessary. Oral analgesics consisting of acetaminophen or a combined opioid and non-steroidal anti-inflammatory agent were gradually substituted for the femoral nerve block and patient-controlled opioid.

In cases of severe posterior knee pain unresponsive to pain medications, sciatic nerve blocks were performed either on the day of surgery or on the first postoperative day. Sciatic nerve block was usually performed *via* a subgluteal approach using ultrasound with nerve stimulation or nerve stimulation alone. Twenty milliliters of 0.1% ropivacaine was injected for the block.

Measurements

Baseline demographic, morphometric, and surgical characteristics were recorded, along with surgical and anesthetic details.

Verbal response scale (VRS) pain scores after surgery—which ranged from 0 (no pain) to 10 (maximum intolerable pain)—were assessed every 30 min in the recovery area and every 4 h thereafter up to 48 h postoperatively. These individual measurements were averaged for each patient using a time-weighted formula. (For a given patient, the observed VRS pain score profile as a function of time was linearly interpolated and integrated using the trapezoidal rule, and then, the time-weighted average was calculated as the value of this integral divided by the total monitoring time of 48 h.) All opioid administrations within the first 48 h postoperatively were converted to IV morphine equivalent and totaled for each patient.⁹

Block performance time was characterized by the time elapsed from beginning the block to catheter placement; specifically, from time of the Tuohy needle insertion to the time of its removal.

Statistical Methods

SAS software version 9.3 (SAS Institute) and R software version 2.15.2 (The R Foundation for Statistical Computing, Vienna, Austria) were used for all data analyses. Our primary analysis was intent-to-treat, such that all randomized patients who received a study intervention (even if crossed over from the randomized intervention) were included. For all analyses, we planned to adjust for any baseline characteristics displaying clinically relevant imbalance between groups.

Primary Outcome: Pain Management

We defined quality of postoperative pain management as a combination of low pain scores and low opioid requirement within the first 48 h postoperatively. We evaluated these outcomes using joint hypothesis testing¹⁰ because differences in pain scores and opioid consumption are difficult to interpret in isolation. We thus considered a block approach superior only if it was shown to be noninferior on both pain and opioid consumption and superior on at least one of the two outcomes. Superiority was thus tested only for treatments that were significantly noninferior to a comparator intervention on both outcomes.

Noninferiority was defined by a mean postoperative VRS pain score profile not more than 0.5 points greater and a mean total postoperative morphine equivalent dose not more than 25% greater than the comparison group mean. The overall significance level was 0.025 for assessing noninferiority among the three treatments for each of pain and opioid consumption. We made no correction to the significance criterion for testing both pain and opioid consumption because both were required to be significant to claim one treatment better than another (*i.e.*, an intersection-union

test). Within an outcome, noninferiority was assessed in both directions for each of the three treatment comparisons, for a total of six tests. Using the Holm–Bonferroni sequential multiple comparison procedure¹¹ with an overall significance level (α) of 0.025, *P* values were ordered smallest to largest and compared with significance criteria of 0.025/6, 0.025/5, ..., 0.025/1.

The primary analysis for pain was a linear regression model comparing two groups on the mean pain score for a patient in the first 48 h. Noninferiority analysis used a 0.5-point noninferiority delta in a one-tailed test of the treatment effect regression parameter (*i.e.*, testing the null hypothesis that mean A minus mean B is >0.5 points).

Total opioid requirement during the first 48 postoperative hours generally followed a lognormal distribution (*i.e.*, where the observations are normally distributed after taking their logarithm). Such an analysis changes the interpretation of the effect of catheter insertion technique from that of estimating the difference in arithmetic means to estimating the ratio (or percent difference) of geometric means. We thus used a linear regression model of log-transformed total IV morphine equivalent observations as the response and randomized catheter insertion technique as the treatment of interest.

Given one treatment was found noninferior to another on both outcomes, superiority was assessed with a one-tailed global test (same direction as noninferiority results) on both outcomes simultaneously, at an overall 0.025 significance level. If significant, superiority was further tested for pain and opioid consumption individually, applying the Holm–Bonferroni approach to adjust for testing two outcomes. This step was required because only one superiority test was needed to be significant and thus claim a treatment more effective. Specifically, we used the multiple outcomes nonparametric sum of ranks global test of O'Brien¹² to assess superiority over the vector of outcomes (pain, opioids). Patients were ranked on each outcome from largest value (worst) to smallest value (best), and the two ranks were then summed within each patient. Randomized groups were then compared on the mean sum of ranks with a one-tailed *t* test or analysis of covariance model. The significance criterion for a particular global test (here called α -global) was 0.025 divided by the number of pairs of interventions that passed initial noninferiority testing.

