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ORIGINAL ARTICLE

Knee strength retention and analgesia with continuous perineural fentanyl infusion after total knee replacement: randomized controlled trial

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Abstract
Purpose Despite providing adequate pain relief, a femoral nerve block can induce postoperative muscle weakness after total knee arthoplasty (TKA). Fentanyl has been shown to have peripheral effects but has not been used as a perineural infusate alone after TKA.
Methods Sixty patients scheduled for TKA were randomized to one of three blinded groups: a continuous 24 h infusion of either fentanyl 3 μg/ml, ropivacaine 0.1 %, or 0.9 % normal saline through a femoral nerve sheath catheter at 10 ml/h. The main outcome was maximum voluntary isometric contraction (MVIC) in the quadriceps femoris (knee extension), measured by a handheld dynamometer (Nm/kg). Other variables assessed were preoperative and postoperative visual analog scale (VAS) scores, hamstrings MVIC (knee flexion), active range of motion of the operative knee, distance ambulated, incidence of knee buckling, supplemental morphine usage, postoperative side effects, and serum fentanyl levels.
Results Quadriceps MVIC values were significantly greater in the fentanyl group compared to the group that received ropivacaine (median values, 0.08 vs. 0.03 Nm/kg; $p = 0.028$). The incidence of postoperative knee buckling upon ambulation was higher in the ropivacaine group compared to the fentanyl group, although not statistically significant (40 % vs. 15 %, respectively; $p = 0.077$). VAS scores while ambulating were not significantly different between the fentanyl group and the ropivacaine group ($p = 0.270$). Postoperative morphine consumption, nausea and vomiting, and resting VAS scores were similar among the three groups.
Conclusions A continuous perineural infusion of fentanyl produced greater strength retention than ropivacaine post-TKA.

Keywords Total knee arthroplasty · Femoral nerve block · Fentanyl · Knee strength · Knee flexion and extension

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Introduction

Major knee surgery is often associated with severe postoperative pain, contributing to delayed recovery and

extended hospital stay [1–3]. Femoral nerve blocks by either continuous infusion or single injection of local anesthetics provide an effective method for analgesia while minimizing the need for systemic opioid therapy, reducing opioid-induced side effects, and facilitating early ambulation [4–7]. Despite these benefits, local anesthetics can decrease efferent nerve fibers (motor blockade) [8, 9].

Recent literature investigating femoral nerve sheath (FNS) catheter administration of ropivacaine 0.1 % as a bolus or a varying basal rate showed that motor blockade occurred to a similar degree regardless of method of administration [10]. Another report showed the administration of perineural ropivacaine at concentrations of 0.1 % and 0.4 % and at basal rates of 12 and 3 ml/h, respectively, resulted in equivalent analgesia and muscle weakness in subjects who underwent bilateral total knee arthroplasty (TKA) [11]. Additionally, a causal relationship has been found between FNS infusion with ropivacaine and the risk of falls after hip replacement and TKA [12].

Opioid antinociception via peripheral opioid receptors remains controversial [13–16]; however, fentanyl has been shown to inhibit voltage-gated Na^+ channels [17] and discharges of C and A nociceptors [18]. In our practice, we have observed the clinical ability of administering fentanyl as a peripheral nerve block adjuvant to be as effective as local anesthetics for analgesia, although an improvement in strength retention is unknown.

We therefore tested the hypothesis that the administration of fentanyl as a continuous femoral nerve block may induce less motor weakness compared to ropivacaine following TKA. The primary objective of this study was to compare postoperative maximum voluntary isometric contraction (MVIC) between continuous FNS catheter administration of fentanyl and ropivacaine alone. Secondary objectives were postoperative analgesia and supplemental morphine requirements.

Materials and methods

This was a prospective, randomized, double-blinded study performed at Tampa General Hospital (TGH), Tampa, FL (USA), between April and November 2011. The study was approved by the Institutional Review Board (IRB) at the University of South Florida. Written informed consent was obtained from each patient. The trial was prospectively registered at clinicaltrials.gov (NCT01620047).

