Section Editor: **Richard Brull**

Effect of Total Dose of Lidocaine on Duration of Adductor Canal Block, Assessed by Different Test Methods: A Report of Two Blinded, Randomized, Crossover Studies in Healthy Volunteers

Pia Jæger, MD, PhD,* Zbigniew J. Koscielniak-Nielsen, MD, DMSci,* Karen Lisa Hilsted, RN,* Ulrik Grevstad, MD, PhD,† Volkert Siersma, PhD,§ Maria Louise Fabritius, MD,* and Jørgen Berg Dahl, MD, DMSci, MBA‡

BACKGROUND: The binary aims of this study were to investigate the effect of total dose of lidocaine on duration of an adductor canal block (ACB) and to validate different methods used to assess nerve blocks.

METHODS: We performed 2 blinded, randomized, controlled crossover trials, including healthy, young men. In study 1, 14 subjects received 4 ACBs with saline and 40, 80, and 160 mg lidocaine. In study 2, 14 new subjects received 2 ACBs with 100 and 300 mg lidocaine. We kept volume constant at 20 mL for all blocks, only altering concentration. ACB duration was assessed every hour postblock using mechanical (primary outcome) and temperature discrimination; warmth and heat pain detection thresholds; pain during heat stimulation; and tolerance to electrical current in the saphenous distribution. Finally, we measured quadriceps femoris muscle strength (clinical trial registration: NCT02172729).

RESULTS: In study 1, block duration assessed by mechanical discrimination differed significantly when comparing the 40-mg dose with the 80-mg dose (mean difference, 1.15 hours; 99% confidence interval [CI], 0.38–2.09 hours) and with the 160-mg dose (mean difference, 0.92 ours; 99% CI, 0.17–1.62). However, there was no difference between the 80-mg and 160-mg doses (mean difference, −0.23 hour; 99% CI, −1.12 to 0.46 hours). Neither for the secondary outcomes were there any differences between the 80- and 160-mg doses (99% CI including 0). Because of 38% (5/13) failed blocks in the 40-mg group, we decided to perform study 2. In study 2, all but 1 test showed no difference in duration despite a 3-fold increase in dose. The temperature discrimination test showed 100% sensitivity and specificity for differentiating between the presence and absence of block and was the only test with scores >90% for both parameters.

CONCLUSIONS: We did not find evidence that increasing the total dose of lidocaine may prolong duration of an ACB. The temperature discrimination test was the only test with scores >90% for both specificity and sensitivity. (Anesth Analg 2016;123:1026–32)

Success rate, onset time, and duration are important clinical factors for determining the effectiveness of a peripheral nerve block (PNB). Pharmacodynamics of local anesthetics (LAs) such as volume, concentration, and total dose are believed to affect these determinants, but the evidence is contradictory.[1–14] Some of the discrepancy found in past studies may be explained by differences in the applied regional techniques, anatomic locations, LA types, volumes and concentrations, and methods used to assess block characteristics.

Although motor block is usually assessed by voluntary muscle contraction, the somatosensory system includes different submodalities, and several measurement tools can be used. Many of these assessment tools have been validated in other settings, but their accuracy in determining the presence or absence of a PNB is unknown.

We performed 2 separate but conceptionally identical studies in healthy volunteers. There were 2 aims for the studies: (1) to investigate the effect of LA dose on block duration; and (2) to validate different measurement tools that can be used to detect the presence of a PNB. We hypothesized that increasing the total dose of lidocaine prolongs duration of an adductor canal block (ACB) assessed by discrimination of mechanical discrimination (pinprick, primary outcome). The secondary outcomes were duration of block assessed by temperature discrimination (alcohol swab), warmth and heat pain detection thresholds (HPDTs), pain during tonic heat stimulation, tolerance to transcutaneous electrical current, and quadriceps muscle strength. A placebo group was included as a gold standard for our second aim to assess

From the *Department of Anaesthesia, Centre of Head and Orthopaedics, Copenhagen University Hospital, Rigshospitalet, Denmark; †Department of Anaesthesia and Intensive Care Medicine, Copenhagen University Hospital, Gentofte Hospital, Hellerup, Denmark; ‡Department of Anaesthesia and Intensive Care Medicine, Copenhagen University Hospital, Bispebjerg Hospital, Copenhagen, Denmark; and §The Research Unit for General Practice and Section of General Practice, Department of Public Health, University of Copenhagen, Copenhagen, Denmark.

Accepted for publication June 28, 2016.

Funding: Departmental.

The authors declare no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.anesthesia-analgesia.org).

Reprints will not be available from the author.

Address correspondence to Pia Jæger, MD, PhD, Department of Anaesthesia, Centre of Head and Orthopeadics, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark. Address e-mail to pia.therese.jaeger@regionh.dk.

DOI: 10.1213/ANE.0000000000001517

the accuracy of the different test methods. Study 2 was performed because we considered the results of study 1 inconclusive.