Secondary Outcomes

Block performance time among the three groups was summarized graphically using a three-group boxplot and analyzed for difference using one-way ANOVA. The overall hypothesis of at least one group exhibiting different average block time from the others was first assessed using an *F* test. Provided there was a significant overall difference, we then proceeded to pairwise comparisons between the three groups (under the Bonferroni correction for three simultaneous

assessments, controlling the nominal type I error for this secondary outcome at 0.05).

The proportion of patients requiring sciatic nerve block was reported for each group, but not formally tested due to limited power for detecting clinically relevant differences in risk.

Interim Analyses

At each of four equally spaced analyses (three interim plus a final, as needed), we planned to evaluate both efficacy and futility using one-sided noninferiority and superiority tests (see Materials and Methods). We used a group sequential design with a γ spending function (γ parameter of -4 for efficacy [α] and -2 for futility [β]). P values constituting the efficacy boundary at each of the four planned analyses were, respectively, $P \leq 0.000134$, $P \leq 0.000390$, $P \leq 0.00117$, and $P \leq 0.00347$; likewise, the P values constituting the futility boundary were $P > 0.612$, $P > 0.199$, $P > 0.0359$, and $P > 0.00347$.

P value boundaries were adjusted for six simultaneous one-sided comparisons across two outcomes using a Bonferroni correction; they therefore correspond to the most significant comparison (efficacy) and the least significant comparison (futility) within the Holm–Bonferroni method. Study progress, safety, and results were evaluated at each interim analysis by an Executive Committee (A.K., E.J.M., and D.I.S.).

Sample Size Considerations

Sample size was based on having 90% power at the overall 0.025 significance level to detect noninferiority for both primary outcomes for any pair of treatments at the given noninferiority deltas. Using an overall noninferiority significance level of 0.025, with six such tests (three pairs of treatment times two directions for each), the lowest significance criterion to be used was 0.00417 (*i.e.*, 0.025/6). Tests for superiority were done at higher significance levels as explained above (see Statistical Methods, under “Primary Outcome: Pain Management”) and thus had greater than 90% power for detecting differences at least the size of the prespecified noninferiority deltas.

Sample size was based on opioid consumption because adequately-powered analysis of the outcome required more patients than that of the VRS pain score outcome. The SD of total IV morphine equivalents for total knee arthroplasty patients receiving a femoral nerve block at 24 h postoperatively has been estimated at 10.5 mg.¹³ This SD was 43.4% of the mean of 24.2 mg. We conservatively assumed that the true coefficient of variation (*i.e.*, SD/mean) of 50% of the mean. Under this assumption, a maximum of 453 patients (151 in each catheter insertion technique group, assuming 100% accrual) would provide approximately 90% power to detect noninferiority (using a noninferiority delta of 25% of the reference mean) at the 0.00417 significance level (*i.e.*, 0.025/6).

At the third interim analysis, all four noninferiority tests involving the ultrasound-alone group crossed the futility boundary of P value greater than 0.0359: in comparing ultrasound alone *versus* stimulating needle and stimulating catheter, respectively, we observed $P = 0.18$ and $P = 0.46$ for mean VRS pain and $P = 0.06$ and $P = 0.11$ for mean IV morphine equivalent dose. The Executive Committee nonetheless chose to continue randomized allocation through the entire planned enrollment to improve precision of noninferiority tests relative to the ultrasound-only group.

Economic Analysis

Using the results of the primary hypothesis, a cost-minimization analysis was conducted from the hospital perspective. This form of economic analyses compares the costs of interventions that are proven to be clinically equivalent. The analysis aims to guide efficient healthcare resource allocation by identifying the intervention that achieves the clinical outcome at the least cost.

Information on clinical equivalency was abstracted from the results of the primary and secondary aims. Cost data were abstracted from Cleveland Clinic Purchasing Department at 2013 values. The incremental cost between strategies was calculated as the additional cost of one strategy to the next less costly strategy. Simplified sensitivity analysis was conducted to determine the robustness of choice of least costly intervention to changes in acquisition costs.

