Optimizing Pain and Rehabilitation After Knee Arthroplasty: A Two-Center, Randomized Trial

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BACKGROUND: This randomized trial compared (1) continuous femoral nerve block (cFNB), (2) single femoral nerve block (sFNB), and (3) local infiltration analgesia (LIA) with respect to analgesic and functional outcomes after primary tricompartmental knee arthroplasty (TKA).
METHODS: One hundred twenty patients undergoing primary tricompartmental knee arthroplasty were randomly assigned to 1 of 3 interventions for postoperative analgesia: (1) cFNB—preoperative bolus of ropivacaine 0.5% 20 mL followed by ropivacaine 0.2% 5 mL per hour for 48 hours; (2) sFNB—preoperative bolus of ropivacaine 0.5% 20 mL with placebo 0.9% saline 5 mL per hour for 48 hours; or (3) LIA—intraoperative tricompartmental injection of ropivacaine 0.2% (150 mL) with epinephrine (10 μg/mL) and ketorolac 30 mg with femoral placebo 0.9% saline 20 mL preoperative bolus and 0.9% saline placebo 5 mL per hour for 48 hours. All participants received an identical, standardized, postoperative multimodal analgesic regimen. Participants, health care providers, data collectors, and analysts were blinded. All participants received identical perineural catheters and perineural/LIA solution (depending on randomized intervention) to maintain blinding. The primary outcome measure was numeric rating scale for pain (NRS) during physiotherapy on postoperative day (POD) 2 at 9:00 AM. Secondary outcomes included opioid consumption, NRS on POD 1 (rest/physiotherapy/worst), functional outcomes, and block complications.
RESULTS: For the primary outcome, pain during physiotherapy on POD 2 at 9:00 AM, the overall analysis of covariance (ANCOVA) was significant ($P = .049$), but pairwise comparisons did not demonstrate any significant differences between treatment arms. NRS was 4.6 (95% confidence interval [CI], 3.3–6.0) for the cFNB group, 4.6 (95% CI, 3.3–6.0) for the sFNB group, and 3.4 (95% CI, 2.2–4.8) for the LIA group. The following is the mean difference in NRS on POD 2 at 9:00 AM among groups: cFNB–LIA (1.2, 95% CI, −0.1 to 2.5; $P = .073$); sFNB–LIA (1.2, 95% CI, −0.2 to 2.5; $P = .097$); cFNB–sFNB (0.0, 95% CI, −1.3 to 1.4; $P = .996$). There were no statistically significant differences between groups in cumulative 48-hour opioid consumption or functional outcomes. cFNB and LIA were superior to sFNB for NRS on POD 1 for worst pain experienced and pain during physiotherapy, respectively. There were no adverse events associated with study procedures reported among participants in the 3 groups.
CONCLUSIONS: Our findings suggest no clinically significant differences between cFNB, LIA, and sFNB for pain during physiotherapy on POD 2 after TKA. Secondary analyses suggest that cFNB and LIA are superior to sFNB for early analgesic outcomes (NRS on POD 1) after TKA.   (Anesth Analg 2016;123:00–00)

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Total knee arthroplasty (TKA) is a widely performed surgical procedure, with >700,000 per annum performed in the United States and >60,000 per annum in Canada.[1,2] Pain after TKA is severe without significant targeted interventions, with approximately 30% of patients suffering chronic pain after surgery.[3] Postoperative pain after TKA is a major contributor to delayed rehabilitation and has implications with regard to quality-of-life costs to both patient and society.[3,4]

Currently, patients undergoing TKA are routinely treated with systemic analgesia (acetaminophen, nonsteroidal anti-inflammatory drugs, and opioids) alone or in combination with regional anesthesia techniques including epidural analgesia, femoral nerve block, adductor canal block (ACB), or local infiltration analgesia (LIA). Systematic reviews have confirmed superior analgesia for single/continuous femoral nerve block (s/cFNB) compared with systemic analgesia (intravenous patient-controlled analgesia [IV-PCA])[5,6] and epidural analgesia with a superior side effect profile.[7,8]

The development of LIA at the surgical site for a number of surgical procedures has generated interest and can

produce effective analgesia,[9–12] with relative technical simplicity compared with other regional anesthesia techniques.[13] Importantly, although FNB provides analgesia from the sensory block, it can also cause motor block and weakness that is thought to potentially delay aggressive physiotherapy and increase the risk of falls in the absence of appropriate preventive measures.[14–16] At present, the relative analgesic efficacy between LIA, sFNB, and cFNB after TKA is unclear. LIA is an easy-to-perform technique; however, the current literature is inconclusive with respect to its analgesic superiority compared with cFNB.[17,18]

This 2-center, blinded, randomized controlled trial was designed to compare the effects of cFNB, sFNB, and LIA on acute postoperative analgesia, opioid analgesic consumption (in the first 2 days postoperatively), and rehabilitation outcomes (at 6 weeks and 4.5 months postoperatively) after primary TKA in adults. Our hypothesis was that LIA is the superior analgesic method for numeric rating scale for pain (NRS) during physiotherapy on POD 2 at 9:00 AM (primary outcome).

METHODS
This study was conducted at 2 tertiary care academic health sciences centers, Sunnybrook Health Sciences Centre (SHSC) and St. Joseph's Healthcare (SJH), Hamilton. The Research Ethics Boards of SHSC and SJH approved the study in July 2012 and October 2012, respectively. Regulatory approval was sought and received from Health Canada for the off-label use of ketorolac tromethamine (subcutaneous injection). The trial was registered with www.clinicaltrials.gov (June 2012, NCT01616836). Adults (18 to 85 years) with American Society of Anesthesiologists (ASA) status I to III, scheduled to undergo primary tricompartmental TKA, were eligible for enrolment. Exclusion criteria were allergy/intolerance/contraindication to any study medication, inability to walk independently before TKA, inability to comprehend French or English, use of antipsychotics, ASA IV or V, body mass index >40 kg/m², or opioid tolerance (defined as >30 mg oral morphine equivalent per day). Trained research personnel recruited patients in the preoperative anesthesia clinics of participating centers.

