

In patients undergoing fast track total knee arthroplasty, addition of buprenorphine to a femoral nerve block has no clinical advantage

A prospective, double-blinded, randomized, placebo controlled trial

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Abstract

Background: Several adjuvants have been proposed to prolong the effect of peripheral nerve blocks, one of which is buprenorphine. In this randomized double blinded placebo controlled trial we studied whether the addition of buprenorphine to a femoral nerve block prolongs analgesia in patients undergoing total knee arthroplasty in a fast track surgery protocol.

Methods: The treatment group (B) was given an ultrasound-guided femoral nerve block with ropivacaine 0.2% and 0.3mg buprenorphine. We choose to use 2 control groups. Group R was given a femoral nerve block with ropivacaine 0.2% only. Group S also received 0.3mg buprenorphine subcutaneously. Only patients with a successful block were enrolled in the study.

Results: We found no difference in our primary outcome parameter of time to first rescue analgesic. We found lower opioid use and better sleep quality the first postoperative night in patients receiving buprenorphine perineurally or subcutaneously. Buprenorphine did not lead to any significant change in pain or mobilization. We found a high overall incidence of nausea and vomiting.

Conclusion: In patients undergoing total knee arthroplasty, in the setting of a fast track surgery protocol, the addition of buprenorphine to a femoral nerve block did not prolong analgesia.

Abbreviations: ASA = American Society of Anesthesiology, BMI = body mass index, eGFR = estimated glomerular filtration rate, JPH = Jens Peter Hering, LIA = local infiltration analgesia, NRS = numeric rating scale, OBAS = overall benefit of anesthesia score, RvB = Rienk van Beek.

Keywords: addition of buprenorphine, clinical advantage, double-blinded randomized controlled trial, fast track total knee arthroplasty, femoral nerve block

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RvB: wrote the research protocol, oversaw conduct of the study, and wrote the manuscript. HZ: contributed to writing the research protocol and conducting the study, and performed data extraction. TvdP: performed statistical analysis. JS: helped writing the manuscript. PL: contributed to writing the manuscript. MWH: helped in drafting the research protocol and writing the manuscript.

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1. Introduction

Total knee arthroplasty is frequently associated with severe postoperative pain, which may delay recovery and discharge from the hospital.^[1] During the last decade improvement of postoperative analgesia and early mobilization have been emphasized. A multimodal analgesic regimen is often used to treat postoperative pain, facilitating early ambulation after surgery. This typically includes paracetamol, a nonsteroidal anti-inflammatory agent, steroids, antineuropathic agents, and opioids.^[2] In addition, regional anesthesia techniques to expedite postoperative recovery have become more targeted, moving from epidural anesthesia to combined femoral-sciatic, and now to adductor canal blocks, and/or local infiltration analgesia (LIA).^[3]

Several adjuvants have been proposed to prolong the analgesic effect of peripheral nerve blocks, one of which is buprenorphine.^[4] The possible mechanism of action by which buprenorphine acts as an analgesic at the peripheral nerve has not been entirely clarified. Fields et al^[5] described the presence of multiple opiate receptor sites on primary afferent nerve fibers.^[5] On the other hand, Leffler et al^[6] showed that buprenorphine also has an inhibitory effect on voltage-gated Na(+) channels, thereby acting as a local anesthetic.^[6] Clinically, buprenorphine added to a local anesthetic leads to longer lasting postoperative analgesia in some

Table 1**Description of medication given in treatment groups.**

	Group B	Group R	Group S
Perineural medication	Ropivacaine 0.2% 20 mL Buprenorphine 0.3 mg	Ropivacaine 0.2 20 mL	Ropivacaine 0.2 20 mL
Subcutaneous medication	NaCl 0.9% 1 mL	NaCl 0.9% 1 mL	Buprenorphine 0.3 mg

types of blocks.^[7–12] More recently, Kosel et al^[13] found lower numeric rating scale (NRS) pain scores with buprenorphine added to single-shot bupivacaine femoral nerve blocks in patients undergoing total knee arthroplasty. However, whether buprenorphine has any clinically relevant benefit when used in the context of both contemporary multimodal analgesic regimens and fast track surgery protocols has not been investigated.

Therefore, in patients undergoing total knee arthroplasty embedded in a fast track surgery protocol, we set out to test whether the addition of buprenorphine 0.3 mg to a single-shot femoral nerve block would prolong postoperative analgesia.