Results

Among 453 enrolled patients, 143 (32%) were randomized to the stimulating catheter, 157 (35%) were randomized to the stimulating needle, and 153 (34%) were randomized to receive ultrasound alone. Among these, four had to be removed due to enrollment in a competing study; four were removed in light of a postrandomization determination that all inclusion/exclusion were not met; one was removed due to equipment failure; three were removed due to cancellation of surgery or change in surgical plan; and four were removed due to unavailable outcomes. Four hundred thirty-seven patients were thus available for analysis.

One patient randomized to receive the stimulating catheter actually received a nonstimulating catheter. In addition, electrical stimulation failed in seven patients randomized to the stimulating catheter and four randomized to the stimulating needle. The needle was thus inserted with ultrasound alone in these patients (3.8% of cases randomized to receive either type of stimulation; fig. 1). Two thirds of the patients received neuraxial anesthesia for the total knee-replacement procedures. All patients were analyzed according to their randomized allocation in accordance with our intention-to-treat plan.

Baseline patient and surgical characteristics were reasonably balanced among the three groups (table 1); thus, no baseline variables were included as covariables in the analysis. Table 2 summarizes opioid administration by drug.

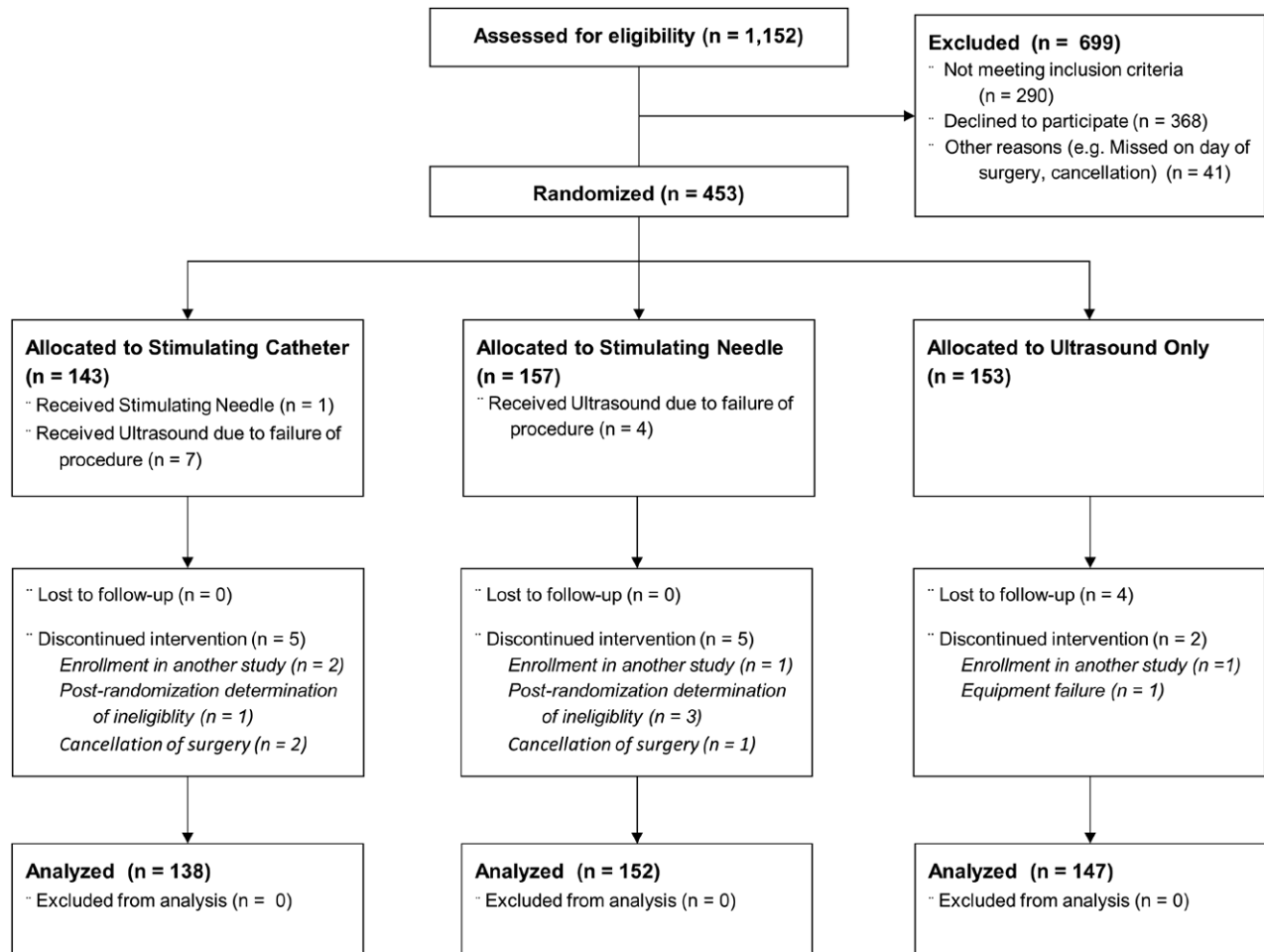


Fig. 1. Trial diagram.

Analgesia

The distribution of VRS pain scores over postoperative time is summarized graphically for each of the three randomized groups in figure 2. A scatterplot of the two primary outcomes in figure 3 suggests moderate correlation between postoperative pain score and postoperative opioid requirement, as expected. Estimated means for the three groups, given in the margins of the scatterplot, were largely similar.

In the primary analysis, the stimulating needle group was significantly noninferior to both the stimulating catheter (difference [95% CI] in mean VRS pain score [stimulating needle *vs.