The coordinating institution was SHSC. The Applied Health Research Centre (AHRC) of the Li Ka Shing Knowledge Institute of St. Michael's Hospital (Toronto, Canada) provided statistical and organizational support. Participants were randomly assigned (1:1:1), stratified by center, to 1 of 3 groups (see Figure 1). Randomly permuted blocks of sizes of 6 and 9 were used within each stratum. An independent, blinded statistician at the AHRC created the computer-generated randomization sequence. The randomization list was kept in the independent research pharmacy of each institution to maintain blinding and allocation concealment. Upon recruitment to the study, the pharmacy prepared study kits of identical appearance containing the appropriate solutions (initial catheter bolus—ropivacaine 0.5% or 0.9% saline placebo, LIA solution or 0.9% saline placebo 150 mL; postoperative infusion solution—ropivacaine 0.2% or 0.9% saline placebo) for each of the 3 groups. Investigators, research assistants/nurses, participants, outcome assessors, and data analysts were blinded to group allocation. Data were collected by blinded research assistants electronically and stored on secure servers at the AHRC.

Assigned Interventions
See Figure 1 for graphical representation of blinded study interventions.
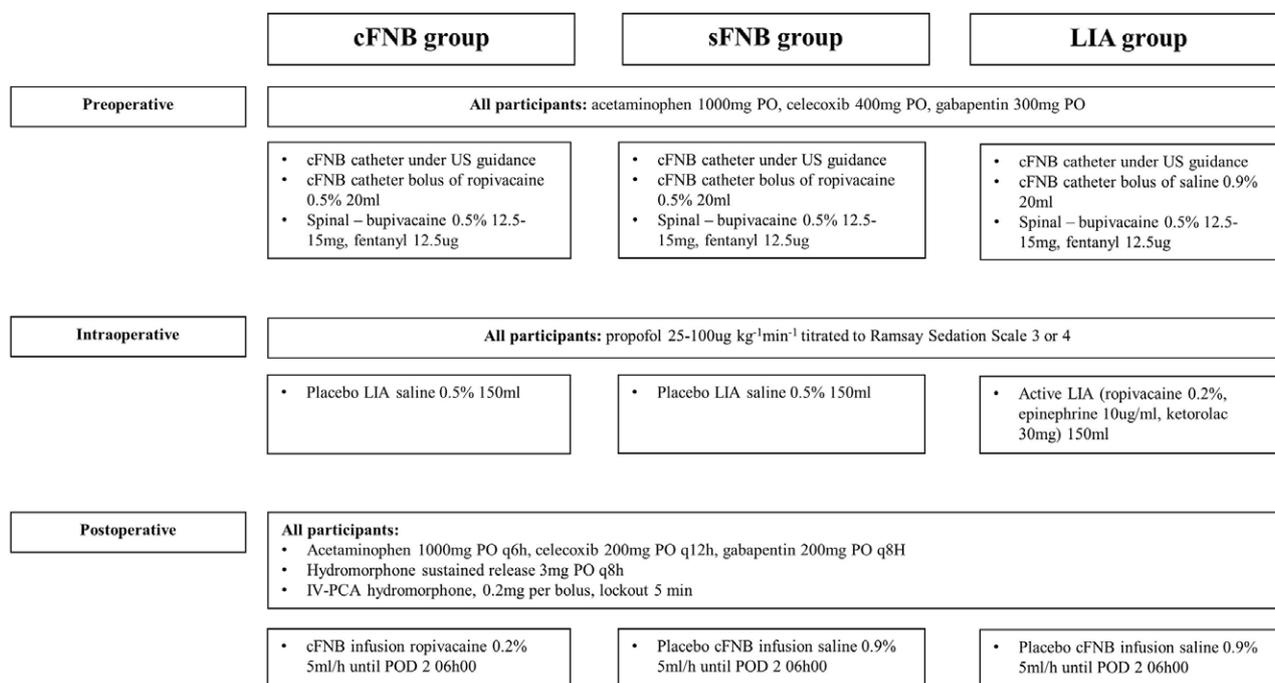
Figure 1. Flow diagram of randomized interventions. cFNB indicates continuous femoral nerve block; IV-PCA, intravenous patient controlled analgesia; LIA, local infiltration analgesia; POD, postoperative day; and sFNB, single-injection femoral nerve block.

Continuous femoral nerve block group. Preoperative cFNB sited and bolused with ropivacaine 0.5% 20 mL. Intraoperative placebo LIA with saline 0.9% 150 mL. Postoperative cFNB infusion with ropivacaine 0.2% 5 mL per hour until POD 2 at 6:00 AM.

Single-injection femoral nerve block group. Preoperative cFNB sited and bolused with ropivacaine 0.5% 20 mL. Intraoperative placebo LIA with saline 0.9% 150 mL. Postoperative placebo cFNB infusion with saline 0.9% 5 mL per hour until POD 2 at 6:00 AM.

LIA group. To maintain blinding, anesthesiologists not otherwise involved in the study sited a preoperative fascia iliaca catheter that was bolused with saline 0.9% 20 mL. Intraoperative active LIA as described by Kerr and Kohan[19] (ropivacaine 0.2% with epinephrine 10 µg/mL, 150 mL, ketorolac 30 mg). Postoperative placebo cFNB infusion with saline 0.9% 5 mL per hour until POD 2 at 6:00 AM.

Single-orifice 19G stimulating peripheral nerve block catheters (Arrow Stimuplex, Teleflex Medical, Markham, Canada) were placed in a sterile fashion with the use of ultrasound guidance (Sonosite M-Turbo, Bothell Washington) by experienced anesthesiologists or by supervised trainees after participants were premedicated with intravenous midazolam (2 mg). The femoral nerve was identified in the short-axis plane immediately below the inguinal ligament. After skin infiltration (lidocaine 2%, 3 mL), a 17G Tuohy needle (Arrow Stimuplex peripheral nerve block kit, Teleflex, Morrisville, NC) was placed such that the tip was inferior to the nerve. The peripheral nerve block catheter was advanced via Seldinger technique approximately 1 to 2 cm beyond the tip of the needle such that the end was visible immediately inferior to the femoral nerve while maintaining appropriate quadriceps stimulation at 0.5 mA. The individuals siting the peripheral nerve block catheters were otherwise not involved in outcome assessment to maintain blinding.

Study participants in all 3 groups received standard preoperative analgesic medication including oral acetaminophen 1000 mg (650 mg if <50 kg), celecoxib 400 mg, and gabapentin 300 mg. Surgical anesthesia was achieved with intrathecal bupivacaine 0.5% (12.5–15 mg) and fentanyl (12.5 µg). Intraoperatively, patients were sedated with propofol 25–100 µg/kg/min titrated to a Ramsay Sedation Score of 3 or 4.