2. Methods

After approval from the institutional research and ethics committee (M013–030 METC Noord-Holland, Nassauplein 10, 1815 GM Alkmaar) and the Dutch Ministry of Health (CCMO NL45134.094.13), the study was registered in the EU Clinical Trials Register (EudraCT number 2013-002449-12). We screened all patients (aged 50–80 years) scheduled for primary total knee arthroplasty under spinal anesthesia for eligibility from December 2013 to April 2014 in Westfries Medical Centrum, Hoorn, the Netherlands. All patients signed informed consent. Patients who were not ambulant preoperatively or able to understand and complete the questionnaires, patients with fever on the day of surgery, known allergy to buprenorphine, nonsteroidal anti-inflammatory agents or local anesthetics, opioid treatment before surgery, a skin infection at injection site, or renal disease (estimated glomerular filtration rate <50 mL/min) were excluded.

The treatment group (B) was given a femoral nerve block with ropivacaine 0.2% and 0.3 mg buprenorphine. We choose to use 2 control groups. Group R was given a femoral nerve block with ropivacaine 0.2% only. Group S also received 0.3 mg buprenorphine subcutaneously, as was proposed by Candido et al.^[10] In this way, the central antinociceptive effects of buprenorphine becomes more clear as differences can be seen between group B and S.

2.1. Randomization

Patients were electronically randomized (www.randomizer.org) to 1 of 3 treatment groups (Table 1), using a prerandomized list of numbers, which was generated by an independent research assistant. Anesthesiologists and patients were blinded to group randomization and medication administered. Our pharmacy department prepared the study medication and blinded syringes to content.

2.2. Study interventions

Subjects were all premedicated with paracetamol 1000 mg and gabapentin 600 mg *per os* 1 hour preoperatively. One of 2 designated anesthesiologists (JPH and RvB) performed an ultrasound-guided femoral nerve block (SonoPlex Stim cannula, 50 mm needle, Pajunk, Geisingen, Germany) before surgery.

Standard monitoring during the procedure consisted of electrocardiogram, noninvasive blood pressure, and oxygen saturation.

Femoral nerve block was tested for efficacy after 15 minutes by cold perception. Only patients with a successful block were enrolled in the study. Perioperatively all patients received a spinal anesthesia using 10 to 12.5 mg bupivacaine with glucose.

Total knee arthroplasty was performed using a pneumatic tourniquet at thigh level with an inflation pressure of 300 mm Hg. Before placing the prosthesis, the orthopedic surgeon performed LIA of the posterior capsule by using 100 mL ropivacaine 0.2% with epinephrine 1:200,000.

A multimodal analgesic regimen was prescribed according to hospital protocol (Table 2).

2.3. Primary endpoint

We chose time to first rescue analgesic as our primary outcome parameter. Pain was measured using the NRS at selected time intervals. We registered the total amount of opioids used during the first 48 postoperative hours in milligram(s) of oxycodone, where *i.v.* piritramide was converted to *p.o.* oxycodone (1:1).

2.4. Secondary endpoints

We noted postoperative nausea and vomiting or itching as parameters of patient wellbeing and comfort (yes/no). We investigated the quality of sleep on a 10-point Likert scale on the first 2 postoperative nights and we measured the overall benefit of anesthesia score (OBAS) on postoperative days 1 and 2. Furthermore, we registered the time to first mobilization (30-m walking). We measured nausea, vomiting, and itching at the time points 1, 6, 12, 24, 36, and 48 hours after nerve block and report them as being absent or present.

2.5. Sample size calculation

Based on the studies by Candido et al,^[8,10] where time to first analgesia was considerably prolonged (e.g., 5 hours without buprenorphine as compared to 17 hours with buprenorphine) a

Table 2**Multimodal analgesic regimen.**

	Day 0	POD1 and further
Routine medications	Paracetamol 4dd 1000 mg Naproxen 2dd 500 mg Gabapentin 1dd 600 mg premedication Gabapentin 1dd 300 mg in the evening Dexamethasone 8 mg at start of surgery Ondansetron 2dd 4 mg	Paracetamol 4dd 1000 mg Naproxen 2dd 500 mg Gabapentin 2dd 300 mg Ondansetron 2dd 4 mg
Rescue medications	Piritramide 4dd 15 mg s.c.	Oxycodone 6dd 5 mg <i>p.o.</i>

Medications used routinely and if necessary on day 0 and POD1 and further.

Day 0 = day of operation, *p.o.* = postoperative; POD1 = postoperative day 1; s.c. = subcutaneously.