* stimulating catheter] of -0.16 [-0.61 to 0.29], $P < 0.001$, and percentage difference in mean IV morphine equivalent dose of -5% [-25 to 21%], $P = 0.002$; both statistically significant after application of the Holm–Bonferroni testing procedure) and ultrasound only (difference in mean VRS pain score of -0.28 [-0.72 , 0.16], $P < 0.001$, and percentage difference in mean IV morphine equivalent dose of -2% [-22 to 25%], $P = 0.006$; both significant after the Holm–Bonferroni procedure) on pain management (fig. 4). For these two comparisons, we thus proceeded to assessing superiority.

Global superiority tests (on both pain and opioid use) were not significant. Specifically, the P value was 0.32 for global superiority test of the stimulating needle group over the stimulating catheter group; and the P value was 0.20 for global superiority of the stimulating needle group over the ultrasound-only group.

Interim analyses on the primary outcomes of VRS pain score and opioid consumption for efficacy and futility as outlined above did not result in the Executive Committee stopping the study early. Figure 5 shows the interim monitoring results for noninferiority testing over time on both outcomes for each comparison of interest.

Secondary Outcomes

Estimated mean block performance time (Bonferroni-adjusted 95% CI) was 177 s (151 to 202 s) for the stimulating catheter group, 150 s (126 to 175 s) for the stimulating needle group, and 110 s [85 to 135 s] for the ultrasound-only group. Mean block performance time for the ultrasound-alone group was significantly lower than that for both other groups. Specifically, the difference in means compared with the stimulating catheter group was 67 s (31 to 102 s) ($P < 0.001$, Wald test).

Table 1. Summary of Demographic, Morphometric, and Surgical Characteristics

	Stimulating Catheter (N = 138)	Stimulating Needle (N = 152)	Ultrasound Alone (N = 147)
Sex, female, N (%)	76 (55)	80 (53)	80 (54)
Race, Caucasian, N (%)	128 (93)	136 (89)	131 (89)
Age, yr, mean \pm SD	63 \pm 9	61 \pm 13	62 \pm 9
ASA physical status, N (%)			
I	0 (0)	4 (3)	2 (1)
II	45 (33)	54 (36)	58 (39)
III	91 (66)	90 (59)	84 (57)
IV	2 (1)	4 (3)	3 (2)
BMI, kg/m ² , median [quartiles]	33 [29, 38]	31 [27, 36]	32 [28, 36]
General anesthesia vs. spinal, N (%)	29 (21)	38 (25)	37 (25)
Use of ketorolac, N (%)	4 (3)	5 (3)	8 (5)
Intraoperative IV morphine equivalent dose, mg, median [quartiles]	5 [0, 10]	2 [0, 10]	2 [0, 10]

ASA = American Society of Anesthesiologists; BMI = body mass index; IV = intravenous.