Postoperatively, participants received a standard multimodal analgesic regimen consisting of IV-PCA for 48 hours (hydromorphone bolus 0.2 mg, lockout 5 minutes, 1 hour maximum 2.4 mg) followed by oral hydromorphone 1–4 mg every 2 hours as necessary after discontinuation of IV-PCA, acetaminophen 1000 mg (650 mg if <50 kg) every 6 hours for 20 doses, celecoxib 200 mg every 12 hours for 10 doses, sustained release of hydromorphone 3 mg every 8 hours for 12 doses, and gabapentin 200 mg every 8 hours for 12 doses. Participants experiencing severe pain (Numeric Rating Scale [NRS] > 7) during the first 48 hours despite use of rescue analgesia with IV-PCA received a 10-mL bolus of ropivacaine 0.5% through the peripheral nerve block catheter and an increase of IV-PCA bolus dose in 0.1-mg increments to achieve an NRS for pain of < 4.

All study participants received the institutional standard of care mobilization and rehabilitation protocol with assisted weight bearing on POD 1, followed by ambulation on POD 2. Participants were discharged home between POD 3 and POD 5 after achieving institutional discharge criteria and received a prescription for Tylenol #3, oxycocet (1–2 tablets every 4–6 hours as needed), or hydromorphone (1–3 mg every 4–6 hours as needed).

Outcomes. The primary outcome was NRS for pain during physiotherapy at 9:00 AM on POD 2. NRS at 9:00 AM was selected a priori after discussion with physiotherapists at SHSC who begin intensive mobilization of patients on the morning of POD 2 and note that the primary impediment for initiating the rehabilitation program, and subsequent delay in discharge, is from inadequate analgesia. Secondary outcomes were as follows: NRS for pain at rest POD 1 at 9:00 AM; NRS for pain during physiotherapy POD 1; worst NRS POD 1; NRS at 4.5 months; incidence of chronic neuropathic pain at 4.5 months evaluated by the S-LANSS; 48 hours of opioid consumption; requirement for additional peripheral nerve block local anesthetic boluses; active knee range of motion (ROM) 4.5 months postoperatively; timed up and go (TUG) on POD 2; 6-minute walk test (6-MWT), Western Ontario and McMaster University Osteoarthritis Index (WOMAC), and Lower Extremity Functional Scale (LEFS) at 6 weeks and 4.5 months postoperatively; or complications of sFNB, cFNB, or LIA (hematoma, infection, persistent neurologic deficit, and motor block impairing rehabilitation). To facilitate data analysis, equianalgesic conversion ratios were employed according to the general monograph for opioids in the Canadian Pharmacists' Association Compendium of Pharmaceuticals and Specialties (hydromorphone:morphine = 1:5; oxycodone:morphine = 2:3; codeine:morphine = 6.6:1; IV:oral = 1:2).

Sample size calculation. The sample size required to detect a clinically significant difference of 2 in the mean NRS,[20] assuming a standard deviation of 3,[21] given a 2-sided $\alpha = 0.05$, and $\beta = 0.2$, was 40 patients per group (total sample size = 120). Simulations performed using a variety of plausible values for mean NRS score in each group confirmed that the power for the primary analysis (ANCOVA for any difference) exceeded 80%.

Statistical Analysis

Statistical analysis was performed using R (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org). Baseline characteristics are presented as mean (standard deviation) for continuous variables and count for categorical variables (Table 1). The primary outcome (NRS 9:00 AM POD 2) is presented as mean (95% CI) and was compared between groups using ANCOVA, adjusting for baseline NRS with Tukey multiple range test for pairwise comparisons if the overall ANCOVA was significant. The treatment effect was estimated as the adjusted difference of means, and 95% CIs were calculated. Results were considered statistically significant if adjusted P values were <.05.

Secondary outcomes were considered to be exploratory. Continuous outcomes were compared with ANOVA with Tukey multiple range test for pairwise comparisons if the overall ANOVA was significant. Binary outcomes were compared using Fisher exact test. The Holm–Bonferroni

Table 1. Demographic/Preoperative Baseline Data

	cFNB[a] (n = 40)	sFNB[b] (n = 39)	LIA[c] (n = 41)
Age (y)	64.0 (7.4)	65.2 (9.2)	65.9 (8.0)
Sex (M:F)	18 {44}:23 {56}	20 {51}:19 {49}	20 {49}:21 {51}
BMI[d] (kg/m²)	30.1 (3.5)	31.4 (4.7)	29.3 (4.8)
ASA[e] I/II/III	4/19/18	3/21/17	1/18/20
Preoperative NRS[f]	6.0 (2.2)	5.9 (2.8)	6.0 (2.7)
Preoperative 6-MWT[g] (m)	385 (116)	365 (137)	372 (116)
Preoperative TUG[h] (s)	10.8 (3.1)	11.8 (3.9)	13.2 (6.0)
Preoperative knee flexion (°)	115 (19)	110 (15)	112 (17)
Preoperative WOMAC[i]	41 (13.9)	43.0 (18.9)	46 (20.4)

Data presented as mean (SD), count {%}.
[a]Continuous femoral nerve block.
[b]Single-injection femoral nerve block.
[c]Local infiltration analgesia.
[d]Body mass index.
[e]American Society of Anesthesiologists' classification.
[f]Numeric rating scale for pain.
[g]Timed up and go.
[h]Six-minute walk test.
[i]Western Ontario and McMaster University Arthritis Index.

correction was applied to adjust P values for multiple testing with respect to the secondary outcomes to which inferential testing was applied.

The funding agencies (Canadian Anesthesia Research Foundation and Physicians' Services Incorporated Foundation, Toronto, Ontario, Canada) had no role in the design, conduct, or analysis of the study. This article adheres to the applicable EQUATOR guidelines (CONSORT).

