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Effect of adductor-canal-blockade on established, severe post-operative pain after total knee arthroplasty: a randomised study

P. Jæger, U. Grevstad, M. H. Henningsen, B. Gottschau, O. Mathiesen and J. B. Dahl
Department of Anaesthesia, Copenhagen University Hospital, Gentofte, Denmark

Background: In this proof-of-concept study, we investigated the effect of the predominantly sensory adductor-canal-blockade on established pain in the early post-operative period after total knee arthroplasty (TKA). We hypothesised that the adductor-canal-blockade would reduce pain during flexion of the knee (primary end point) and at rest, as well as reducing morphine consumption and morphine-related side effects (secondary outcomes) compared with placebo.
Methods: We enrolled patients scheduled for elective TKA into this double-blind, placebo-controlled, randomised study. During general anaesthesia, we placed a catheter in the adductor canal, and after obtaining pre-block pain scores 30 min post-operatively, we injected 30 ml of ropivacaine 0.75% ($n = 21$) or saline ($n = 20$) according to randomisation. Clinicaltrials.gov Identifier: NCT01261897.
Results: Forty-two patients were randomised, and 41 were analysed. Mean (standard deviation) pain scores during flexion of the knee at 1 h post-operatively were 58 (22) mm and 67 (29) mm, ropivacaine and placebo group, respectively ($P = 0.23$) but was significantly reduced in the ropivacaine group when calculated as area under the curve for the interval 1–6 h ($P = 0.02$). There were no statistically significant differences regarding pain at rest ($P = 0.08$), morphine consumption ($P = 0.06$), nor morphine-related side effects, apart from nausea ($P = 0.04$).
Conclusion: This proof-of-concept study shows promising results regarding the analgesic efficacy of adductor-canal-blockade in post-operative pain treatment after TKA, with a significant reduction in pain during flexion of the knee in the early post-operative period compared with placebo. However, the study was not sufficiently powered to permit final conclusions.

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Total knee arthroplasty (TKA) is a frequently performed procedure associated with intense post-operative pain. Early post-operative mobilisation is important both to reduce immobility-related complications and to get the best functional result following surgery. Relieving pain without compromising motor function is a challenge in early post-operative pain treatment.

The femoral nerve block (FNB) is often considered as the gold standard for pain alleviation after TKA. Although effective for pain relief, this block reduces muscle strength,[1] thereby potentially compromising mobilisation. Furthermore, the FNB is associated with the risk of falling.[2] Techniques for effective pain treatment with preserved muscle function are warranted.

The adductor-canal-blockade (ACB) may offer an alternative method for pain treatment after TKA.[3] The ACB is an almost pure sensory nerve blockade. It blocks the two largest sensory contributions from the femoral nerve to the knee – the saphenous nerve and the nerve to the vastus medialis – in their path through the adductor canal (the Hunters canal).[3] In addition to the sensory nerves from the femoral nerve, the terminal end of the posterior branch of the obturator nerve enters the distal part of the canal, and injecting a large volume of ropivacaine into the canal will theoretically disperse these fibres, thereby adding to the analgesic effect.[3] The only potentially affected muscle function is that of the vastus medialis, which makes this block an almost pure sensory blockade.

In this proof-of-concept study, we aimed to investigate the adjunctive effect of ACB on established pain in the early post-operative period after TKA in patients receiving general anaesthesia and a basic

analgesic regimen with paracetamol, ibuprofen, and patient-controlled intravenous morphine. We hypothesised that the ACB would reduce pain during flexion of the knee (primary end point) and at rest, as well as reducing morphine consumption and morphine-related side effects (secondary outcomes) compared with placebo.

Methods

The trial was registered at http://www.clinicaltrials.gov (NCT01261897), and approval was obtained from the local Regional Ethics Committee (H-2–2010-088), the Danish Medicines Agency (2010–021918-30), and the Danish Data Protection Agency. This prospective, randomised, double-blind, parallel group, placebo-controlled study was undertaken at Gentofte University Hospital, the Capital Region of Denmark. The study was monitored by the Copenhagen University Hospital Good Clinical Practice (GCP) unit and conducted in accordance with the guidelines for GCP and the Helsinki Declarations. Data are presented in accordance with the CONSORT statement.