Table 2. Opioid Equivalents and Total Amounts Given to Study Participants within the First 48 h Postoperatively

Medication	Route	Equivalent Analgesic Dose (mg)	Total Amount Administered (mg)	IV Morphine Equivalent Dose (mg)	Percentage of Total IV Morphine Equivalent Dose Administered
Morphine	Intravenous	10	1,012	1,012	2.9
	Oral	30	650	217	0.6
Fentanyl	Intravenous	0.1	81	8,087	22.8
	Oral	0.23	0	9	0.0
Meperidine	Intravenous	75	125	17	0.0
Oxycodone	Oral	20	37,328	18,664	52.6
Hydrocodone	Oral	30	900	300	0.8
Tramadol	Oral	150	1,450	97	0.3
Hydromorphone	Intravenous	1.5	1,011	6,739	19.0
	Oral	7	143	205	0.6
Methadone	Oral	20	50	25	0.1
Codeine	Oral	200	30	2	0.0
Tapentadol	Oral	75	675	90	0.3

IV = intravenous.

and the difference in means compared with the stimulating needle group was 40 s (6 to 75 s) ($P = 0.01$). In contrast, the two stimulation groups did not differ significantly on block performance time ($P = 0.11$).

Sciatic nerve blocks were required in 18 patients (13.0%) randomized to stimulating catheter, 20 patients (13.2%) randomized to stimulating needle, and 15 patients (10.2%) randomized to ultrasound alone.

Cost

For our cost-minimization analysis, the source of cost variability between strategies was identified. All the consumables required for the strategies are supplied in kit form, specific for femoral nerve blocks. The kits differ between strategies only by the type of needle and catheter they contain. The contractual price of standard kit, containing a standard needle and standard catheter is \$30. The contractual price of a stimulating kit and stimulating catheter is \$80. As a contractual price was not available for a kit containing a stimulating needle

and a standard catheter, the item price of a stimulating needle (\$14) was added to the contractual price of a standard kit, giving a total cost of \$44. All other costs were not different between strategies. Because the cost analysis only considers cost differences, including nonvariable costs was not necessary; therefore, only the cost of the kits was considered.

The incremental costs between the kits required for each strategy were as follows: ultrasound alone and stimulating needle, \$14; stimulating needle and stimulating needle/catheter, \$36; and ultrasound alone and stimulating needle/catheter, \$50. As contractual prices can vary between hospitals, a sensitivity analysis was performed to see how robust the choice strategy was to changes in price. The sensitivity analysis demonstrated that only if the price of a standard kit increased by 47% or the price of a stimulating needle kit decreased by 32% would the stimulating needle strategy become the choice strategy. Due to the high relative cost of a stimulating catheter/needle kit, it was dominated in price by both alternate strategies. In addition, the cost analysis was

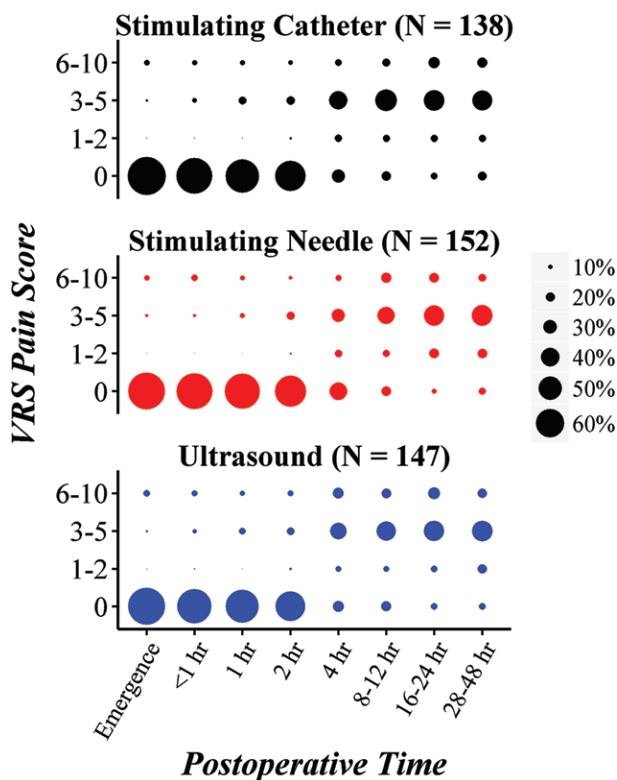


Fig. 2. Distribution of verbal response scale (VRS) pain scores over postoperative time for each of the three randomized catheter-insertion technique groups. *Plotted points* are proportional in size to the percentage of patients within a given group for a given time interval.

conservative, including only consumable costs. If the failure rate of the stimulating needle and stimulating needle/catheter strategies was included, the additional costs of consumables and time would only increase the cost difference between a standard kit and a stimulating kit. This would further strengthen the ultrasound only as the choice strategy.