Subjects scheduled to receive a unilateral, primary, tricompartmental TKA, utilizing cruciate-retaining knee components, were evaluated for eligibility. All procedures were performed by the same surgeon (T.B.). Adults (older than 18 years of age) of American Society of Anesthesiologists (ASA) physical status I–III were included in the study. Subjects who were either pregnant, on anticoagulant therapy, allergic to opioids or local anesthetics, chronic pain patients, with central or peripheral neuropathies (or those at risk of developing them, e.g., diabetes), or had a history of traumatic lower extremity injury were excluded from the study.

The primary endpoint was to compare postoperative quadriceps femoris strength (knee extension) between fentanyl and ropivacaine FNS infusions. The secondary endpoints were to assess pain using the visual analog scale (VAS) during rest and ambulation, knee buckling upon ambulation, hamstring strength (knee flexion), serum fentanyl levels, and supplemental morphine requirements among the three groups.

Baseline evaluation included history and physical, standard anesthetic preoperative evaluation, pre-intervention isometric dynamometry (flexion and extension of the knee), and resting VAS.

Randomization

On the day of admission, in the preoperative holding area, patients were randomized to one of three treatment groups using a computer-generated randomization scheme that was controlled and recorded by the study pharmacist. The three treatment groups (20 patients per group) were fentanyl 3 μg/ml, ropivacaine 0.1 %, and the control group, which received 0.9 % normal saline, all of which were delivered through a FNS catheter at a basal rate of 10 ml/h. The group that received saline through the FNS catheter received a continuous intravenous infusion of fentanyl 5 μg/ml via a patient-controlled analgesia (PCA) pump at 6 ml/h. The groups that received either fentanyl or ropivacaine through the FNS catheter received saline intravenously, to maintain the study blind. All study personnel and hospital staff, except the study pharmacist, were blinded until all data analyses were complete. After completion of enrollment and data collection, the pharmacy assigned blinded group numbers for purposes of analysis.

At the conclusion of the operative procedure and upon the patient's arrival to the post-anesthesia care unit (PACU), a PCA pump (PCA III; Hospira LifeCare, Lake Forest, IL, USA) was attached to the FNS catheter; an additional Baxter I PCA pump (Baxter, Deerfield, IL, USA) was attached to the IV catheter. The blinded study medication was continuously infused for a 24-h period.

Placement of femoral nerve sheath

In the preoperative area, after standard ASA monitoring, each patient underwent placement of the FNS catheter (StimuCath; Arrow, Reading, PA, USA) by the same anesthesiologist in all cases (D.M.). Catheter placement

was performed under sedation with propofol (1–2 mg/kg) using a nerve stimulator technique. Initial stimulation of the 17-gauge insulated peripheral nerve-stimulating needle used for catheter placement was performed with 1.5 mA stimulation voltage and observation of patellar snap, followed by refinement of catheter placement with reduced voltage, looking for loss of patellar snap (below 0.03 mA). Final catheter tip position was confirmed following catheter tunneling using the nerve stimulator. All subjects received 20 ml 0.5 % ropivacaine via the catheter. All patients received a single-injection sciatic nerve block preoperatively, placed via the anterior approach using the nerve stimulator, and received 10 ml 0.5 % ropivacaine. Adequacy of motor block was assessed preoperatively in all major muscle groups of the operative limb with a score of 0 of 5, and sensory block was assessed for sharp–dull sensation and temperature discrimination.

Anesthetic technique

The anesthetic regimen was standardized utilizing 1–2 mg preoperative midazolam sedation, 2 mg/kg intravenous propofol, and 100 μg fentanyl for induction; succinylcholine or rocuronium neuromuscular blockade was used to facilitate tracheal intubation, followed by sevoflurane and oxygen/air mixture (1:1) for maintenance of anesthesia. All patients received a radial artery catheter for continuous blood pressure monitoring. Hemodynamic stability was maintained as indicated by mean arterial pressure >60 mmHg and urine output >0.5–1 ml/kg/h. Intraoperative opioids were limited to the use of morphine at a total dosage not to exceed 0.3 mg/kg for intraoperative management of pain-associated tachycardia and hypertension.