From January 2011 to August 2011, we screened all patients scheduled for TKA for inclusion into the study. Written informed consent was obtained from all subjects prior to enrolment. Eligibility criteria were: primary, unilateral TKA under general anaesthesia, age 40–85 years, body mass index 18–40, and American Society of Anesthesiologists I–III. Exclusion criteria included a daily intake of strong opioids (morphine, oxycodone, methadone, fentanyl, ketobemidone), alcohol or drug abuse, inability to cooperate, inability to speak or understand Danish, and allergy to any drug used in the study.

Interventions

One hour prior to surgery, 400 mg of ibuprofen and 1 g of paracetamol were given orally as premedication. General anaesthesia was induced with propofol, and maintenance was achieved with propofol (variable rate) and remifentanil 30 µg/kg/h (fixed rate). Intraoperative fluid therapy was administered at the discretion of the anaesthetist. All patients received a femoral tourniquet perioperatively to obtain a bloodless field. Measurement of blood loss was based upon clinical estimation (measuring blood in suction bottles and estimation of volume in blood-soaked gauze pieces). Thirty minutes prior to awakening patients were given morphine 0.15 mg/kg and fentanyl 2.5 µg/kg intravenously.

A 21-gauge catheter was inserted in the adductor canal after surgery, with the patient still under general anaesthesia. Following proper sterile preparations, a systematically cross-sectional anatomical survey, from proximal to distal thigh, was performed with a linear high-frequency ultrasound transducer (GE Logiq e, Waukesha, WI, USA). The adductor canal was identified approximately at the mid-thigh level, with the femoral artery, femoral vein, and the saphenous nerve deep to the sartorius muscle between the vastus medialis muscle and the adductor longus muscle. At this point, the saphenous nerve usually lies anterior to the femoral artery. Parallel to and in plane with the transducer, a 10-cm, 18-gauge, Tuohy needle (Braun Medical, Melsungen Germany) was inserted in an anteromedial to posterolateral direction. With the tip of the needle located in the adductor canal close to the saphenous nerve (if seen), 10 ml of NaCl was injected to distend the canal and to facilitate catheter threading. A 21-gauge catheter was inserted approximately 5 cm beyond the needle tip. The catheter was then slowly retracted, during real-time ultrasound-guided assessment of the spread of 5- to 10-ml NaCl injected through the catheter to obtain and verify the correct position. All catheters were inserted by one of two anaesthesiologists (UG, BG), both with considerable experience in ultrasound-guided nerve blocks.

According to randomisation, 30 ml of ropivacaine 0.75% or saline was given via the catheter after obtaining a pre-blockade pain score. The administration of study medication was protocolled for 30 min post-operatively (T = 0 defined as end of surgery). All patients received a patient-controlled analgesia (PCA) pump with morphine intravenously (bolus 2.5 mg, lock-out time 10 min, no background infusion). In addition, supplemental boluses of 2.5 mg morphine and/or 0.05 mg fentanyl were administered intravenously if analgesia was inadequate, as considered by the patient in the post-operative care unit (0.1 mg of fentanyl was considered equipotent with 10 mg of morphine). In case of moderate-to-severe nausea or vomiting, patients received 4 mg of ondansetron intravenously, with supplemental doses of 1 mg if needed.

Outcomes

The primary end point was pain during 45-degree active flexion of the knee at 1 h post-operatively, 30 min after administration of study medication. Secondary end points included pain during active flexion of the knee and at rest calculated as area under the curve (AUC) for the interval 1–6 h

post-operatively, changes in pain scores from 0.5 to 1 h post-operatively between groups, cumulated morphine consumption for the interval 0.5–6 h post-operatively, post-operative nausea and vomiting, ondansetron consumption, and sedation.