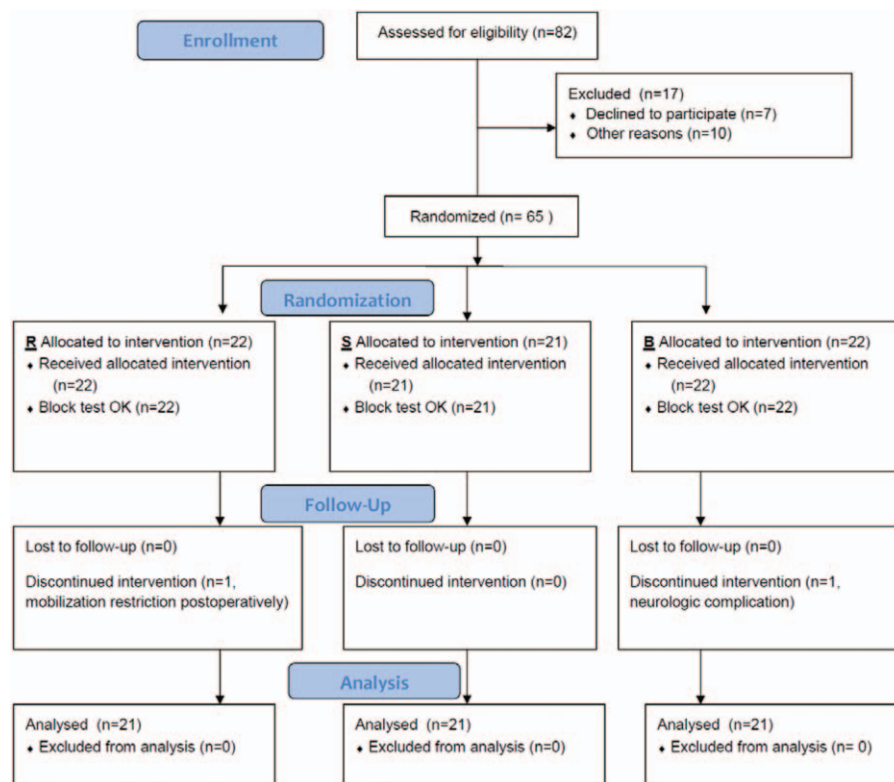


Figure 1. CONSORT flowchart of patient flow through the study.

power analysis was done to detect a large effect size ($f=0.4$) on time to first rescue analgesic with respect to the 3 subgroups (B, S, and R) assuming a type I error (α) of 0.05 and a type II error (β) of 0.20 (power=0.80), leading to 21 patients in each group. We considered a drop out of 20%.

2.6. Statistical analysis

Statistical analysis was performed using SPSS18. Frequency tables describe nominal and ordinal variables. Interval ratio variables are described as mean with standard deviation. Nominal variables such as gender, American Society of Anesthesiology classification, nausea, vomiting, and itching with respect to the subgroups (B, R, and S) were analyzed using the χ^2 test. Continuous variables, such as age, body mass index, operating time, opioid use, time to mobilization, OBAS, and sleep quality with respect to subgroups (B,R and S) were analyzed

using the Kruskal–Wallis test. We considered a prolongation of time to first rescue analgesic of 6 hours clinically relevant.

There is no prior published data in this manuscript. A P-value $<.05$ was considered significant.

3. Results

Out of 82 patients assessed for eligibility, 65 were enrolled in the study. Two patients discontinued the study for reasons stated in Fig. 1, resulting in 63 patients for the final analysis. Patient characteristics were comparable (Table 3) between groups. The time period for data collection was December 2013 to April 2014.

We found no difference in our primary outcome parameter of time to first rescue analgesic ($P=.191$) (Fig. 2).

The total dose of postoperative opioid consumption was highest in group R ($P=.013$), as shown in Table 4. This table also shows that sleep quality postoperative night 1 was worse in group

Table 3

Patient characteristics.

	Group B	Group R	Group S	P value
Age, y	66.6 (6.9)	65.7 (6.1)	67.5 (6.3)	.537
% Women	47.6	28.6	28.6	.327
ASA 1, n (%)	2 (9.5)	4 (19.0)	1 (4.8)	.608
ASA 2, n (%)	16 (76.2)	15 (71.4)	16 (76.2)	
ASA 3, n (%)	3 (14.3)	2 (9.5)	4 (19.0)	
BMI	29.2	29.5	28.9	.185
Operating time, min	68.2 (15.2)	66.2 (10.9)	64.1 (7.3)	.194

Interval ratio variables are described as mean with standard deviation. ASA = American Society of Anesthesiology, BMI = body mass index.