Postoperative strength measurements

Muscle strength in the operative knee was assessed 24 h after the start of the study medication (before removal of the FNS catheter) as MVIC using a handheld Nicholas Manual Muscle Tester (MMT) Dynamometer (Lafayette Instruments, Lafayette, IN, USA). Such dynamometers provide a record of applied force throughout a joint range of motion [10, 11, 19]. Normative muscle strength was quantified as torque per kilogram body weight (Nm/kg). The following equation was used to calculate strength:

$$\text{Strength} = \frac{((\text{MMT reading in newtons}) \times (\text{distance}))}{\text{bodyweight in kilograms}}$$

Strength retention was assessed, once per patient, by the same two study members while the patient was in a sitting position [20]. The assessor sat in front of the patient and held the dynamometer in position 10 cm below the tibiofemoral joint while the patient was asked to flex and extend the leg to maximal effort for 2 s and then relax.

During the first postoperative session of physical therapy (within 18–24 h post surgery), a physical therapist (same throughout the study) assisted the patient with ambulation and assessed weakness in the operative knee by recording incidences of knee buckling (sudden loss of postural support in the knee while walking). Active range of motion on the operative knee was also assessed. Patients were allowed to ambulate as far as tolerated and within any amount of time. All patients received the blinded study drug infusions during the first session of physical therapy. After removal of the FNS catheter, physical therapy assessments on postoperative day (POD) 2 and 3 and at the 6-week follow-up visit were analyzed for length of ambulation, range of motion, weakness, and stressed VAS scores. At the 6-week follow-up visit, Knee Society scores (a subjective questionnaire with a maximum score of 100) were collected and compared among the three groups.

Postoperative pain side and effects assessment

Pain during ambulation (stressed VAS) was assessed by the physical therapist. Assessment of the patient's pain levels involved a series of resting postoperative VAS assessments measured by study personnel (every 2 h for the first 12 h, then at 16, 20, and 24 h postoperatively). Patients who complained of breakthrough pain were given morphine 4–8 mg IV every 2 h as needed until a VAS score of <5 was attained. No other adjuvant analgesics were given to the patients postoperatively. The incidence of opiate-induced side effects was documented by the nursing staff and included nausea, vomiting, constipation, respiratory depression, pruritus, and sedation.

Plasma fentanyl measurement

To determine plasma fentanyl levels and whether they contributed to the level of analgesia, we drew venous blood samples from all patients immediately after discontinuation of the study drug at 24 h ± 5 min after its initiation. The purpose of this analysis was to determine if the minimum effective concentration (MEC) of fentanyl (0.63 ng/ml) [21] was achieved in the patients receiving fentanyl perineurally and intravenously. All patients had 5 ml blood drawn in a red-top vacutainer and centrifuged at 2,800 rpm for 15 min to isolate serum. The serum was blinded and transported to Quest Diagnostics for evaluation of the fentanyl level via liquid chromatography/tandem mass spectrometry (specificity, 100 %; precision, 7.7 %; limit of quantitation, 0.1 ng/ml).

Statistical analysis

The normality and variance of the group distributions were first assessed using the Kolmogorov–Smirnov test and the Levene's statistic. All group comparisons were conducted using analysis of variance (ANOVA) or Kruskal–Wallis test as appropriate. Finally, a repeated-measures analysis was performed to assess the changes in the VAS scores over time from preoperative to 24 h postoperative. Results are expressed as median (range) for nonparametric continuous variables. A p value <0.05 was considered statistically significant.

Sample size was calculated based on a similar previously completed study by our group [22]. Based on the postoperative extension strength data from this previous study [fentanyl extension data were mean (SD) 0.17 ± 0.12 Nm/kg, ropivacaine data 0.06 ± 0.05 Nm/kg, and control data 0.06 ± 0.02 Nm/kg], we calculated that the minimum total sample size of 57 (19 per group) was necessary to detect a difference in means with 95 % power and an alpha level of 0.05 using a one-way ANOVA.

Results

All 60 patients completed the study and all femoral nerve blocks were successfully placed. There were no statistically significant differences among the groups with regard to age, body mass index (BMI), or length of hospital stay (Table 1). The comparability of the groups was found to be adequate as there were no statistically significant differences in preoperative flexion force, extension force, or VAS scores (Table 2).