Assessment of outcomes

Outcomes were assessed at 0.5, 1, 2, 3, 4, 5, and 6 h post-operatively. A visual analogue scale (VAS) was used to evaluate pain (0 mm = no pain, and 100 mm = worst imaginable pain). A four-point scale was used to evaluate nausea and sedation (0 = no nausea/sedation, 1 = light, 2 = moderate, 3 = severe), and number of vomiting episodes (with a volume grater than 10 ml) was registered. The investigators tutored all patients pre-operatively in the use of the PCA system and in the VAS. All outcomes were assessed by one of the two investigators MHH or PJ. Following completion of the study, all patients received a bolus of 30-ml 0.75% ropivacaine through the catheter. The success rate of the block was assessed by testing for sensation of cold at 6.5 h post-operatively in the middle part on the medial side of the lower leg.

Sample size

We estimated a mean visual analogue pain score during flexion of the knee of 75 mm [standard deviation (SD) 20][4] and considered a reduction of 20 mm to be clinically relevant. With $\alpha = 0.05$ and a power of 80%, 17 patients would be required in each group. To compensate for dropouts, we planned for an inclusion of 40 patients.

Randomisation and blinding

The pharmacy prepared the study medication in identical pre-packed boxes, one for each patient. These were consecutively numbered according to a computer-generated block randomisation list performed by the pharmacy in a 1:1 ratio, each block containing 10 numbers, except for the last block which only contained four numbers. The study participants were assigned consecutive numbers upon inclusion to the study and received the study medication in the corresponding boxes. The box containing the study medication was given to a nurse not involved in the study or in the care of the patient and administered in neutral syringes and handed over to the investigators.

All investigators, staff, and patients were blinded to the treatment groups. When enrolment of all patients was completed and data were computed, the pharmacy provided the randomisation key dividing patients into blinded intervention groups (named A and B) for statistical analyses. The randomisation key was first broken once the statistical analyses had been performed.

Statistical analysis

Statistical analyses were performed using SPSS 18 (SPSS, Chicago, IL, USA). The Kolmogorov–Smirnov test was used to test for normality, and data are presented as mean and SD, or with medians and range as appropriate. The AUC was calculated for VAS pain scores for the period 1–6 h post-operatively. The independent samples *t*-test was used to compare data that were normally distributed (morphine consumption and pain scores), while data that were not normally distributed were compared using the Mann–Whitney *U*-test for unpaired data (nausea, number of vomits, and sedation). We calculated the arithmetic mean scores for comparison of nausea and sedation, by attributing numerical values to the scores from each patient. Categorical data (ondansetron) were analysed using the chi-squared test. The nature of the hypothesis testing was two-tailed. A P value of less than 0.05 was considered statistically significant. The investigators performed all statistical analyses.

Results

Of 290 patients screened for inclusion, 42 patients were randomised, and 41 patients were analysed. One patient was randomised but excluded perioperatively before receiving the study medication because of the exclusion criterion: a daily intake of strong opioids (oxycodone). Another patient (ropivacaine group) withdrew her consent at 4 h post-operatively (available data for the first 4 h included in the analyses). For further details on patient flow through the study, see Fig. 1. Baseline values were similar between the groups (see Table 1).

At 1 h post-operatively, VAS pain scores during 45-degree flexion of the knee (primary end point) were 58 ± 22 mm in the ropivacaine group compared with 67 ± 29 mm in the placebo group, $P = 0.23$. Notably, according to protocol, the study medication was scheduled for administration at 30 min post-operatively, but because of logistic challenges, this was delayed up until 1 h post-operatively in 10 patients (six patients in the ropivacaine group and four patients in the placebo group). After excluding these patients, we performed a per-protocol analysis, which showed that the VAS pain scores during 45-degree flexion of the knee at 1 h