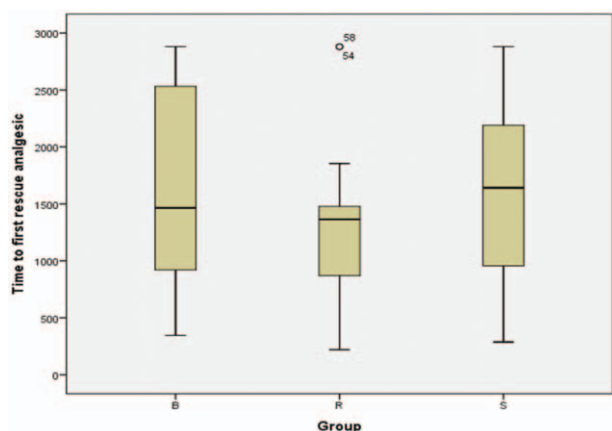


Figure 2. Time to first rescue analgesic. The horizontal lines within the box indicate the median, the bottom and top of the box indicate the first and third percentile, respectively, the lines extending from the boxes indicate minimum and maximum values within 1.5 times the interquartile range, the numbers 54 and 58 represent outliers in the study group R.

R (mean 4.48) as compared to groups B and S. Furthermore, there was no difference in time to first mobilize 30 m ($P = .126$), nausea ($P = .929$), vomitus ($P = .291$), itching ($P = .325$), OBAS 24 hours ($P = .993$), OBAS day 48 hours ($P = .478$) and sleep quality postoperative night 2 ($P = .588$).

There were no neurologic, bleeding, or infectious complications associated with the femoral nerve block, nor did we see any falls related to quadriceps muscle weakness due to the block.

4. Discussion

In this study we found excellent pain relief in the immediate postoperative period as a result of combining LIA of the posterior capsule with a femoral nerve block, providing analgesia for the anterior capsule, supplemented with a multimodal analgesic regimen. Under these circumstances, addition of buprenorphine did not prolong analgesia. The time to first rescue analgesic was comparable between groups, as were patients’ pain perception and functional recovery.

Although mean NRS pain scores showed a trend toward being lower in the buprenorphine groups, this did not reach statistical or, for that matter, clinical significance (Fig. 3). Furthermore,

there was no difference between buprenorphine given perineurally or subcutaneously. Both groups B and S used less opioids postoperatively and sleep quality was better in these groups the first postoperative night compared with patients in group R.

The mean time to first rescue analgesic in the perineural buprenorphine group was approximately 24 hours. This shows that pain relief supplied by the femoral nerve block and posterior capsule infiltration, combined with a multimodal analgesic regimen was excellent and there was no difference between groups. Our findings are in agreement with YaDeau et al,^[12] who studied 90 patients undergoing foot and ankle surgery under multimodal analgesia. Patients were randomized to a sciatic and adductor canal block using bupivacaine with either i.v. dexamethasone, i.v. dexamethasone, and i.v. buprenorphine or perineural dexamethasone and buprenorphine and found no difference in their primary outcome parameter *dynamic pain with movement* when a multimodal approach to pain was used. This study did, however, find that block duration was longer and worst pain reported and postoperative opioid use was lower in the group receiving perineural buprenorphine and dexamethasone. In the studies of Candido et al^[8-10] and Behr et al,^[14] patients were allocated to a brachial plexus block with a local anesthetic or local anesthetic with buprenorphine. They showed an increase in duration of analgesia by the addition of buprenorphine to peripheral nerve blocks. Patients in these studies did not receive any coanalgesics postoperatively until first pain was reported. Kosel et al^[13] did not record coanalgesics administered. The effect of buprenorphine in our study therefore was possibly overshadowed by the multimodal analgesic regimen that was used.

Regarding postoperative opioid use, we found a statistical difference between groups. Both groups receiving buprenorphine had lower consumption of rescue analgesics, but results were comparable whether buprenorphine was given perineurally or subcutaneously. YaDeau et al^[12] found that the group receiving only i.v. dexamethasone 60.7% of patients required opioids on the day of surgery. When i.v. and perineural buprenorphine was administered, only 28.6% of patients required opioids.

We found a high incidence of nausea and vomiting, higher than the studies of Behr et al^[14] and YaDeau et al,^[12] without difference between treatment groups. Buprenorphine may have caused these side effects in groups B and S. Conversely, the increased use of oxycodone may have been responsible in group R.

Table 4

Outcome parameters.