Table 2 lists postoperative MVIC values, incidence of knee buckling, length of ambulation, and active range of motion (flexion and extension). The distribution of postoperative quadriceps femoris MVIC between the three catheter infusates is represented in Fig. 1. MVIC was significantly reduced postoperatively compared to preoperative measurements in the fentanyl, ropivacaine, and saline groups for quadriceps ($p = 0.005$, $p < 0.001$, and $p < 0.001$, respectively) and hamstrings ($p = 0.022$, $p < 0.001$, and $p < 0.001$, respectively). Quadriceps femoris MVIC values were significantly greater in the fentanyl group compared to the ropivacaine group ($p = 0.028$). Hamstrings MVIC values were significantly greater in the fentanyl group compared to the ropivacaine and saline control group ($p = 0.038$ and $p = 0.018$, respectively). There was no statistically significant difference between the ropivacaine and saline control group with regard to quadriceps or hamstrings MVIC. Overall, there were no differences in extension range of motion among the groups. The group that received ropivacaine had a significantly greater flexion range of motion compared to the saline control group ($p = 0.030$), but it was not significantly greater than the fentanyl group ($p = 0.383$). Three patients (15 %) in the fentanyl group and eight (40 %) patients in the ropivacaine group had incidences of knee bucking ($p = 0.077$). Patients who received ropivacaine had a significantly greater incidence of knee buckling in the operative knee compared to the saline control group ($p = 0.003$).There were no differences in distance of ambulation among the groups observed on the first physical therapy session. Physical therapy sessions on POD 2 and day 3 and on the 6-week follow-up visit revealed no significant differences with respect to knee flexion, extension, length of ambulation, or knee society score.

There were no differences in postoperative morphine supplementation among the groups (Table 1). The only opioid-induced side effects our subjects experienced were nausea and/or vomiting; however, no statistically significant differences in percentage of incidence were detected among the groups (Table 1).

The distribution of VAS pain scores upon ambulation at the first physical therapy session is represented in Fig. 2. The fentanyl group had significantly less pain than the saline control group (0.044) but not the ropivacaine group (0.270) (Table 2). Resting VAS pain scores were acceptable in all three groups (VAS < 5), and there were no statistically significant differences at any time point up to 24 h postoperatively. There was no statistically significant difference over time between groups when the VAS pain scores were examined using a repeated-measures analysis ($p = 0.905$).

Venous blood collected at 24 h postoperatively revealed median serum fentanyl levels that were significantly lower in the group in which fentanyl was infused via the FNS catheter compared to the saline group that received IV fentanyl [0.3 (range, 0.1–0.8) vs. 0.6 ng/ml (range, 0.1–11.2), respectively; $p = 0.011$]. The median fentanyl levels were 0.3 ng/ml lower than the MEC of fentanyl (Fig. 3).

Discussion

The main findings of our study are (1) FNS catheter infusions of fentanyl resulted in significantly greater postoperative retention of muscle strength compared to infusions of ropivacaine, and (2) the analgesic effect found by the infusion of perineural fentanyl was superior to the administration of fentanyl into the systemic circulation (saline control group) while the patient was ambulating but was similar to ropivacaine.

An ideal analgesic technique for TKA provides complete pain relief with minimal motor blockade. The greater

Table 1 Patient characteristics, morphine requirements, and postoperative nausea and vomiting

	Fentanyl ($n = 20$)	Ropivacaine ($n = 20$)	Saline control ($n = 20$)	p value
Male/female	9/11	7/13	6/14	0.605
Age (years)	71 (53–85)	69 (48–86)	65.5 (53–83)	0.618
BMI (kg/m^2)	30.4 (21.6–37.6)	30.6 (19.2–44.0)	31.2 (18.9–37.1)	0.865
Length of hospital stay (days)	4 (2–7)	5 (3–8)	4 (3–7)	0.257
Cumulative morphine in PACU (mg)	3 (0–12)	0 (0–12)	2 (0–14)	0.871
Cumulative morphine on nursing floor up to 24 h postop (mg)	12 (0–72)	22 (0–52)	14 (0–64)	0.413
Patients experiencing nausea or vomiting	9 (45 %)	5 (25 %)	10 (50 %)	0.233