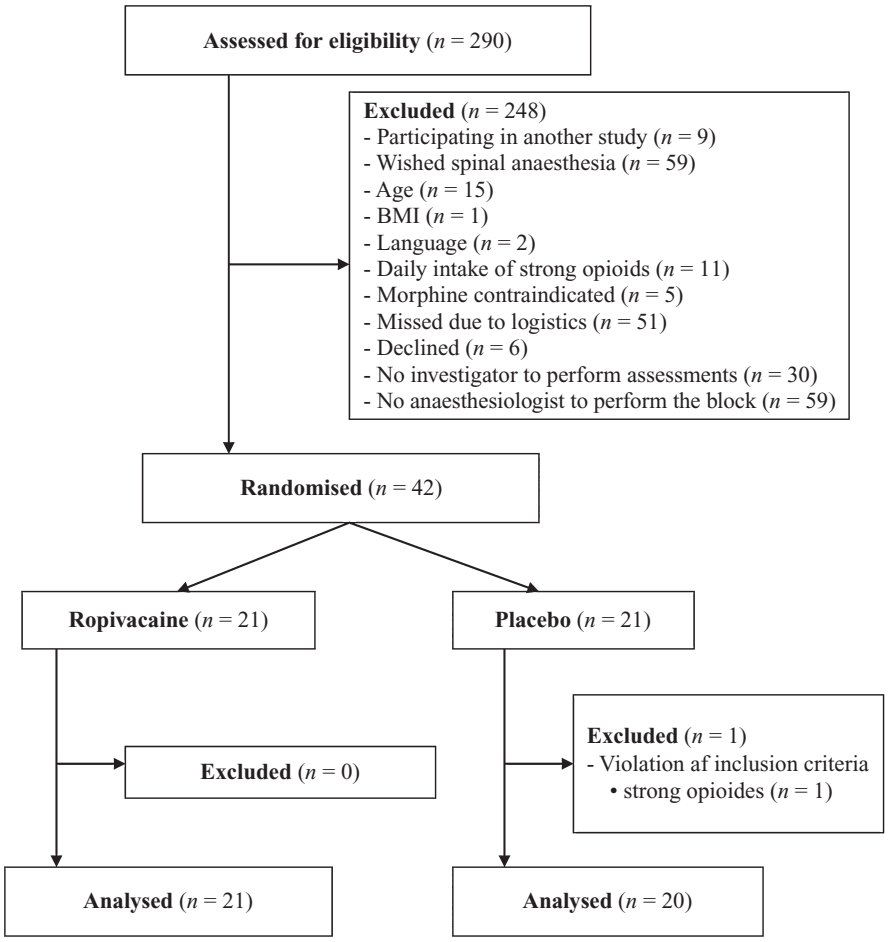

Fig. 1. Flow diagram of patients enrolled in the study. BMI, body mass index.

post-operatively were 56 ± 32 mm in the ropivacaine group and 68 ± 38 mm in the placebo group. However, there was still no statistically significant difference between the groups, $P = 0.19$.

Pain during flexion of the knee calculated as AUC for the interval 1–6 h post-operatively was significantly reduced in the ropivacaine group compared with the placebo group: mean difference in averaged VAS = –12 mm, 95% confidence interval (CI) = –2 to –21 mm, $P = 0.02$ (Fig. 2). No significant difference was demonstrated for pain at rest calculated as AUC: mean difference in averaged VAS = –7 mm, 95% CI = +1 to –16 mm, $P = 0.08$ (Fig. 3).

Patients had severe and comparable pain at 0.5 h post-operatively (before administration of study medication), both during flexion of the knee (66 ± 23 mm vs. 67 ± 31 mm) and at rest (58 ± 26 mm vs. 62 ± 30 mm, mean ± SD) in the ropivacaine and placebo group, respectively. From 0.5 to 1 h post-operatively, pain during flexion of the knee was reduced with mean 9 ± 23 mm in the ropivacaine group compared with an increase of 0.2 ± 17 mm in the placebo group ($P = 0.16$ between groups). Pain at rest during the same time interval was reduced with 10 ± 22 mm in the ropivacaine group compared with 0.0 ± 16 mm in the placebo group ($P = 0.11$).