Our study indicates that neither the stimulating needle combined with ultrasound nor the stimulating needle and stimulating catheter combined with ultrasound for femoral perineural catheter are better than ultrasound alone. Furthermore, use of ultrasound alone was both faster and less expensive.

Discussion

Most^{1,14,15} but not all⁶ studies report no analgesic benefit for stimulating *versus* nonstimulating catheters when inserted without ultrasound guidance. Postoperative analgesia is also similar with stimulating and nonstimulating catheters under ultrasound guidance for femoral nerve blocks.¹⁶ Furthermore, ultrasound alone for femoral nerve catheters provides comparable postoperative analgesia to the combination of ultrasound guidance and nerve stimulation and involved fewer manipulations and less procedure-related pain.^{8,17} Our study, though, is the first adequately powered trial comparing clinically important outcomes—pain and opioid consumption—among the three techniques.^{3,8,16,18}

48-Hour Postoperative Outcomes

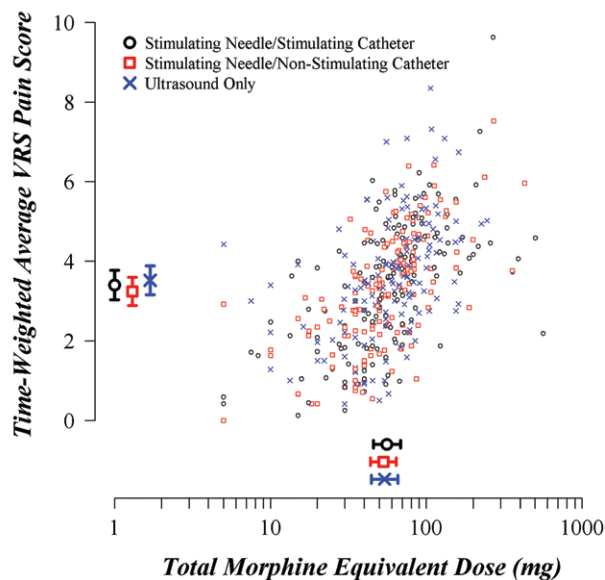


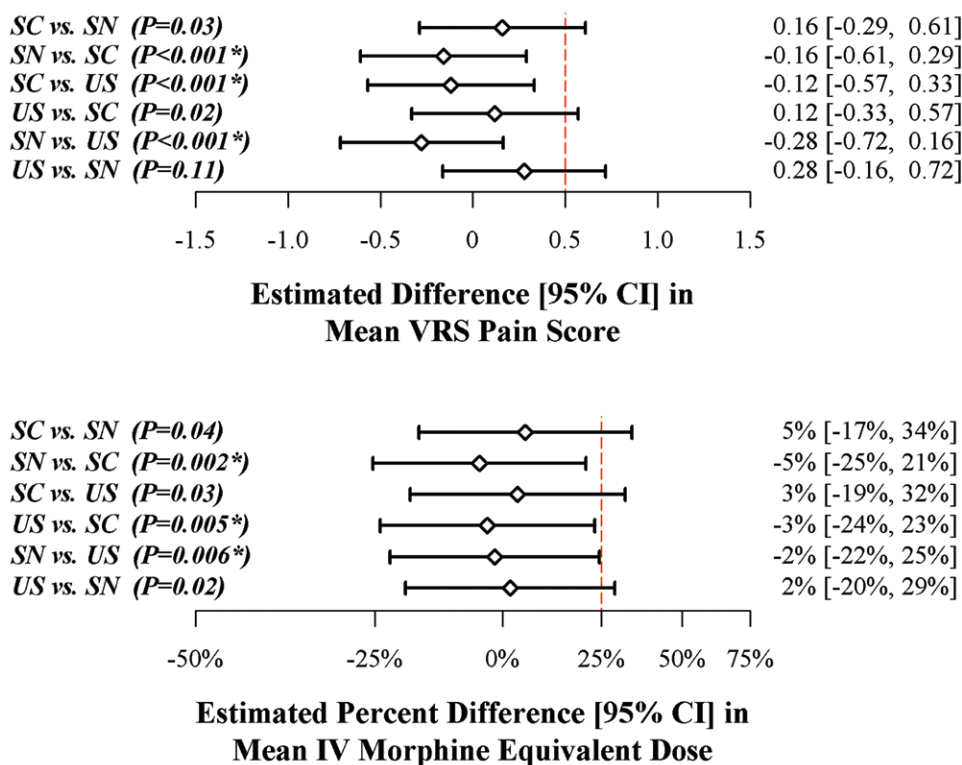
Fig. 3. Scatterplot of primary outcomes for the enrolled patients. Estimated means for each outcome and corresponding simultaneous 95% CIs are provided by group in the margins. CIs used a nominal significance criterion of 0.0023, reflecting the Bonferroni correction for six simultaneous estimates and the adjustment for interim monitoring. VRS = verbal response scale.