Values expressed as median (range) or number of subjects (percentage). *BMI* body mass index, *PACU* post-anesthesia care unit

quadriceps MVIC values generated with perineural fentanyl is a reflection of a treatment with minimal motor block, compared to muscle weakness induced by a local anesthetic. We believe the significantly reduced strength measured in the saline control group (no nerve block) was caused by a reduction of range of motion (ROM) caused by greater localized pain; we can only offer this as a hypothesis as pain was not measured during the strength assessments.

Similar improvements in strength following TKA have been reported by Singelyn et al. [6]. In this study, regional anesthesia techniques (epidural analgesia or femoral nerve block) resulted in significantly greater postoperative knee flexion values compared to intravenous PCA morphine. The authors concluded that the benefits of better postoperative knee flexion did not affect outcome at a 3-month follow-up examination.

Femoral nerve block with anesthetics provides superior pain relief and results in fewer side effects compared with conventional IV PCA with morphine [6, 23–25]. In the current study, we were unable to demonstrate statistically significant differences in resting pain scores or opiate-induced side effects among the treatment arms, possibly because our study was not powered to investigate these endpoints. However, continuous fentanyl infusions via the FNS catheter provided superior pain relief while ambulating at the first physical therapy session compared to the control group receiving a continuous IV fentanyl infusion. Pain relief was not significantly different amongst the groups upon ambulation on POD 2, POD 3, or the 6-week follow-up, which may be the result of the fast recovery from TKA.

Several studies showed no effect of adding fentanyl to peripheral nerve blocks. Fanelli and colleagues [26] added 1 μg/kg fentanyl to ropivacaine 7.5 mg/ml for axillary brachial plexus blocks and compared the intraoperative quality of nerve block to ropivacaine 7.5 mg/ml alone. No differences were found between the groups with regard to nerve block characteristics in terms of onset time, quality of nerve blockade, or duration of postoperative analgesia. In a similar study, Magistris and colleagues [27] compared the combination of fentanyl 1 μg/kg with 0.75 % to 0.75 % ropivacaine alone in a sciatic–femoral nerve block and found no differences in the degree of sedation or postoperative analgesia. The effect of fentanyl may have been overshadowed by the intensity of motor or sensory blockade from the 0.75 % ropivacaine plus a low dose of fentanyl. Because prior studies failed to show a benefit with 1 μg/ml fentanyl, we chose to use a higher dose (3 μg/ml) of fentanyl for continuous infusion. The higher dose, 3 μg/ml fentanyl, rather than the 1 μg/ml dose used in the other studies, and the administration of fentanyl alone (not in combination with any local anesthetic) may be responsible for the difference in our observed strength retention.

By contrast, the addition of 100 μg fentanyl to an axillary brachial plexus block in a study by Nishikawa and colleagues [28] significantly prolonged the onset of analgesia and duration of sensory blockade compared to patients who received 1.5 % lidocaine plus saline or 100 μg fentanyl IV. The authors postulate three possible mechanisms of action for the improved analgesia. First, fentanyl could act directly on the nervous system by way of opioid-binding sites or penetration of the nerve membrane and direct action at the dorsal horn. Second, fentanyl may diffuse from the brachial plexus sheath and bind to the opioid receptor of the dorsal horn. Third, fentanyl may reach the systemic circulation and potentiate local anesthetic action via central opioid receptor-mediated analgesia.

We designed our study to test the third hypothesis by including a systemically administered control group that received the same continuous dose of fentanyl. The average serum fentanyl concentrations at 24 h post-TKA were significantly (50 %) lower when administered perineuronally compared to systemic administration. Although both routes of administration resulted in similar postoperative pain while resting, perineuronal administration of fentanyl resulted in significantly less pain while ambulating, hence discrediting the third postulate.