RESULTS

One hundred sixty-eight of 1031 patients approached provided written and informed consent to participate in the study between January 2012 and January 2015. Seven hundred sixty-two patients indicated that they were not interested in participating in any research, and 269 declined participation because of the study interventions. Forty-eight of the 168 patients providing consent were not randomly assigned because of exclusion criteria. One hundred twenty patients without any exclusion criteria were randomized. Each patient randomized was followed in hospital, until they were discharged home. The trial was stopped once the planned sample size of 120 participants was randomly assigned. Forty patients were randomly assigned to the cFNB group, 39 patients to the sFNB group, and 41 patients to the LIA group. All patients allocated to the cFNB group received the intended treatment. Among the 39 participants randomly assigned to the sFNB group, 3 received standard-of-care cFNB analgesia because of study kit unavailability and 1 participant did not receive anything because of technical difficulties (unable to place perineural catheter). Among the 41 participants randomly assigned to the LIA group, 3 received standard-of-care cFNB because of study kit unavailability. All randomly assigned participants were analyzed according to an intention-to-treat principle. The CONSORT flow chart specifically details the number of participants who received the allocated intervention and reasons for protocol deviations if any (Figure 2).

Patient characteristics were similar between groups with respect to age, sex, body mass index, and ASA physical status (PS) (Table 1).

Primary Outcome

The ANCOVA for NRS on POD 2 at 9:00 AM indicated that the differences among the 3 analgesic modalities were statistically significant. Pairwise comparisons, however, were not statistically significant. NRS was 4.6 (95% CI, 3.3–6.0) for the cFNB group, 4.6 (95% CI, 3.3–6.0) for the sFNB group, and 3.4 (95% CI, 2.2–4.8) for the LIA group. The mean difference in NRS among groups is as follows: cFNB–LIA (1.2, 95% CI, −0.1 to 2.5; P = .073); sFNB–LIA (1.2, 95% CI, −2.5 to 0.2; P = .097); cFNB–sFNB (0.0, 95% CI, −1.3 to 1.4; P = .996; Figure 2)

Secondary Outcomes

There was no significant difference in 48 hours of opioid consumption associated with cFNB compared with sFNB (P = .124) (Figure 3). Intravenous morphine equivalent consumption (mg) for the cFNB group was 76.1 (±40.5); for the sFNB group, 93.7 (±45.2); and for the LIA group, 77.2 (±40.8). Opioid consumption on POD 1 for the cFNB group was 40.6 (±15.8); for the sFNB group, 49.5 (±24.5); and for the LIA group, 39.6 (±20.4). Opioid consumption on POD 2 for the cFNB group was 35.5 (±28.6); for the sFNB group, 44.2 (±29.1); and for the LIA group, 37.5 (±26.6).

The NRS during physiotherapy on POD 1 for each group was as follows: cFNB, 4.8 (95% CI, 3.9–5.6); sFNB, 6.4 (95% CI, 5.6–7.3); and LIA, 4.4 (95% CI, 3.6–5.2). LIA was superior to sFNB. Pairwise comparisons yielded the following mean differences in NRS: cFNB–LIA (0.35, 95% CI, −1.0 to 1.7; P = .999); cFNB–sFNB (−1.7, 95% CI, −3.1 to −0.3; P = .252); and LIA–sFNB (−2, 95% CI, −3.4 to −0.6; P = .040).

The following differences were observed for NRS at rest on POD 1: cFNB, 2.7 (95% CI, 2.0–3.4); sFNB, 3.9 (95% CI, 3.2–4.6); and LIA, 2.5 (95% CI, 1.8–3.2). Pairwise mean differences were as follows: cFNB–LIA (0.3, 95% CI, −1.0 to 1.4; P = .856); cFNB–sFNB (−1.2, 95% CI, −2.7 to 0.0; P = .944); and LIA–sFNB (−2, 95% CI, −2.6 to −0.2; P = .255).

The worst NRS experienced on POD 1 for each group was cFNB, 4.1 (95% CI, 2.8–5.4); sFNB, 6.3 (95% CI, 5.0–7.5); and LIA, 4.7 (95% CI, 3.7–5.9). cFNB was superior to sFNB. Pairwise comparisons yielded the following mean differences in NRS: cFNB–LIA (−0.6, 95% CI, −1.8 to 0.7; P = .999);
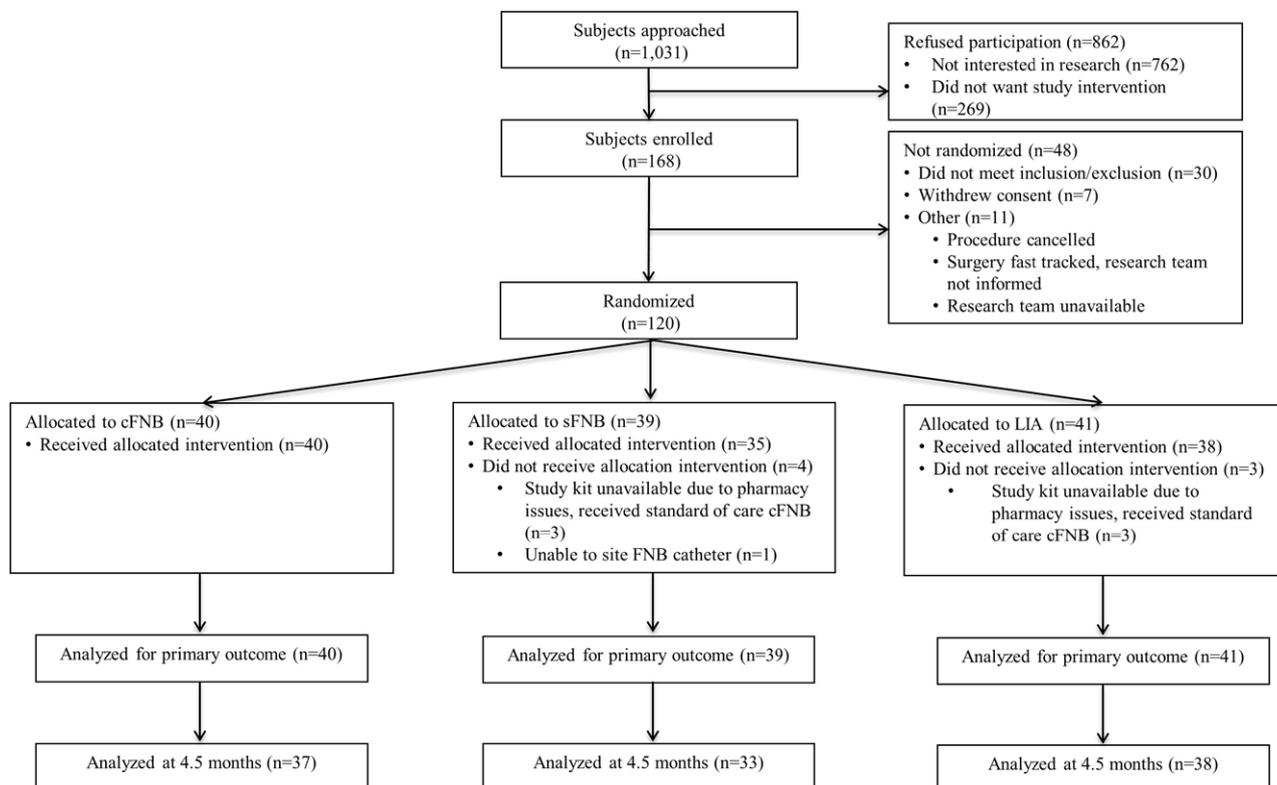
Figure 2. CONSORT flow diagram of screened, enrolled, randomized, and analyzed participants. cFNB indicates continuous femoral nerve block; LIA, local infiltration analgesia; and sFNB, single-injection femoral nerve block.
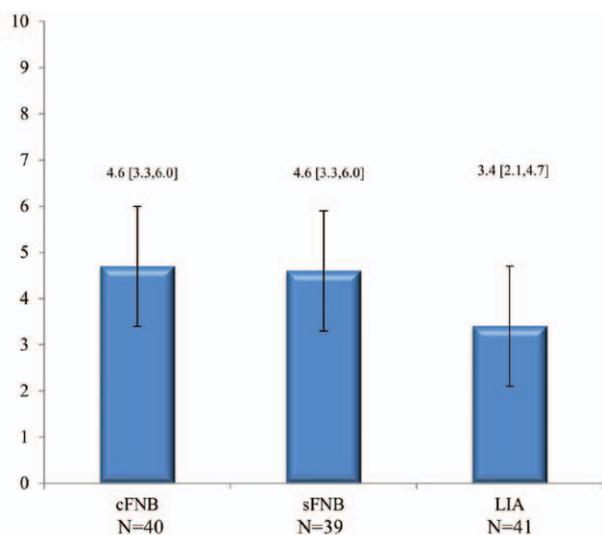
Figure 3. Numeric rating scale for pain with physiotherapy, postoperative day 2 9:00 AM. Presented as mean (adjusted 95% CI). ANCOVA indicates analysis of covariance; cFNB, continuous femoral nerve block; LIA, local infiltration analgesia; and sFNB, single-injection femoral nerve block.