METHODS

We conducted 2 separate, blinded, and randomized controlled crossover studies at Rigshospitalet, University of Copenhagen, Copenhagen, Denmark. Approval was obtained from the Regional Research Ethics Committee (H-4-2013-051 and H-6-2014-025), the Danish Medicine Agency (2013-001822-24 and 2014-001752-31), and the Danish Data Protection Agency before study commencement. Both studies were monitored by the Copenhagen Good Clinical Practice Unit, Copenhagen University and prospectively registered at the EudraCT database (2013-001822-24 and 2014-001752-31 for studies 1 and 2, respectively). Fourteen subjects were included into study 1, from June 13 to 27, 2013, and another 14 subjects into study 2, from June 30 to July 4, 2014. We obtained written informed consent from all participants before study entry.

Study 2 was identical to study 1 in all aspects, except for lidocaine doses, study population, and that study 1 included a placebo treatment. We included men aged 18 to 30 years with a body mass index of 18 to 25 kg/m^2 and American Society of Anesthesiologists physical status I. Exclusion criteria were allergy to LAs, non-Danish speakers, inability to cooperate, alcohol or drug abuse, neuromuscular pathology, previous trauma or surgery to the leg, diabetes mellitus, intake of opioids, or steroids within the last 4 weeks or intake of any analgesic during the past 48 hours. In addition, for study 2, it was an exclusion criterion to have participated in study 1.

Block Performance

Each subject received bilateral ACBs with 20 mL of study medication on each of the study days. The blocks were performed at the midthigh level using a linear 12-L ultrasound probe (Logiq e; GE, Waukesha, WI) and a 22-gauge, 80-mm, long insulated needle (Stimuplex D Plus; B. Braun Medical, Melsungen, Germany). Twenty milliliters of study medication was injected into the adductor canal, lateral to the femoral artery and in proximity of the saphenous nerve, using an in-plane technique as described previously.[15] All blocks were performed by anesthesiologist experienced in PNBs (Z.J.K.-N., D.L.I., and U.G.).

We monitored the subjects for any serious adverse events, both deathly and life-threatening, and events leading to hospitalization, disability, or permanent damage. The subjects were under constant observation by the investigators during the complete study period, until the block had completely wore off and muscle strength and sensation had returned to normal. Thus, any toxic reaction or nerve damage would present under the observation of the investigators.

Study Medication and Blinding

In study 1, each subject received 4 different treatments: placebo, 40, 80, and 160 mg lidocaine (20 mL of isotonic saline and 0.2%, 0.4%, and 0.8% lidocaine, respectively). The 4 treatments were administered as bilateral blocks during 2 study days separated by a minimum of a 2-day washout period in between. In study 2, each subject received 2 treatments during 1 single study day: 100 and 300 mg lidocaine (20 mL of 0.5% and 1.5% lidocaine, respectively). The treatments were administered as bilateral ACBs in a randomized order.

The pharmacy prepared computer-based randomization lists and the study medication for both studies. The study medication was prepared in identical glass containers. Both isotonic saline and lidocaine are transparent liquids identical in appearance, ensuring blinding of subjects and all personnel (including outcome assessors, investigators, and anesthesiologists performing the blocks). The glass containers were labeled with subject numbers, right or left leg, and study day 1 or 2 (only applicable in study 1). Subjects were assigned consecutive numbers on inclusion into the study and received the corresponding study medication, thus ensuring allocation concealment. For each study, blinding was retained until completion of data analysis (data were analyzed using a blinded group nomination provided by the pharmacy).

Outcome Assessments

All sensory tests were performed within the saphenous nerve distribution: in the medial part of the lower leg, distal to the tibial tubercle, and proximal to the medial malleolus. The mechanical discrimination (pinprick, 18-G needle) and temperature discrimination (alcohol swab) tests were assessed using the lateral part of the ipsilateral thigh as a reference. The response was dichotomized into normal sensation (inducing sharp/cold sensation equal to that in the reference area) or abnormal (blunt or absent) sensation. We assured normal sensation in the reference area preblock. An ACB does not affect the lateral part of the thigh, and sensation in the reference area did not change during the study period.

Warmth detection threshold (WDT), HPDT, and maximum pain during tonic heat stimulation were assessed using a computer-controlled thermode (2.5 cm^2, Thermotest; Somedic A/B, Hörby, Sweden). The baseline value for the thermode during the WDT and HPDT was 32°C with an incremental increase in temperature by 1°C every 1 second. The subjects were instructed to press a button once they felt warmth (WDT) or at the first sensation of pain (HPDT). Pressing the button terminated the assessment. If no threshold was detected, the test was terminated when the thermode reached a temperature of 52°C. The mean value of 4 tests performed at each time point was used for analysis. For the tonic heat stimulation test, the temperature of the thermode was increased to 45°C and retained for 30 seconds. Subjects were instructed to report maximum pain during the test on a visual analog scale (0–100 mm).

We assessed tolerance to transcutaneous electrical current using a peripheral nerve stimulator (TOF-Watch-SX monitor; Organon Ireland Ltd., a division of MSD, Swords, Co., Dublin, Ireland). Current was increased from 0 mA, in 5-mA increments, until the subject reported mild discomfort or the maximum stimulation of 60 mA was reached.