The results were clear: ultrasound combined with a stimulating needle was significantly noninferior to both ultrasound combined with stimulating nerve catheter and ultrasound alone. More importantly, neither stimulating needle nor stimulating nerve catheter was found superior to ultrasound alone. Furthermore, adding stimulation prolonged block time and outright failed in 3.8% of the cases.

Superiority of one intervention *versus* another on pain management is sometimes assessed using either pain scores or opioid consumption in isolation. However, better pain scores with more opioid consumption, or *vice versa*, would not usually be accepted as the better management. It thus seems reasonable to define a more effective regimen as being better on either pain or opioid consumption, but not worse on either. We therefore used a joint hypothesis testing methodology to assess whether one treatment for pain management was more effective than another.¹⁰

To be considered more effective, a treatment needed to be noninferior (*i.e.*, not worse) on both outcomes and superior on at least one of them. This is much preferable to simply requiring superiority on one or both outcomes, because a nonsignificant test for superiority could be consistent with inferiority or lack of power. Instead, we defined noninferiority margins for both outcomes *a priori* (25% worse for opioids and 0.5 points worse for pain), and then claimed noninferiority *versus* a comparator if the upper limit of the treatment effect CI was not larger than the stated margin.

Assessing Noninferiority on Both Pain and Opioid Consumption



*Statistically significant noninferiority after Holm-Bonferroni procedure.

Fig. 4. Results of simultaneous noninferiority hypothesis tests among randomized femoral nerve catheter insertion treatments given as estimates and 95% CIs (CIs adjusted for simultaneous inference and interim monitoring). One treatment (say, SN) was declared noninferior to another treatment (say, US) on mean verbal response scale (VRS) pain score when the estimated difference in means was significantly less than the prespecified noninferiority delta of 0.5 points (given as the dashed vertical line). Likewise, SN was declared noninferior to US on mean total IV morphine equivalent dose if the mean for SN was significantly not more than 25% greater than the mean for US. Significant noninferiority (as assessed by the Holm-Bonferroni step-down method) is given by asterisks next to the raw P values. SC = stimulating catheter + needle; SN = stimulating needle; US = ultrasound alone.

Superiority of one treatment over another was assessed only if noninferiority was found on both outcomes.

Besides providing meaningful assessment of pain management, our joint hypothesis framework used the intersection-union principle to efficiently control the type I error at 0.025 across all of the noninferiority and superiority testing. For example, because for a particular comparison noninferiority was required on both outcomes before claiming “noninferiority,” the significance criterion for a particular test did not need to be adjusted for testing multiple outcomes (*i.e.*, intersection-union test). Likewise, because both noninferiority and superiority were required before claiming one intervention better than another, no adjustment for testing both noninferiority and superiority was needed. We did adjust for multiple testing due to comparing three groups and for assessing noninferiority in both directions. However, we conserved α by using the Holm-Bonferroni

method,¹¹ which was less conservative than the traditional Bonferroni multiple comparison procedure. Finally, we used a flexible nonparametric global test to assess superiority across a vector of outcomes which could be on quite different scales with very different distributions (*e.g.*, pain and opioid consumption).¹²

Ultrasound alone had the lowest cost and neither the stimulating needle nor stimulating catheter improved pain management. Ultrasound alone is thus the preferred intervention in that it achieved the desired outcome at the lowest cost. Our cost-minimization analysis was conservative in that it included only the cost of consumables. Not included was the cost of additional time required for the stimulating needle or stimulating catheter and needle or the additional time and consumables required when stimulation fails and the ultrasound-only strategy must be implemented. If these additional costs were included,