cFNB–sFNB (-2.7, 95% CI, -3.5 to -0.9; $P < .001$); LIA–sFNB (-1.6, 95% CI, -2.9 to -0.3; $P = .228$).

There were no statistically significant differences observed between treatment groups for rebolusing the peripheral nerve block catheter. There were no statistically significant differences observed between groups with long-term functional outcomes. Participants in all groups demonstrated improvements from baseline to 4.5 months in ROM, the 6-MWT, WOMAC, and LEFS (Table 2). Inferential statistical testing was not performed between baseline and 4.5-month data within groups, as it was not specified a priori. The prevalence of motor block observed by blinded physiotherapists was minimal on POD 1 (cFNB, 3 of 40; sFNB, 2 of 39; and LIA 2 of 41) and not observed at all on POD 2. There were no complications associated with study procedures experienced by any participants (falls, infection, and persistent neurologic deficit).

DISCUSSION

This study compared the effects of 3 analgesic modalities, cFNB versus sFNB versus LIA, in patients undergoing tricompartmental TKA with concomitant systemic multimodal analgesia. Pairwise comparisons were unable to conclusively identify differences among the groups. We did not observe any significant differences between groups for the primary outcome of NRS during movement on POD 2 at 9:00 AM (Figure 3). The data did demonstrate that cFNB and LIA were superior to sFNB for worst pain experienced and pain during physiotherapy on POD 1, respectively (Table 3). There were no significant differences in 48 hours of opioid

Table 2. Functional Outcomes

Immediate Postoperative	cFNB[a] (n = 40)	sFNB[b] (n = 39)	LIA[c] (n = 41)	Adjusted P*
Preoperative	10.8 (3.1)	11.8 (3.9)	13.2 (6.0)	—
POD 2 TUG[d] (s)	76.6 (59.4)	61.1 (35.4)	73.7 (52.6)	.999
Late Outcomes	cFNB (n = 37)	sFNB (n = 33)	LIA (n = 38)	Adjusted P*
Baseline ROM[e]	115 (19)	110 (15)	112 (17)	—
Active ROM 4.5 months (°)	120 (13)	116 (12)	119 (9)	.999
6-MWT[f] (m)				
Baseline	385 (116)	365 (137)	372 (116)	—
6 wk	383 (93)	350 (110)	356 (99)	.999
4.5 mo	451 (75)	406 (200)	397 (12)	.999
WOMAC[g]				
Baseline	41.0 (13.9)	43.0 (18.9)	46.0 (20.4)	—
6 wk	24.1 (12.3)	25.9 (14.8)	30.0 (11.5)	.999
4.5 mo	19.1 (17.3)	15 (14.7)	16.3 (16.6)	.999
LEFS[h]				
Baseline	25.6 (11.8)	26.5 (14.5)	25.3 (16.7)	—
6 wk	43.0 (11.2)	45.4 (12.7)	42.2 (14.7)	.999
4.5 mo	55.9 (14.6)	59.0 (15.7)	57.4 (16.3)	.999

Data presented as mean (SD).
[a]Continuous femoral nerve block.
[b]Single-injection femoral nerve block.
[c]Local infiltration analgesia.
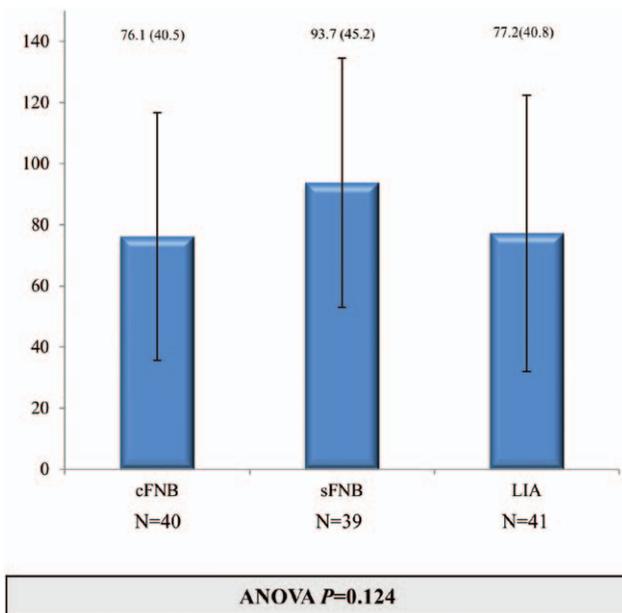[d]Timed up and go.
[e]Range of motion.
[f]Six-minute walk test.
[g]Western Ontario and McMaster University Arthritis Index.
[h]Lower extremity functional scale.
*P values adjusted with Holm–Bonferroni correction.