Finally, we assessed quadriceps muscle strength as maximum voluntary isometric contraction (MVIC) with a handheld dynamometer (Lafayette Instrument, Lafayette, IN). As described previously, we placed the subjects in a seated position and placed the dynamometer under a nonelastic Velcro strap attached to the examination couch.[15] At each

time point, the subject performed 3 contractions, and the mean value was calculated. The postblock values were then calculated as a percent of the preblock baseline value.

Subjects were trained and familiarized with the tests before baseline assessment. All tests were performed preblock (baseline values) and every hour postblock until normalization of values. The following criteria were used for defining normalization of values: sensation corresponding to reference area (mechanical and temperature discrimination tests), thresholds <2°C above the baseline value (WDT and HPDT), pain scores <10 mm above the baseline value (tonic heat test), tolerance corresponding to <5 mV above the baseline value (electrical current), and quadriceps strength <10% below baseline value (MVIC). The cutoff points applied were chosen based on a pilot study performed before study commencement. The same investigator performed all measurements in 1 single subject (P.J., U.G., K.L.H., or M.L.F.).

The primary outcome for both studies was the difference in block duration between lidocaine doses assessed by mechanical discrimination. Secondary outcomes were difference in duration assessed by temperature discrimination, WDT, HPDT, pain during tonic heat stimulation, tolerance to transcutaneous electrical current, and MVIC. Finally, we examined the validity of the measurement tools in differentiating between the presence and absence of block and compared different cutoff points, when appropriate.

Statistics

The distributions of the baseline data and the various measurements of block duration are presented as medians (range). We evaluated the differences in block duration among the 3 lidocaine doses (40, 80, and 160 mg) in study 1 and the 2 doses (100 and 300 mg) in study 2, respectively, as mean block duration between the dose groups.

We used the 1-hour postblock assessments from both studies and all test methods to assess the accuracy of the different tests by calculating their predictive quality. Because there is no recognized gold standard for assessing the presence or absence of a block, we classified subjects according to whether they had received a block with lidocaine (block group) or placebo (no block group). However, failed blocks (defined as no change in any of the sensory tests at 1 hour postblock) were moved to the no block group. Predictive quality was evaluated as sensitivity and specificity for the various test methods for various cutoff values and their respective area under the curve; for binary predictors, this is the mean of the sensitivity and specificity.

To reduce the chance of false-positive findings, we constructed 99% confidence intervals (CIs) for the mean differences in block duration and the measures of predictive quality using a nonparametric bootstrap method. By this method, bootstrapped replicate data sets are generated separately for the 2 studies by sampling an equally sized data set with replacement from the study participants (not the individual observations), thereby retaining possible correlation of observations on the same study participant in the replicated data. The 99% CI is then constructed using the 0.5% and 99.5% percentiles from 10,000 bootstrapped replicates of the corresponding estimate. The method has no distributional assumptions. We considered a 99% CI not including 0 to be statistically significant.

Finally, we performed a simulation study (Supplemental Digital Content, Appendix 1, http://links.lww.com/AA/B467) showing that a nonparametric bootstrapped 99% CI using data from only 14 observations still gives CIs with the nominal 99% coverage.

Sample Size Calculation

We considered a 60-minute prolongation of the block to be clinically relevant. On the basis of a previous study of an intermediate-acting LA, we assumed a SD for the duration of 60 minutes.[5] With this SD assumption, a significance level of 0.05%, and a power of 90%, 13 subjects would be needed to detect a mean difference of 60 minutes between groups. Assuming an equal prolongation of effect between each doubling of the total dose (40 mg vs 80 mg vs 160 mg), we considered a total of 13 subjects to be sufficient for study 1 using a crossover design. To compensate for dropouts and uncertainty in the SD, we planned to include a total of 14 subjects. We made the same assumptions for study 2 and included 14 new subjects.

RESULTS

In study 1, we included 14 subjects. All subjects completed the study except 1, who fell sick on day 2 (resulting in missing data for the paired analysis, but available data are included in the Figures and in the assessment of validity). For study 2, we included 14 new subjects, who all completed the study and were included in the data analysis. There were no adverse or serious adverse events in either study. Complete block resolution was observed in all subjects, meaning that all assessments returned to values within the predefined reference value for normalized data described in the "Methods" section. Subjects' characteristics are presented in Table 1.

Study 1

Duration of sensory block assessed by mechanical discrimination (primary outcome) differed statistically significantly when the 40-mg dose was compared with both the 80-mg dose (mean difference, 1.15 hours; 99% CI, 0.38–2.09 hours) and with the 160-mg dose (mean difference, 0.92 hours; 99% CI, 0.17–1.62 hours). However, there was no difference between the 80- and 160-mg doses (mean difference, –0.23 hours; 99% CI, –1.12 to 0.46 hours). For the secondary endpoints, the only statistically significantly differences in duration (99% CI not including 0) were seen in the temperature discrimination test and the MVIC assessment. Similar to the mechanical discrimination test, there were no differences (<1 hour difference in mean duration and 99% CI including 0) between the 80- and 160-mg doses (Table 2).