The ropivacaine group had a total morphine consumption (0.5–6 h post-operatively) of 18 ± 11 mg compared with 28 ± 21 mg in the placebo group, mean difference = –10 mg, 95% CI = +0.6 to –21 mg, $P = 0.06$ (Fig. 4).

Patients in the ropivacaine group experienced significantly less nausea than patients in the placebo group ($P = 0.04$), but there were no other differences between the groups regarding side effects: sedation $P = 0.53$, vomiting episodes $P = 0.15$, ondansetron consumption $P = 0.77$.

The success rate of the block, assessed as loss of sensation of cold in the saphenous area, was 95% (35/37, both block failures were in the placebo group, four patients not tested). There were no harms registered during the study or the following 24 h.

Table 1

Patient characteristics and perioperative data.

	Ropivacaine group	Placebo group
Number of patients	21	20
Sex (male/female)	12/9	11/9
Age (years)	66 (11)	69 (11)
Height (cm)	172 (10)	172 (9)
Weight (kg)	90 (16)	82 (13)
Preoperative VAS pain at rest (mm)	2 (6)	8 (17)
Preoperative VAS pain at 45-degree flexion of the knee (mm)	13 (21)	13 (20)
Habitual analgesics:		
None	11/21	11/20
Paracetamol and/or ibuprofen	6/21	7/20
Weak opioids*	4/21	2/20
Operated side (right/left)	9/12	11/9
Duration of surgery (min)	73 (16)	72 (11)
Blood loss (ml)	42 (55)	27 (44)
Isotonic sodium chloride (ml)	869 (256)	837 (369)
Hydroxyethyl starch colloids (ml)	24 (109)	0 (0)

Values are reported as number of subjects or mean (standard deviation).
*Weak opioids = codeine or tramadol.
VAS, visual analogue scale.

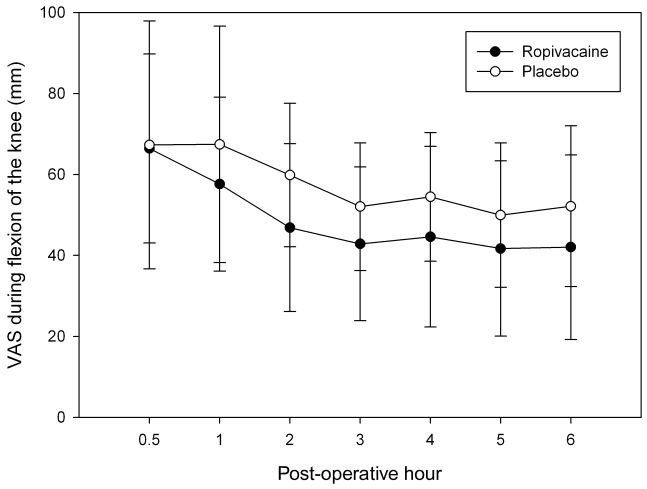

Fig. 2. Visual analogue scale (VAS) scores (0–100 mm) for pain during 45-degree flexion of the knee in patients receiving adductor-canal-blockade with ropivacaine or saline. Values are mean (error bars are standard deviation). There was no difference between the groups at 1 h post-operatively (P = 0.23), but pain scores calculated as area under the curve for the interval 1–6 h post-operatively were significantly reduced in the ropivacaine group compared with the placebo group (P = 0.02). VAS = visual analogue scores.