	Group B	Group R	Group S	P
Time to first rescue analgesic, min	1665 (891)	1286 (676)	1699 (831)	.191
Opioid consumption, mg	14.3 (15.6)	30.0 (24.1)	13.6 (14.4)	.013*
Time to first mobilization, minutes	702 (502)	902 (630)	1133 (594)	.126
Nausea overall (%)	33.3	28.6	33.3	.929
Vomiting overall (%)	19.0	9.5	28.6	.291
Itching overall (%)	19.0	9.5	4.5	.325
OBAS t=24	3.95 (3.19)	4.19 (3.49)	4.19 (3.82)	.993
OBAS t=36	4.52 (3.40)	4.86 (3.41)	4.29 (3.29)	.849
OBAS t=48	3.52 (3.19)	3.76 (3.30)	4.48 (3.11)	.478
Sleep quality 24	6.24 (2.45)	4.48 (2.79)	6.62 (2.06)	.028*
Sleep quality 48	7.00 (2.12)	6.62 (2.94)	6.19 (2.36)	.588

Interval ratio variables are described as mean with standard deviation.

OBAS = overall benefit of anesthesia score.

* Statistically significant.

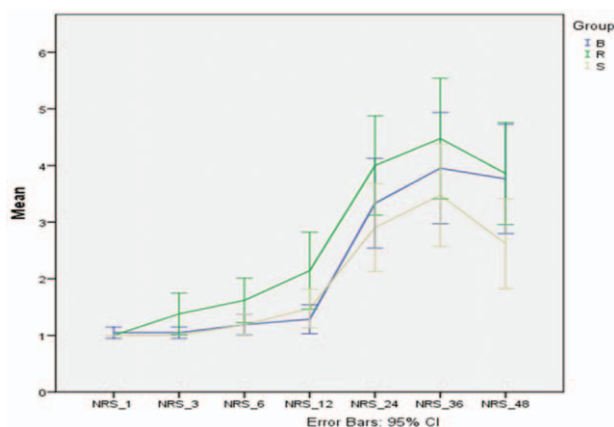


Figure 3. NRS scores. Blue, brown, and green lines represent mean NRS at 1, 3, 6, 12, 36, and 48 hours regarding Group B, R, and S, respectively. Vertical lines indicate 95% confidence interval. NRS = numeric rating scale.

In a fast track surgery protocol, patients are encouraged to walk 4 to 6 hours after surgery. In our study, we did not only find that there is a rather large spread in block duration, but also that the median time to first mobilization, defined as the ability to walk 30 m, was quite long, ranging from 11.7 to 18.9 hours. This might well be the result of motor blockade from the femoral nerve block, which could lead to postoperative falls.^[15,16] This should be taken into account while mobilizing these patients.

To our knowledge, we are the first to report on sleep quality in patients receiving buprenorphine as an adjuvant for peripheral nerve blockade. Sleep is detrimentally disturbed the first 3 nights after knee arthroplasty.^[17] In our study, buprenorphine seems to have some positive effect, with better sleep quality on the first postoperative night, but no difference thereafter.

Our study has 1 important limitation. Our patients were studied in a fast track protocol using a multimodal analgesic regimen. As was mentioned earlier, the effect of buprenorphine was most likely overshadowed by the co-analgesics administered. On the other hand, evaluations of treatments are optimally undertaken against the backdrop of contemporary current practice.^[18] Furthermore, the study was powered to show a difference in time to first rescue analgesic. Regarding our secondary outcome parameters, the study may not have sufficient power to interpret the data.

Computerized randomization was performed and the patients and caregivers were blinded to the study medication used. There were only 2 anesthesiologists performing the ultrasound-guided nerve blocks, with a 100% block success rate and there was a short period of enrollment, without any changes in medical or physiotherapy protocols. And, most importantly, we studied 3 patient groups, as was suggested by Candido et al.^[10] Group R, not receiving any buprenorphine, served as the control group, whereas group S, receiving subcutaneous buprenorphine, showed the possible systemic effects of the opioid.

In conclusion, in the setting of a fast track surgery protocol using a multimodal analgesic regimen, the addition of bupre-

norphine to a femoral nerve block using 20 mL of ropivacaine 0.2% did not result in clinically relevant benefits. We did find lower opioid use and better sleep quality the first postoperative night in patients receiving buprenorphine either perineurally or subcutaneously. Buprenorphine did not lead to any significant change in pain or functional outcome criteria, and we found a high incidence of nausea and vomiting in all groups.

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