Table 1. Subjects' Characteristics

	Study 1	Study 2
Age (y)	25 (21–26)	23 (18–29)
Height (cm)	183 (175–194)	183 (169–191)
Weight (kg)	74 (63–85)	76 (60–89)

Data are reported as median (range).

Table 2. Duration of Adductor Canal Block Across Lidocaine Doses in Study 1

	Median Block Duration (h)			Mean Difference (99% CI) (h)		
Test Method	40 mg	80 mg	160 mg	40 vs 80 mg	40 vs 160 mg	80 vs 160 mg
Mechanical discrimination	2 (0 to 4)	2 (0 to 5)	2 (0 to 4)	1.15 (0.38 to 2.09)[a]	0.92 (0.17 to 1.62)[a]	−0.23 (−1.12 to 0.46)
Temperature discrimination	2 (0 to 4)	4 (2 to 5)	4 (2 to 5)	1.23 (0.28 to 2.25)[a]	1.23 (0.38 to 2.05)[a]	0.00 (−1.00 to 0.89)
WDT	2 (0 to 4)	2 (1 to 3)	2 (0 to 5)	0.23 (−0.47 to 1.09)	0.38 (−0.31 to 1.25)	0.15 (−0.87 to 1.09)
HPDT	1 (0 to 5)	2 (0 to 5)	2 (0 to 3)	0.77 (−0.15 to 1.66)	0.46 (−0.80 to 1.60)	−0.31 (−1.23 to 0.54)
Tonic heat stimulation	2 (0 to 4)	3 (0 to 4)	3 (0 to 5)	0.61 (−0.27 to 1.55)	0.54 (−0.40 to 1.53)	−0.08 (−0.71 to 0.42)
Electrical current	0 (0 to 4)	0.5 (0 to 4)	0 (0 to 3)	0.60 (−0.85 to 1.91)	1.00 (−0.32 to 2.45)	0.25 (−0.75 to 1.04)
MVIC	0 (0 to 3)	1 (0 to 4)	0 (0 to 3)	0.69 (0.01 to 1.24)[a]	0.46 (−0.42 to 1.23)	−0.23 (−1.00 to 0.43)

Data are presented as median (range) and differences between lidocaine doses as mean values with constructed nonparametric bootstrapped 99% CIs. See the Supplemental Digital Content (Appendix 1, http://links.lww.com/AA/B467) for the Monte Carlo simulation showing the coverage of the 99% 2-sided CIs. Mechanical discrimination was the primary outcome of the study, and the other assessment methods were secondary outcomes.

Abbreviations: CI, confidence interval; HPDT, heat pain detection threshold; MVIC, maximum voluntary isometric contraction; WDT, warmth detection threshold.

[a]Marks statistical significance according to the bootstrapped 99% CIs.

Study 2

In study 2, we found no difference in mean duration of block assessed by mechanical discrimination between the 100- and 300-mg doses: median duration, 3.5 hours (0–5 hours) versus 3.5 hours (1–5 hours; mean difference, 0.00 hour; 99% CI, −0.93 to 1.00). Neither were there any statistically significantly differences in the secondary outcomes, apart from in the HPDT test (Table 3).

Predictive Quality of the Different Assessment Tools

Five of the 13 subjects in study 1 only had partial blocks after an ACB with 40 mg lidocaine (defined as no change in at least 2 of the sensory tests at 1 hour postblock). Because of the many unreliable blocks obtained with this treatment, we decided to exclude the 40-mg dose for the predictive quality assessments. Furthermore, 1 subject had a failed block (100 mg lidocaine, study 2) with no change in any of the sensory tests at 1 hour postblock, and this subject was moved to the no block group for the quality assessments.

The temperature discrimination test was the only test displaying sensitivity and specificity >90% for both parameters with 100% specificity and 100% sensitivity (Table 4). Receiver operating characteristic curves for the different tests and the corresponding area under the curve are presented in the Figure and Table 3. Using electrical stimulation and MVIC for diagnosing the presence or absence of block was no better than guessing.

DISCUSSION

This study did not find evidence to support the hypothesis that increasing total dose of lidocaine prolongs duration of an ACB. In study 1, block duration was shorter after an ACB with 40 mg lidocaine, but there were no differences among the higher doses (mean differences, <1 hour and 99% CI including 0). Importantly, 5 of 13 subjects receiving the 40-mg dose only had partial blocks, considerably affecting block duration in this group. To ensure we were not overlooking a possible effect of total mass on block duration, we decided to perform study 2, administering higher doses of lidocaine with a larger increment between doses. Study 2 supported the findings of study 1 showing no statistically significant or clinically relevant difference in block duration despite a 3-fold increase in dose. The only significant difference between doses was seen in the HPDT test, showing a prolongation in block duration of 1 hour (99% CI, 0.07–2.00) in favor of the 300-mg dose. Considering the discrepancy in this finding compared with the other tests, and the finding that HPDT was not the test method with the highest predictive quality (Table 3), this is likely to be a result of chance (type 1 error). Thus, it seems that once we have achieved a full block, there is nothing gained in duration by simply increasing the total dose.