Figure 4. Forty-eight hours intravenous morphine equivalent consumption (in milligram). Presented as mean (SD). ANOVA indicates analysis of variance, cFNB, continuous femoral nerve block; LIA, local infiltration analgesia; and sFNB, single-injection femoral nerve block.

consumption, incidence of chronic pain, or functional outcomes between the 3 groups.

Surprisingly, there were no differences observed in the primary outcome between cFNB and sFNB. Furthermore, although there was a trend toward reduced 48 hours opioid consumption with cFNB compared with sFNB, it was not statistically significant. This is in contrast to previous studies that have demonstrated the superiority of cFNB over sFNB

for pain and opioid consumption in the first 24 hours postoperatively.[22–25] The current findings may be a function of selecting a primary outcome that was measured on POD 2

Within-group changes from preoperative baseline for pain and functional outcomes were not specified a priori for inferential statistical testing, and thus, not specifically reported in the results section; however, there are several patterns that emerge that warrant discussion (Tables 2 and 3). First, compared with preoperative baseline, all 3 groups demonstrated a reduction in NRS at 4.5 months of approximately 4 points. This exceeds the minimal clinically important difference (MCID) of 20 mm,[20] as well as reducing the mean NRS from moderate-level to low-level pain. Second, only the cFNB group demonstrated an improvement over baseline in the 6-MWT (66 m) exceeding the MCID of 61.3 m.[26] Third, all 3 analgesic modalities exceeded the MCID for the WOMAC of 9.1 points over baseline,[27] and the cFNB group did not score below that, which is commonly considered a successful WOMAC score after TKA of 16.5.[28] Fourth, all 3 analgesic modalities greatly exceeded the MCID over baseline for the LEFS of 9 points.[26] Although it is possible that these improvements are because of successful surgery in and of itself, superior acute postoperative analgesia may allow more aggressive physiotherapy in the early postoperative period and may positively influence long-term functional outcomes. Future studies with larger sample sizes with adequate power will be necessary to test such hypotheses.

Several systematic reviews assessing LIA have been published recently, and although LIA appears to be superior to placebo for analgesia after TKA, results compared with FNB are inconclusive. Each of these reviews noted heterogeneous comparator groups with and without opioid-sparing adjuncts (rather than consistently in both groups

Table 3. Secondary Pain Outcomes

Immediate Postoperative	cFNB[a] (n = 40)	sFNB[b] (n = 39)	LIA[c] (n = 41)	Adjusted P*
NRS[d] POD[e] 1 (PT[f]) 9:00 AM	4.8 (3.9 to 5.6)	6.4 (5.6 to 7.3)	4.4 (3.6 to 5.2)	.002
Pairwise comparisons: mean difference NRS		cFNB–LIA: 0.35 (−1.0 to 1.7)		.999
		cFNB–sFNB: −1.7 (−3.1 to −0.3)		.252
		LIA–sFNB: −2 (−3.4 to −0.6)		.040
NRS POD 1 (resting) at 9:00 AM	2.7 (2.0 to 3.4)	3.9 (3.2 to 4.6)	2.5 (1.8 to 3.2)	.013
Pairwise comparisons: mean difference NRS		cFNB–LIA: 0.3 (−1.0 to 1.4)		.856
		cFNB–sFNB: −1.2 (−2.7 to 0)		.944
		LIA–sFNB: −2 (−2.6 to −0.2)		.255
Worst NRS POD 1	4.1 (2.8 to 5.4)	6.3 (5.0 to 7.5)	4.7 (3.7 to 5.9)	<.001
Pairwise comparisons: mean difference NRS		cFNB–LIA: −0.6 (−1.8 to 0.7)		.999
		cFNB–sFNB: −2.7 (−3.5 to −0.9)		<.001
		LIA–sFNB: −1.6 (−2.9 to −0.3)		.228
Bolus of catheter (n)	3 {8}	5 {13}	2 {5}	.380
4.5 mo	cFNB (N = 37)	sFNB (N = 33)	LIA (N = 38)	Adjusted P*
NRS baseline	6.0 (2.2)	5.9 (2.8)	6.0 (2.7)	—
NRS at 4.5 mo	2.4 (2.5)	2.1 (2)	1.9 (2.2)	.654
S-LANSS[g] 4.5 mo	6.0 (6.6)	6.3 (7.1)	4.2 (5.9)	.322

Data presented as mean (SD) or (95% CI), count {%}.
[a]Continuous femoral nerve block.
[b]Single-injection femoral nerve block.
[c]Local infiltration analgesia.
[d]Numeric rating scale for pain.
[e]Postoperative day.
[f]Physiotherapy.
[g]Self reported Leeds Assessment of Neuropathic Symptoms and Signs pain scale.
*P values adjusted with Holm–Bonferroni correction.

studied) and methodological issues potentially introducing bias. Two systematic reviews comparing LIA with placebo indicate that LIA has superior analgesia and reduced opioid consumption, although the included studies were at high risk of bias because of poor blinding.[10,29] Three meta-analyses specifically assessed LIA compared with FNB. Among them, 2 included studies comparing LIA with cFNB or sFNB,[9,30] whereas 1 compared LIA with cFNB.[31] Yun et al[30] determined that there were no statistically significant differences in pain or opioid consumption comparing LIA with cFNB or sFNB, but that the evidence was of low to moderate quality. Using similar methodology, Fan et al[9] concluded that LIA had better early analgesia (NRS, −0.49 for LIA). Finally, Mei et al[31] concluded that cFNB had superior dynamic analgesia compared with LIA on POD 1 with other outcomes being comparable (NRS, −0.62 for cFNB). Although statistically significant, given that the MCID for NRS is 20 mm, the clinical significance of these differences is muted.[20]

The strength of this trial stems from its methodological rigor and standardization of a multimodal analgesic regimen across comparators that address the identified deficiencies in the existing literature. This includes blinding of participants, surgeons, outcome assessors; the standardized and comprehensive multimodal opioid-sparing analgesic regimen; and the standardized postoperative care pathway for all participants that serve to increase internal validity and minimize bias in the observed data.