Gourlay and colleagues [21] determined a relationship between blood fentanyl concentration and analgesic effect and found the mean minimum effective analgesia

Table 2 Strength measurements and physical therapy outcomes

	Fentanyl (F) ($n = 20$)	Ropivacaine (R) ($n = 20$)	Saline control (S) ($n = 20$)	Overall p value and individual pair-wise comparisons
Preoperative				
Quadriceps[a] MVIC (Nm/kg)	0.13 (0.05–0.39)	0.11 (0.03–0.40)	0.13 (0–0.37)	0.786
Hamstrings[b] MVIC (Nm/kg)	0.15 (0.05–0.40)	0.16 (0.04–0.48)	0.16 (0–0.34)	0.901
Resting VAS score	3.9 (0–10)	3.9 (0–10)	4.0 (0–9)	0.643
24 h postoperative				
Quadriceps[a] femoris MVIC (Nm/kg)	0.08 (0.01–0.28)	0.03 (0.01–0.17)	0.05 (0–0.13)	0.052
				F vs. R: 0.028*
				R vs. S: 0.365
				F vs. S: 0.075
Hamstrings[b] MVIC (Nm/kg)	0.11 (0.03–0.21)	0.04 (0.01–0.22)	0.07 (0–0.16)	0.038*
				F vs. R: 0.038*
				R vs. S: 0.792
				F vs. S: 0.018*
Incidence of knee buckling	3/20 (15 %)	8/20 (40 %)	0/20 (0 %)	F vs. R: 0.077
				R vs. S: 0.003*
				F vs. S: 0.231
Length of ambulation (feet)	15 (2–150)	15 (0–150)	5 (0–75)	0.109
AROM flexion (°)	71 (51–86)	75 (48–90)	64 (45–86)	0.067
				F vs. R: 0.383
				R vs. S: 0.030*
				F vs. S 0.107
AROM extension (°)	6 (2–10)	6 (3–12)	6 (2–10)	0.934
VAS scores during ambulation	3.5 (0–9)	4 (2–8)	6 (1–9)	0.084
				F vs. R: 0.270
				R vs. S: 0.181
				F vs. S: 0.044*
Postoperative day 2				
Length of ambulation (feet)	125 (1–400)	110 (20–400)	125 (4–250)	0.632
AROM flexion (°)	80 (45–102)	85 (75–95)	80 (65–90)	0.437
AROM extension (°)	5 (2–12)	5 (3–20)	6 (2–30)	0.465
VAS scores during ambulation	3 (0–9)	3.5 (1–6)	3 (2–7)	0.972
Postoperative day(POD) 3				
Length of ambulation (feet)	150 (2–250)	150 (100–750)	175 (11–300)	0.943
AROM flexion (°)	85 (75–105)	85 (78–90)	85 (58–93)	0.136
AROM extension (°)	5 (3–7)	5 (2–10)	5 (0–8)	0.679
VAS scores during ambulation	3.5 (2–8)	4 (2–6)	4 (1–5)	0.662
Six-week follow-up				
AROM flexion (°)	108 (85–130)	106 (95–135)	110 (70–125)	0.403
Knee Society function score	80 (20–100)	95 (45–100)	77.5 (65–100)	0.546
VAS scores during ambulation	2 (0–8)	2 (0–5)	3 (0–7)	0.378

Data are represented as median (range) or number of patients (percentage). *F* fentanyl delivered via a femoral nerve sheath catheter, *R* ropivacaine delivered via a femoral nerve sheath catheter, *S* saline delivered via a femoral nerve sheath catheter, *AROM* active range of motion, *VAS* visual analog score, *MVIC* maximum voluntary isometric contraction, ° degrees,[a] Knee extension,[b] Knee flexion,* p values ≤ 0.05 are considered statistically significant