The primary determinant of LA pharmacodynamics is unknown. Although several previous studies found no relationship between LA pharmacodynamics and block duration,[1–3,8] recent studies using ultrasound have shown that decreasing LA volume, concentration, or dose may shorten block duration.[6,7,9,11,12,14] A possible explanation for the discrepancy among these studies may be that ultrasound has made it possible to reduce volumes to extremes that may compromise the effectiveness of a block. Nader et al[9] found no difference in sciatic block duration among volumes of 10 mL or more, but when volume was reduced to 5 mL or less, block duration was shortened. Nader et al[9] hypothesized that once an adequate number of a long-acting LAs are bound to the ion channels, the remaining molecules are gradually diminished and cannot act as a reservoir for further prolonging the nerve blockade. In our study, we used a fixed volume of 20 mL, but different concentrations of lidocaine, and thereby different total doses. Despite a 3-fold increase in total dose in study 2, we found no difference in duration. Interestingly, despite using an intermediate-acting LA with substantially shorter duration and time for absorption, our results nonetheless support the hypothesis proposed by Nader et al that after injecting a certain threshold dose, there is nothing gained by a simple increase in dose.

Another important finding of this study was that the temperature discrimination test showed 100% sensitivity and specificity for differentiating between the absence and presence of block at 1 hour postblock. Notably, we were not able to calculate CI for the temperature discrimination test's sensitivity and specificity (and a few of the other test methods) using a nonparametric bootstrap method, because all indications were positive and there was no variance. The high predictive quality of the temperature discrimination test was closely followed by the mechanical discrimination and thermal tests, all displaying high sensitivity and specificity, as well as high accuracy in the receiver operating characteristic curves. However, none of the other test methods displayed both sensitivity and specificity scores

Table 3. Duration of Adductor Canal Block Across Lidocaine Doses in Study 2

Test Method	Median (Range) Block Duration (h) 100 mg	300 mg	Mean (99% CI) Difference (h)
Mechanical discrimination	3.5 (0 to 5)	3.5 (1 to 5)	0.00 (−0.93 to 1.00)
Temperature discrimination	5 (0 to 5)	4 (3 to 6)	−0.21 (−1.00 to 0.43)
WDT	3 (1 to 5)	3 (2 to 5)	−0.14 (−0.79 to 0.43)
HPDT	2 (0 to 4)	3 (1 to 5)	1.00 (0.07 to 2.00)[a]
Tonic heat stimulation	3 (0 to 6)	2.5 (1 to 4)	−0.36 (−1.43 to 0.93)
Electrical current	1 (0 to 5)	2 (0 to 4)	0.64 (−0.43 to 1.79)
MVIC	0 (0 to 3)	0 (0 to 3)	0.50 (−0.29 to 1.00)

Data are presented as median (range) and differences between lidocaine doses as mean values with constructed nonparametric bootstrapped 99% CIs. See the Supplemental Digital Content (Appendix 1, http://links.lww.com/AA/B467) for the Monte Carlo simulation showing the coverage of the 99% 2-sided CIs.
Abbreviations: CI, confidence interval; HPDT, heat pain detection threshold; MVIC, maximum voluntary isometric contraction; WDT, warmth detection threshold.
[a]Marks statistical significance according to the bootstrapped 99% CIs.

Table 4. Validity of the Different Measurement Tools Used in the Studies

Variable	Cutoff Values	Sensitivity (99% CI), n = 54	Specificity (99% CI), n = 15	AUC (99% CI), n = 69
Mechanical discrimination	—	0.87 (0.73 to 0.98)	1.00 (0.75 to 1.0)	0.94 (0.86 to 0.99)
Temperature discrimination	—	1.00 (0.92 to 1.0)	1.00 (0.75 to 1.0)	1.00 (0.89 to 1.00)
WDT	1°C	0.96 (0.79 to 0.98)	0.40 (0.14 to 0.93)	0.68 (0.54 to 0.93)
	2°C	0.94 (0.82 to 0.98)	0.80 (0.06 to 1.00)	0.87 (0.47 to 0.97)
	3°C	0.89 (0.79 to 0.97)	0.87 (0.06 to 1.00)	0.88 (0.44 to 0.98)
HPDT	1°C	0.89 (0.75 to 0.98)	0.87 (0.06 to 1.00)	0.88 (0.43 to 0.99)
	2°C	0.80 (0.65 to 0.94)	1.00 (0.75 to 1.0)	0.90 (0.83 to 0.97)
	3°C	0.78 (0.62 to 0.93)	1.00 (0.75 to 1.0)	0.89 (0.81 to 0.96)
Tonic heat stimulation	5 mm	0.91 (0.80 to 0.98)	0.80 (0.06 to 1.00)	0.85 (0.44 to 0.95)
	10 mm	0.83 (0.69 to 0.96)	0.87 (0.06 to 1.00)	0.85 (0.38 to 0.94)
	15 mm	0.76 (0.61 to 0.89)	1.00 (0.75 to 1.0)	0.88 (0.80 to 0.94)
Electrical current	5 mV	0.52 (0.34 to 0.69)	0.67 (0.07 to 1.00)	0.59 (0.29 to 0.91)
	10 mV	0.37 (0.18 to 0.56)	0.80 (0.06 to 1.00)	0.59 (0.17 to 0.73)
MVIC	75%	0.11 (0.00 to 0.55))	1.00 (0.75 to 1.0)	0.56 (0.12 to 0.72)
	85%	0.28 (0.11 to 0.46)	0.93 (0.07 to 1.00)	0.60 (0.11 to 0.72)
	90%	0.33 (0.02 to 0.37)	0.87 (0.25 to 1.00)	0.60 (0.29 to 0.62)