Several factors related to our study design may have limited the impact of our results. First, LIA provides analgesia to the anterior and posterior compartments, whereas cFNB and sFNB provide analgesia only to the anterior compartment. It has been demonstrated previously that single-injection sciatic nerve block (sSNB) provides (combined with cFNB) approximately 8 to 12 hours of improved analgesia from posterior compartment coverage and cSNB provides even longer duration analgesia when compared with cFNB alone.[32,33] Patients with chronic pain on high-dose opioids preoperatively may benefit with combined cFNB and cSNB. This may have contributed to a lack in any observed differences. Second, the phenomenon of "rebound pain" after a nerve block wears off has been described leading to a sudden, but highly variable, increase in pain scores.[34] Third, the study was powered to identify any difference between the 3 treatment arms and may be underpowered to detect pairwise differences. Fourth, a rigorous multimodal analgesic regimen (acetaminophen, nonsteroidal anti-inflammatory drugs, and gabapentin) may have further obscured differences between groups. Fifth, 3 of 39 participants in the sFNB group and 3 of 41 in the LIA group had protocol deviations and received cFNB potentially further obscuring any differences. Finally, our primary outcome was selected to be clinically relevant and address an analgesic issue identified by our physiotherapists as delaying aggressive rehabilitation, utilizing a time point that occurs after the expected duration of each of the interventions may also have obscured observable differences.

Safety concerns regarding each analgesic technique have been raised, although they are rarely described in the literature. These include nerve palsy associated with peripheral nerve block and infection whether associated with high-volume LIA techniques or continuous perineural catheters of which there are case reports.[35–37] Furthermore, concern has been raised regarding the risk of falls associated with FNB secondary to quadriceps weakness. Recently, the ACB has been introduced into clinical practice to preserve quadriceps strength. ACB clearly preserves quadriceps strength compared with FNB,[38] but trials assessing ACB compared with cFNB after TKA have yet to fully elucidate its analgesic efficacy.[39–42] The potential for falls from quadriceps

weakness associated with FNB can be mitigated with better training and appropriate preventive measures (eg, splints). The experience at our institution utilizing cFNB, in conjunction with a comprehensive fall-prevention program, is a fall rate of <1% associated with cFNB (unpublished safety data). There were no complications associated with any of the interventions observed in this trial.

This trial demonstrated that, although no significant differences in analgesia between cFNB, LIA, and sFNB groups existed on POD 2, cFNB and LIA may provide mildly superior analgesia compared with sFNB on POD 1 after primary TKA. The optimal analgesic method likely depends on several factors. Certainly inadequate analgesia can impair postoperative physiotherapy and rehabilitation, but excessive motor blockade with prolonged peripheral nerve block, though providing excellent analgesia, may do the same. The majority of patients without chronic pain or who are opioid naive will likely have sufficient analgesia with either modality depending on institutional capabilities or physical infrastructure such as a separate block room to maintain workflow efficiency. ■

REFERENCES
1. *National Hospital Discharge Survey: 2010*. Centers for Disease Prevention and Control; 2014.
2. *Canadian Joint Replacement Registry Annual Report*. Canada: Canadian Institute for Health Information; 2015.
3. Puolakka PA, Rorarius MG, Roviola M, Puolakka TJ, Nordhausen K, Lindgren L. Persistent pain following knee arthroplasty. *Eur J Anaesthesiol*. 2010;27:455–460.
4. Barrington JW, Halaszynski TM, Sinatra RS, Expert Working Group On Anesthesia And Orthopaedics Critical Issues In Hip And Knee Replacement Arthroplasty FT. Perioperative pain management in hip and knee replacement surgery. *Am J Orthop (Belle Mead NJ)*. 2014;43:S1–S16.
5. Chan EY, Fransen M, Parker DA, Assam PN, Chua N. Femoral nerve blocks for acute postoperative pain after knee replacement surgery. *Cochrane Database Syst Rev*. 2014;5:CD009941.
6. Paul JE, Arya A, Hurlburt L, et al. Femoral nerve block improves analgesia outcomes after total knee arthroplasty: a meta-analysis of randomized controlled trials. *Anesthesiology*. 2010;113:1144–1162.
7. Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology*. 1999;91:8–15.
8. Al-Zahrani T, Doais KS, Aljassir F, Alshaygy I, Albishi W, Terkawi AS. Randomized clinical trial of continuous femoral nerve block combined with sciatic nerve block versus epidural analgesia for unilateral total knee arthroplasty. *J Arthroplasty*. 2015;30:149–154.
9. Fan L, Zhu C, Zan P, et al. The comparison of local infiltration analgesia with peripheral nerve block following total knee arthroplasty (TKA): a systematic review with meta-analysis. *J Arthroplasty*. 2015;30:1664–1671.
10. Xu CP, Li X, Wang ZZ, Song JQ, Yu B. Efficacy and safety of single-dose local infiltration of analgesia in total knee arthroplasty: a meta-analysis of randomized controlled trials. *Knee*. 2014;21:636–646.
11. Andersen HL, Gyrn J, Møller L, Christensen B, Zaric D. Continuous saphenous nerve block as supplement to single-dose local infiltration analgesia for postoperative pain management after total knee arthroplasty. *Reg Anesth Pain Med*. 2013;38:106–111.