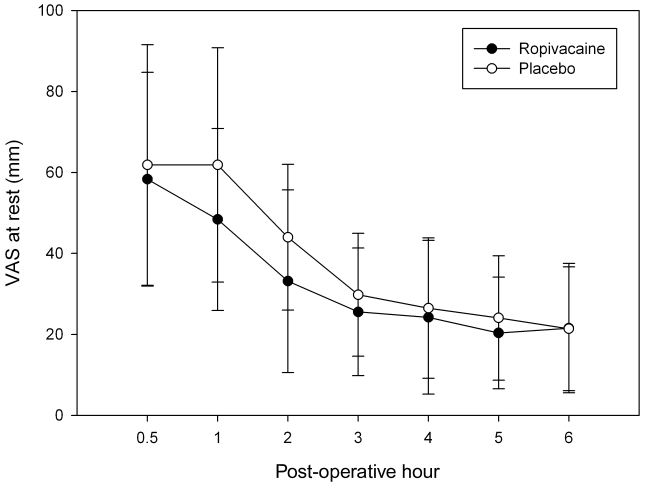

Fig. 3. Visual analogue scale (VAS) scores (0–100 mm) for pain at rest in patients receiving adductor-canal-blockade with ropivacaine or saline. Values are mean (error bars are standard deviation). There was no statistically significant difference in pain scores at rest calculated as area under the curve for the interval 1–6 h post-operatively (P = 0.08).

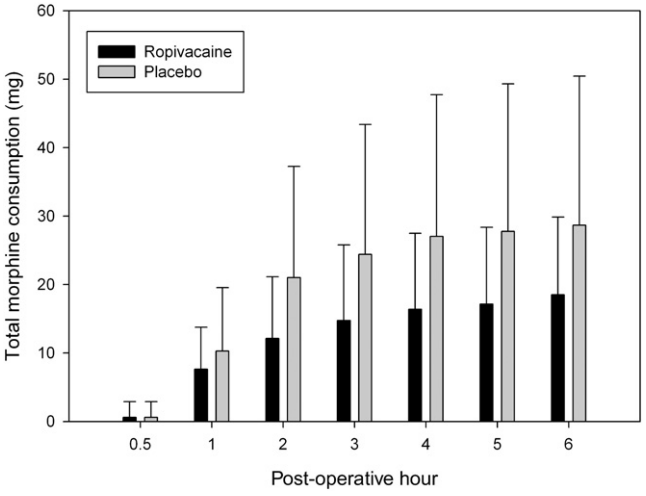

Fig. 4. Cumulative morphine consumption in patients receiving adductor-canal-blockade with ropivacaine or saline. Data are expressed as mean (error bars are standard deviation). Cumulate morphine consumption from 0.5–6 h post-operatively was reduced with 37% in the ropivacaine group compared with the placebo group, but this difference was not statistically significant (P = 0.06).

Discussion

The aim of this proof-of-concept study was for the first time to evaluate the adjunctive analgesic effect of ACB on established pain after TKA in patients receiving general anaesthesia and a basic analgesic regimen with oral ibuprofen 400 mg and paracetamol 1 g. Our primary end point, pain during flexion of the knee at 30 min after administration of study medication, was not significantly different between

groups. We demonstrated, however, that the ACB significantly reduced pain scores during flexion of the knee, calculated as AUC, compared with placebo. In addition, morphine consumption was reduced by 37% in the ropivacaine group compared with the placebo group, although this difference was not statistically significant ($P = 0.06$). Apart from a significant reduction in nausea in the ropivacaine group, there were no differences in morphine-related side effects or in pain at rest between the groups.

Recently, Jenstrup et al.[5] presented the only randomised, controlled trial so far, investigating the analgesic efficacy of continuous ACB, with intermittent boluses, in patients scheduled for TKA in spinal anaesthesia. In that study, the ACB was initiated immediately after surgery when the spinal anaesthetic was still effective and patients were free of pain. The study demonstrated a significant reduction in both morphine consumption and pain at flexion of the knee during a 24-h observation period.

In the present randomised, controlled trial, we investigated the analgesic effect of ACB in patients with established acute, severe post-operative pain documented by pre-blockade pain ratings. Our study confirmed the results obtained by Jenstrup et al.[5], although our observed difference in morphine consumption was not statistically significant.