Validity of the different measurement tools used to detect presence or absence of adductor canal blocks with saline, 80, 100, 160, and 300 mg lidocaine. We classified subjects according to whether they had received a block with lidocaine (block group, n = 54) or saline (no block group, n = 15). However, 1 subject had a failed block (defined as no change in any of the sensory tests at 1 h postblock) and was moved to the no block group. We constructed nonparametric bootstrapped 99% CIs adjusting for within-patient correlation. However, the bootstrap method could not be used when sensitivity and specificity was 1.0, in which cases we estimated the CI using standard formula for proportions. The reader should be aware that there is an increased risk of bias when ignoring the correlation.
Abbreviations: AUC, area under the curve; CI, confidence interval; HPDT, heat pain detection threshold; MVIC, maximum voluntary isometric contraction; WDT, warmth detection threshold.

above 90%. Compared with the thermal tests, the temperature and mechanical discrimination tests are cheaper, less time-consuming, and more feasible. Therefore, they may be preferred, especially in a clinical setting. The slightly lower predictive quality seen with the thermal tests probably reflects the larger reliability in these continuous variables. However, contrary to temperature discrimination, these continuous variables offer a more nuanced interpretation of the effect of the block. Although experimental models cannot substitute clinical studies, not all studies are feasible in a clinical setting. This is why we aimed to validate different measurement tools that can be used in an experimental setting. Because the HPDT and tonic heat stimulation tests assess the function of A and C pain fibers, they may more closely mimic the analgesic effect in a surgical setting than the mechanical and temperature discrimination tests.

The cutoff values used in the MVIC, WDT, HPDT, and tonic heat stimulation tests were chosen based on the results of a small pilot study. According to Table 4, the applied cutoff values showed the highest accuracy among the analyzed cutoff values or were essentially the same as the highest values. However, the choice of a cutoff value for a diagnostic test cannot be based on the accuracy of the test alone, but the relative importance of sensitivity and specificity in a clinical setting needs to be taken into consideration as well.

Contrary to the thermal tests, the MVIC and transcutaneous electrical current tests were no better than guessing in differentiating between the presence and absence of block. From previous studies, it is known that most patients have no affection of their quadriceps muscle after an ACB[15–19] and, therefore, the low sensitivity seen in the MVIC test should come as no surprise. However, specificity was relatively high, corresponding to the high validity and reliability found in previous studies.[20–22] The saphenous innervation in the tested area is limited to the skin. However, electrical current may affect deeper lying tissues, like muscles, and may therefore be unsuited for evaluating the sensory effect of an ACB in this area. Most PNBs affect both efferent and afferent neurons, and electrical current has recently been shown to be a reliable assessment tool for femoral nerve blocks.[23] Thus, the low predictive quality seen for MVIC and transcutaneous electrical current in this study is probably restricted for diagnosing the presence and absence of block after an ACB.

There are several limitations of this study. First, we used lidocaine that is not used clinically for an ACB, and our