12. Perlas A, Kirkham KR, Billing R, et al. The impact of analgesic modality on early ambulation following total knee arthroplasty. *Reg Anesth Pain Med*. 2013;38:334–339.
13. Bianconi M, Ferraro L, Traina GC, et al. Pharmacokinetics and efficacy of ropivacaine continuous wound instillation after joint replacement surgery. *Br J Anaesth*. 2003;91:830–835.
14. Ilfeld BM, Duke KB, Donohue MC. The association between lower extremity continuous peripheral nerve blocks and patient falls after knee and hip arthroplasty. *Anesth Analg*. 2010;111:1552–1554.
15. Wasserstein D, Farlinger C, Brull R, Mahomed N, Gandhi R. Advanced age, obesity and continuous femoral nerve blockade are independent risk factors for inpatient falls after primary total knee arthroplasty. *J Arthroplasty*. 2013;28:1121–1124.
16. Memtsoudis SG, Danninger T, Rasul R, et al. Inpatient falls after total knee arthroplasty: the role of anesthesia type and peripheral nerve blocks. *Anesthesiology*. 2014;120:551–563.
17. Fowler SJ, Christelis N. High volume local infiltration analgesia compared to peripheral nerve block for hip and knee arthroplasty-what is the evidence? *Anaesth Intensive Care*. 2013;41:458–462.
18. Andersen LØ, Kehlet H. Analgesic efficacy of local infiltration analgesia in hip and knee arthroplasty: a systematic review. *Br J Anaesth*. 2014;113:360–374.
19. Kerr DR, Kohan L. Local infiltration analgesia: a technique for the control of acute postoperative pain following knee and hip surgery: a case study of 325 patients. *Acta Orthop*. 2008;79:174–183.
20. Farrar JT, Polomano RC, Berlin JA, Strom BL. A comparison of change in the 0-10 numeric rating scale to a pain relief scale and global medication performance scale in a short-term clinical trial of breakthrough pain intensity. *Anesthesiology*. 2010;112:1464–1472.
21. Carli F, Clemente A, Asenjo JF, et al. Analgesia and functional outcome after total knee arthroplasty: periarticular infiltration vs continuous femoral nerve block. *Br J Anaesth*. 2010;105:185–195.
22. Chan EY, Fransen M, Sathappan S, Chua NH, Chan YH, Chua N. Comparing the analgesia effects of single-injection and continuous femoral nerve blocks with patient controlled analgesia after total knee arthroplasty. *J Arthroplasty*. 2013;28:608–613.
23. Ilfeld BM, Mariano ER, Girard PJ, et al. 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;150:477–484.
24. Ilfeld BM, Le LT, Meyer RS, et al. Ambulatory continuous femoral nerve blocks decrease time to discharge readiness after tricompartment total knee arthroplasty: a randomized, triple-masked, placebo-controlled study. *Anesthesiology*. 2008;108:703–713.
25. Salinas FV, Liu SS, Mulroy MF. The effect of single-injection femoral nerve block versus continuous femoral nerve block after total knee arthroplasty on hospital length of stay and long-term functional recovery within an established clinical pathway. *Anesth Analg*. 2006;102:1234–1239.
26. Binkley JM, Stratford PW, Lott SA, Riddle DL. The Lower Extremity Functional Scale (LEFS): scale development, measurement properties, and clinical application. North American Orthopaedic Rehabilitation Research Network. *Phys Ther*. 1999;79:371–383.
27. Pua YH, Cowan SM, Wrigley TV, Bennell KL. The Lower Extremity Functional Scale could be an alternative to the Western Ontario and McMaster Universities Osteoarthritis Index physical function scale. *J Clin Epidemiol*. 2009;62:1103–1111.
28. Giesinger JM, Hamilton DF, Jost B, Behrend H, Giesinger K. WOMAC, EQ-5D and Knee Society Score thresholds for treatment success after total knee arthroplasty. *J Arthroplasty*. 2015;30:2154–2158.
29. Sun XL, Zhao ZH, Ma JX, et al. Continuous local infiltration analgesia for pain control after total knee arthroplasty: a meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2015;94:e2005.
30. Yun XD, Yin XL, Jiang J, et al. Local infiltration analgesia versus femoral nerve block in total knee arthroplasty: a meta-analysis. *Orthop Traumatol Surg Res*. 2015;101:565–569.
31. Mei S, Jin S, Chen Z, Ding X, Zhao X, Li Q. Analgesia for total knee arthroplasty: a meta-analysis comparing local infiltration and femoral nerve block. *Clinics (Sao Paulo)*. 2015;70:648–653.
32. Safa B, Gollish J, Haslam L, McCartney CJ. Comparing the effects of single shot sciatic nerve block versus posterior capsule local anesthetic infiltration on analgesia and functional outcome after total knee arthroplasty: a prospective, randomized, double-blinded, controlled trial. *J Arthroplasty*. 2014;29:1149–1153.
33. Wegener JT, van Ooij B, van Dijk CN, Hollmann MW, Preckel B, Stevens MF. Value of single-injection or continuous sciatic nerve block in addition to a continuous femoral nerve block in patients undergoing total knee arthroplasty: a prospective, randomized, controlled trial. *Reg Anesth Pain Med*. 2011;36:481–488.
34. Williams BA, Bottegal MT, Kentor ML, Irrgang JJ, Williams JP. Rebound pain scores as a function of femoral nerve block duration after anterior cruciate ligament reconstruction: retrospective analysis of a prospective, randomized clinical trial. *Reg Anesth Pain Med*. 2007;32:186–192.
35. Aveline C, Le Hetet H, Le Roux A, et al. Perineural ultrasound-guided catheter bacterial colonization: a prospective evaluation in 747 cases. *Reg Anesth Pain Med*. 2011;36:579–584.
36. Brull R, McCartney CJ, Chan VW, El-Beheiry H. Neurological complications after regional anesthesia: contemporary estimates of risk. *Anesth Analg*. 2007;104:965–974.
37. Reeves M, Skinner MW. Continuous intra-articular infusion of ropivacaine after unilateral total knee arthroplasty. *Anaesth Intensive Care*. 2009;37:918–922.
38. Grevstad U, Mathiesen O, Valentiner LS, Jaeger P, Hilsted KL, Dahl JB. Effect of adductor canal block versus femoral nerve block on quadriceps strength, mobilization, and pain after total knee arthroplasty: a randomized, blinded study. *Reg Anesth Pain Med*. 2015;40:3–10.
39. Kim DH, Lin Y, Goytizolo EA, et al. Adductor canal block versus femoral nerve block for total knee arthroplasty: a prospective, randomized, controlled trial. *Anesthesiology*. 2014;120:540–550.
40. Memtsoudis SG, Yoo D, Stundner O, et al. Subsartorial adductor canal vs femoral nerve block for analgesia after total knee replacement. *Int Orthop*. 2015;39:673–680.
41. Deloach JK, Boezaart AP. Is an adductor canal block simply an indirect femoral nerve block? *Anesthesiology*. 2014;121:1349–1350.
42. Ziemann-Gimmel P. Is less than 50% more narcotics really non-inferior? *Anesthesiology*. 2014;121:1350–1351.