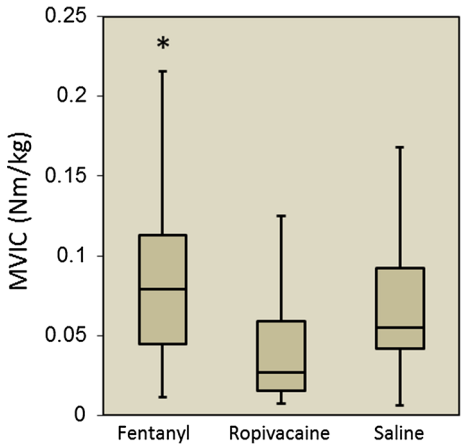

Fig. 1 Box and whisker plot representing knee extension strength in all 60 patients. The ends of the whiskers are set at 1.5 times the interquartile range (*IQR*) above the third quartile (*top* of the box) and 1.5 times IQR below the first quartile (*bottom* of box). The *line* within the box represents the median value. *MVIC* maximum voluntary isometric contraction. *Significantly greater extension strength for fentanyl group compared to ropivacaine group

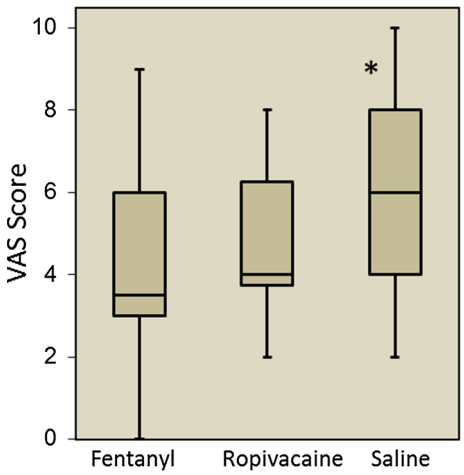

Fig. 2 Box and whisker plot representing visual analog score (*VAS*) scores during ambulation in all 60 patients. The ends of the whiskers are set at 1.5 times the interquartile range (*IQR*) above the third quartile (*top* of the box) and 1.5 times IQR below the first quartile (*bottom* of box). The *line* within the box represents the median value. *Significantly higher VAS scores for the saline control group compared to the fentanyl group

concentration to be 0.63 ng/ml with a fivefold interpatient variation. We therefore believe that the analgesia obtained via the femoral nerve catheter resulted in serum fentanyl levels significantly below the minimum effective analgesic concentration, and we postulate a local analgesic process.

The main limitations to this study are the small sample size (20 patients) of each study group; however, this study was powered to analyze postoperative quadriceps MVIC. Statistical corrections for multiple comparisons were not performed because of concern for overcorrection in this

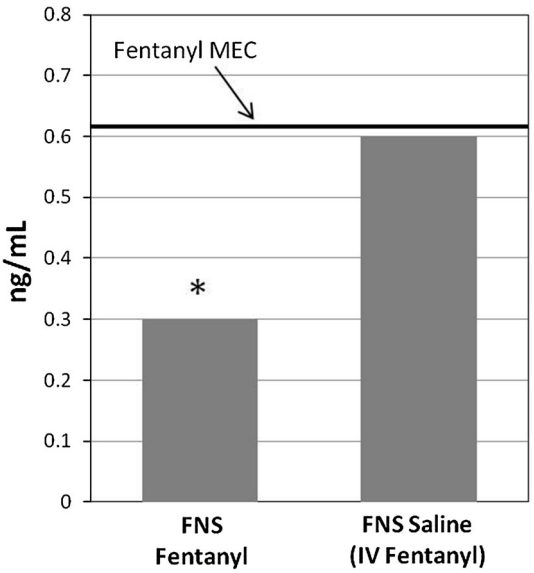

Fig. 3 Median values of serum fentanyl in the fentanyl group and the saline control group. *MEC* minimum efficient concentration, *FNS* femoral nerve sheath. *Statistically significantly lower serum fentanyl levels compared to the saline group

setting, but the possibility of type I errors remains, and the results (especially those with larger *p* values) should be interpreted with caution. Our study did not identify any long-term benefits among any of the groups, possibly because the FNS catheters and study drug infusions were discontinued on POD 1. Prolonging drug infusions to POD 2 or 3 may reveal long-term functional benefit and a reduction of hospital stay. Future studies evaluating a joint hypothesis [29] powered for both muscle strength and analgesia are needed to confirm the efficacy of perineural fentanyl for TKA.

This is the first study demonstrating that higher doses of fentanyl may be the preferred perineural infusate for post-TKA rehabilitation because of its analgesic effectiveness and minimal motor blockade.

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Conflict of interest None.

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