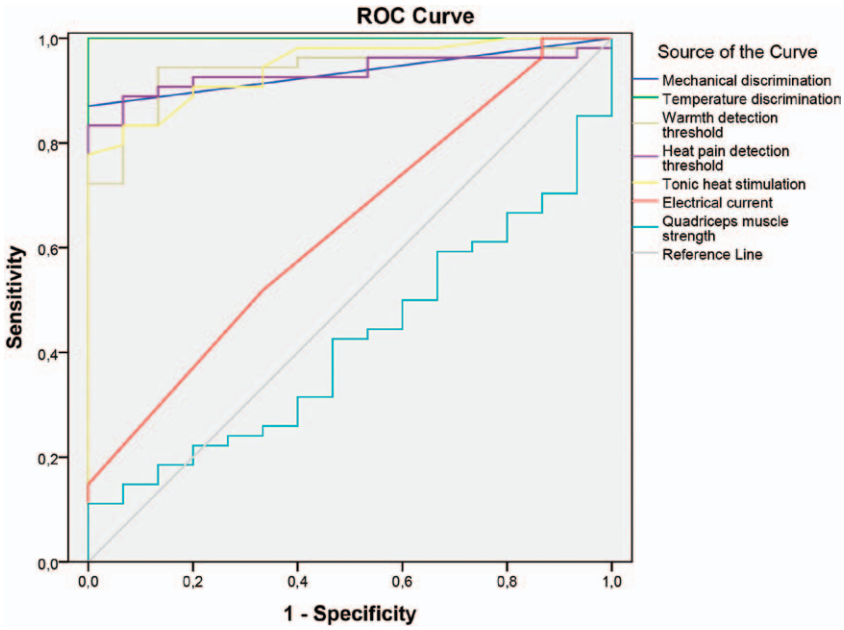

Figure. Receiver operating characteristic (ROC) curves of the accuracy of the different tests in differentiating between the presence and absence of block. The further the curve lays above the reference line, the more accurate the test. Based on their distances from the reference line, the temperature discrimination test is the most accurate test. The area under the curve and corresponding 99% confidence interval (CI) for the different tests were as follows: 0.94 (0.86–0.99) for the mechanical discrimination test, 1.00 (0.89–1.00) for the temperature discrimination test, 0.94 (0.84–1.0) for the warmth detection test, 0.93 (0.73–1.0) for the heat pain detection threshold test, 0.94 (0.86–1.0) for the tonic heat stimulation test, 0.64 (0.45–0.88) for the electrical current test, and 0.58 (0.45–0.80) for the maximum voluntary isometric contraction test. We constructed nonparametric bootstrapped 99% CIs adjusting for within-patient correlation.

results may not be applicable when other types of LA are used. Lidocaine was chosen for logistic reasons. Although the clinical relevance of lidocaine for an ACB may be questioned, it provided us with the interesting finding that even for an intermediate-acting LA, the primary determinant seems to be the initial binding of LA molecules, and no reservoir should be expected. Second, the diluted concentrations of lidocaine tested in study 1 are not used clinically but provided information of a possible threshold value. Considering the lack of difference in block duration (and block success rate) in study 2, despite a 3-fold increase in total dose, it seems unlikely that higher concentrations would have affected the results. Third, the ACB is primarily a sensory block, and the low predictive quality seen with the MVIC test in this study may not be applicable to motor block duration in another setting. Fourth, because of the small sample size, we were not able to test whether there was a differential carryover effect. Because the primary outcome was duration of block, the assessment period continued until all measurements were back to normal, and there was no longer any effect of the medication, thereby minimizing any carryover effect. However, there may have been a systemic carryover effect because of the bilateral treatments. There was no such effect seen in the placebo group (zero block duration for all assessments), but a small carryover effect cannot be entirely excluded. Fifth, although we used conservative CI, we did not adjust for multiple testing in any formal way because this would unreasonably jeopardize power. Therefore, the chance of false-positive findings may be larger than the conventional 5%.

This study involving healthy volunteers enabled us to perform several and frequent measurements postblock, which would not have been feasible in a surgical setting. Although an experimental setting removes the variability because of the surgical impact, the true analgesic effect of the block cannot be assessed. Finally, the findings of this study may not be applicable to other LA types, other volumes, continuous infusion regimens, multiple injection techniques, and anatomic locations.

In conclusion, we found that increasing concentration or total dose of lidocaine for an ACB did not increase block duration. The temperature discrimination test showed 100% specificity and sensitivity in differentiating between the presence and absence of sensory block. The MVIC and transcutaneous electrical current tests, on the other hand, are not reliable when assessing block duration after an ACB.

ACKNOWLEDGMENTS

The authors thank Dan Lou Isbye, MD, PhD, Department of Anaesthesia, Rigshospitalet, Copenhagen, for ensuring efficient study progress by performing blocks at odd hours. They also thank Birgitte Grøn, from Copenhagen University Hospital Good Clinical Practice Unit, Bispebjerg Hospital, Denmark, for monitoring the study.

DISCLOSURES

Name: Pia Jæger, MD, PhD.
Contribution: This author helped design the study, conduct the study, collect the data, analyze the data, and prepare the manuscript.
Name: Zbigniew J. Koscielniak-Nielsen, MD, DMSci.
Contribution: This author helped design the study, conduct the study, and prepare the manuscript.
Name: Karen Lisa Hilsted, RN.
Contribution: This author helped design the study, collect the data, conduct the study, and prepare the manuscript.
Name: Ulrik Grevstad, MD, PhD.
Contribution: This author helped design the study, conduct the study, collect the data, analyze the data, and prepare the manuscript.
Name: Volkert Siersma, PhD.
Contribution: This author helped design the study, analyze the data, and prepare the manuscript.
Name: Maria Louise Fabritius, MD.
Contribution: This author helped design the study, conduct the study, and prepare the manuscript.
Name: Jørgen Berg Dahl, MD, DMSci, MBA.
Contribution: This author helped design the study and prepare the manuscript.

This manuscript was handled by: Richard Brull, MD, FRCPC, and Edward Joseph Mascha, PhD.