As all patients were given a bolus of 20-ml ropivacaine 0.75% at 6 h post-operatively, after performing the 6-h assessments, we were able to calculate the block success rate without unblinding the study. Our block success rate of 94% is comparable with other studies blocking the saphenous nerve in the adductor canal.[6,7] Tsai and colleagues[8] reported a lower success rate, but as this was a retrospective study, the authors could not assess the success rate by sensation of cold but used a more stringent success criterion: no pain (the study did not involve TKA patients). Notably, residents performed 74% of the blocks in the study by Tsai et al.[8] Considering the stringent success criterion and the high proportion of blocks performed by residents, this success rate is relatively high. As the femoral artery is used as a landmark on the US image, it is not necessary to visualise the nerve when performing the block, which makes it a relatively simple technique.

This preliminary study has several limitations. First, our sample size was too small to permit final conclusions. Thus, based on the present data (morphine consumption of 28 ± 21 mg, mean $\pm$ SD), approximately 70 patients should enter a similar study in order to detect a 30% reduction in morphine requirements, with $\alpha = 0.05$ and $\beta = 0.2$. Second, our primary outcome was pain during flexion of the knee at 1 h post-operatively. T = 0 was defined as the time for end of surgery. Because of logistic reasons, 10 patients were still asleep at 0.5 h post-operatively and received the study medication somewhat later than the scheduled 0.5 h post-operatively, not leaving enough time for the block to reach maximum effect. This is indicated by the significant difference in total pain scores during the entire observation period compared with insignificant results at 1 h post-operatively. This could have been avoided if we had defined T = 0 as the time for waking up the patient or injecting the study medication. A per-protocol analysis, excluding the patients who did not receive the study medication as scheduled, resulted in a larger difference between the groups, but this did not meet statistically significance ($P = 0.19$). The large SD and small sample size in the per-protocol analysis is obviously a limitation to this analysis. Our primary and secondary end points were pre-defined in the protocol of the study, reported at http://www.clinicaltrials.gov and in the result section of this manuscript. A post-hoc exploratory analysis reveals, however, that pain during flexion was significantly reduced at 2 h post-operatively compared with baseline values in the ropivacaine ($P = 0.002$), but not in the placebo group ($P = 0.24$), and that the difference between groups at this time point was statistically significant ($P = 0.04$). Third, patients received rather large amounts of morphine and fentanyl in both study groups before receiving the study medication, which together with the ibuprofen and paracetamol administered pre-operatively may have blunted the effect of the ACB, per se. Obviously, in a clinical study of severe pain, it is essential to treat all included patients sufficiently, including a basic analgesic regimen such as paracetamol/ibuprofen and escape treatment with opioids as needed by the patients. Finally, we only assessed patients for 6 h post-operatively. Muscle function and mobilisation were not evaluated. A recent study demonstrated improved ambulation ability with ACB[5] compared with placebo, but further studies are needed to assess quadriceps muscle strength with objective methods.

The most important question, though, is whether the observed analgesic effect of the ACB is to be considered clinically relevant. Based on the calculated mean differences and 95% CIs for pain and morphine requirements reported in this preliminary study (see result section), future well-powered, controlled studies may be able to detect treatment

difference of 20–50% for both end points. We consider such differences to be clinically relevant.

In conclusion, this proof-of-concept study in patients with established and severe pain after TKA shows promising results regarding the analgesic efficacy of ACB, with a significant reduction in pain during 45-degree flexion of the knee in the early post-operative period compared with placebo. However, the study was not sufficiently powered to permit final conclusions, and future well-powered studies are needed to validate the analgesic and opioid-sparing effect of ACB and to investigate the effect of this blockade on muscle strength and ambulation ability.

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Conflicts of interest: None.

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Address:
Pia Jæger
Department of Anaesthesia 4231
Centre of Head and Orthopaedics
Rigshospitalet, Blegdamsvej 9
DK-2100 Copenhagen Ø
Denmark
e-mail: pia.jaeger@rh.regionh.dk