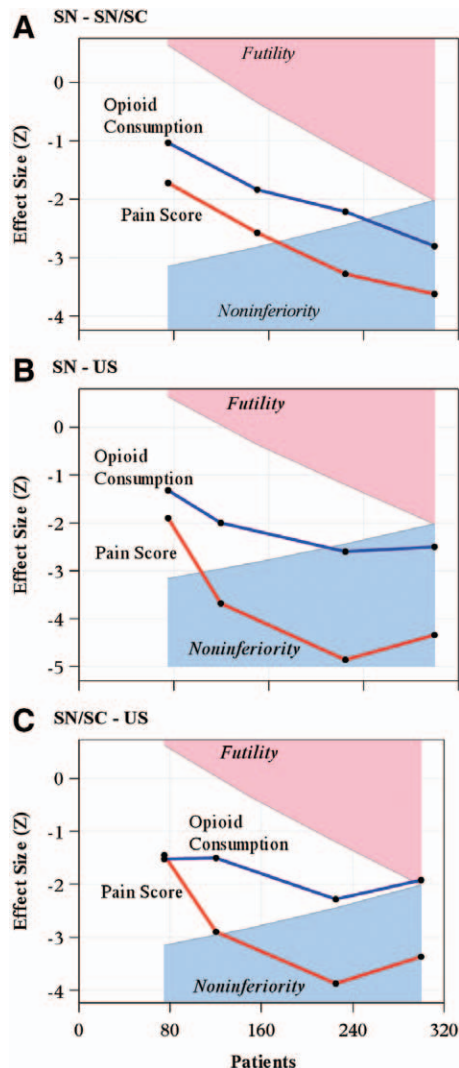


Fig. 5. Results of group sequential monitoring assessing non-inferiority on verbal response scale (VRS) pain score and opioid consumption across the four planned interim analyses. Y-axis is the observed z-statistic representing the treatment effect at the given interim analysis or final analysis, whereas x-axis is the cumulative enrollment over time. Crossing into the blue region indicates a finding of noninferiority of one group over the other, whereas crossing into the pink region indicates an acceptance of the null hypothesis (i.e., intervention at least “delta” worse than comparator) and no claim of noninferiority. We used the γ spending function with $\gamma = -4$ for efficacy and -2 for futility, with $\alpha = 0.025$ overall for noninferiority and 90% power. (A) Stimulating needle (SN) minus stimulating catheter (SC). SN was noninferior to SC on both pain and opioid consumption. (B) SN minus ultrasound (US). SN was noninferior to US on both pain and opioid consumption. (C) SC minus US. SC was noninferior to US on pain score, but not on opioid consumption. Superiority tests were done for comparisons in A and B but were not significant.

results would only further support ultrasound only being the choice strategy.

Available literature suggest that some sort of stimulation in addition to ultrasound is used for most femoral perineural

catheters.¹⁹ Our results and analysis, showing no benefit, thus present a cost-saving opportunity for hospitals. The potential savings on consumables is relatively small (\$14 to \$83) but can be realized for every patient having a femoral nerve block. Furthermore, avoiding stimulation is actually easier for physicians. Our results suggest that stimulation, whether *via* needle or catheter, should be reserved for special cases and only after the additional cost and clinical benefit have been considered.

The clinicians who inserted the blocks in our patients varied from being highly experienced attendings to moderately experienced senior residents. And although there was no obvious difference among the techniques as a function of experience, individual clinicians may have found that electrical nerve stimulation, either with the needle alone or needle and catheter, improved femoral perineural catheters outcomes of ultrasound-guided insertion. It is also possible that individuals will find that nerve stimulation can be substituted for ultrasound guidance—a combination that we did not evaluate. We did not evaluate motor block and it remains possible that one technique or another produced more motor block and consequent risk of falls. And although most of our patients were given spinal anesthesia, some received general anesthesia which might have affected immediate postoperative pain.

In summary, neither ultrasound combined with electrical stimulation of the needle nor ultrasound combined with electrical stimulation of the needle and catheter was found more effective in pain management than ultrasound guidance alone for femoral perineural catheter insertion. Ultrasound guidance alone produced comparable pain scores and opioid requirements—and was faster. Because there is an incremental cost associated with using insulated needles and an even greater incremental cost when using insulated needles and stimulating catheters, using ultrasound alone results in realizable cost savings. We thus conclude that ultrasound alone is both a clinically sufficient and cost-efficient choice for successful placement of femoral perineural catheters.

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Competing Interests

The authors declare no competing interests.

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