REFERENCES

1. Krone SC, Chan VW, Regan J, et al. Analgesic effects of low-dose ropivacaine for interscalene brachial plexus block for outpatient shoulder surgery—a dose-finding study. *Reg Anesth Pain Med*. 2001;26:439–443.
2. Klein SM, Greengrass RA, Steele SM, et al. A comparison of 0.5% bupivacaine, 0.5% ropivacaine, and 0.75% ropivacaine for interscalene brachial plexus block. *Anesth Analg*. 1998;87:1316–1319.
3. Oberndorfer U, Marhofer P, Bösenberg A, et al. Ultrasonographic guidance for sciatic and femoral nerve blocks in children. *Br J Anaesth*. 2007;98:797–801.
4. Riazi S, Carmichael N, Awad I, Holtby RM, McCartney CJ. Effect of local anaesthetic volume (20 vs 5 ml) on the efficacy and respiratory consequences of ultrasound-guided interscalene brachial plexus block. *Br J Anaesth*. 2008;101:549–556.
5. Marhofer P, Eichenberger U, Stöckli S, et al. Ultrasonographic guided axillary plexus blocks with low volumes of local anaesthetics: a crossover volunteer study. *Anaesthesia*. 2010;65:266–271.
6. Ponrouch M, Bouic N, Bringuier S, et al. Estimation and pharmacodynamic consequences of the minimum effective anesthetic volumes for median and ulnar nerve blocks: a randomized, double-blind, controlled comparison between ultrasound and nerve stimulation guidance. *Anesth Analg*. 2010;111:1059–1064.
7. Fredrickson MJ, White R, Danesh-Clough TK. Low-volume ultrasound-guided nerve block provides inferior postoperative analgesia compared to a higher-volume landmark technique. *Reg Anesth Pain Med*. 2011;36:393–398.
8. Sinha SK, Abrams JH, Barnett JT, et al. Decreasing the local anesthetic volume from 20 to 10 mL for ultrasound-guided interscalene block at the cricoid level does not reduce the incidence of hemidiaphragmatic paresis. *Reg Anesth Pain Med*. 2011;36:17–20.
9. Nader A, Kendall MC, De Oliveira GS Jr, et al. A dose-ranging study of 0.5% bupivacaine or ropivacaine on the success and duration of the ultrasound-guided, nerve-stimulator-assisted sciatic nerve block: a double-blind, randomized clinical trial. *Reg Anesth Pain Med*. 2013;38:492–502.
10. Cappelleri G, Ambrosoli AL, Turconi S, Gemma M, Ricci EB, Cornaggia G. Effect of local anesthetic dilution on the onset time and duration of double-injection sciatic nerve block: a prospective, randomized, blinded evaluation. *Anesth Analg*. 2014;119:489–493.
11. Fredrickson MJ, Abeysekera A, White R. Randomized study of the effect of local anesthetic volume and concentration on the duration of peripheral nerve blockade. *Reg Anesth Pain Med*. 2012;37:495–501.
12. Latzke D, Marhofer P, Zeitlinger M, et al. Minimal local anaesthetic volumes for sciatic nerve block: evaluation of ED 99 in volunteers. *Br J Anaesth*. 2010;104:239–244.
13. Taboada Muñiz M, Rodríguez J, Bermúdez M, et al. Low volume and high concentration of local anesthetic is more efficacious than high volume and low concentration in Labat's sciatic nerve block: a prospective, randomized comparison. *Anesth Analg*. 2008;107:2085–2088.
14. Eren G, Altun E, Pektas Y, et al. To what extent can local anesthetics be reduced for infraclavicular block with ultrasound guidance? *Anaesthesist*. 2014;63:760–765.
15. Jaeger P, Nielsen ZJ, Henningsen MH, Hilsted KL, Mathiesen O, Dahl JB. Adductor canal block versus femoral nerve block and quadriceps strength: a randomized, double-blind, placebo-controlled, crossover study in healthy volunteers. *Anesthesiology*. 2013;118:409–415.
16. Kwofie MK, Shastri UD, Gadsden JC, et al. The effects of ultrasound-guided adductor canal block versus femoral nerve block on quadriceps strength and fall risk: a blinded, randomized trial of volunteers. *Reg Anesth Pain Med*. 2013;38:321–325.
17. Jæger P, Zaric D, Fomsgaard JS, et al. Adductor canal block versus femoral nerve block for analgesia after total knee arthroplasty: a randomized, double-blind study. *Reg Anesth Pain Med*. 2013;38:526–532.
18. 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.
19. 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.
20. Stark T, Walker B, Phillips JK, Fejer R, Beck R. Hand-held dynamometry correlation with the gold standard isokinetic dynamometry: a systematic review. *PM R*. 2011;3:472–479.
21. Lu YM, Lin JH, Hsiao SF, Liu MF, Chen SM, Lue YJ. The relative and absolute reliability of leg muscle strength testing by a handheld dynamometer. *J Strength Cond Res*. 2011;25:1065–1071.
22. Lu TW, Hsu HC, Chang LY, Chen HL. Enhancing the examiner's resisting force improves the reliability of manual muscle strength measurements: comparison of a new device with hand-held dynamometry. *J Rehabil Med*. 2007;39:679–684.
23. Gaudreault F, Drolet P, Fallaha M, Varin F. The reliability of the current perception threshold in volunteers and its applicability in a clinical setting. *Anesth Analg*. 2015;120:678–683.