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Journal

Regional Anesthesia & Pain Medicine, 44(3)

ISSN

1098-7339

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Publication Date

2019-03-01

DOI

10.1136/rapm-2018-100089

Peer reviewed

Systemic dexmedetomidine is not as efficient as perineural dexmedetomidine in prolonging an ulnar nerve block

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ABSTRACT

Background We tested the joint hypotheses that both perineural and systemic dexmedetomidine prolong the duration of an ulnar nerve block (UNB) compared with ropivacaine alone and that systemic dexmedetomidine is noninferior compared with perineural dexmedetomidine in block prolongation.

Methods We performed bilateral UNBs in 22 healthy volunteers on two separate days. On the first day, each arm was randomized to either 4 mL ropivacaine 5 mg/mL+1 mL dexmedetomidine 100 µg/mL (Perineural) or 4 mL ropivacaine 5 mg/mL+1 mL saline (Systemic). On the subsequent treatment day, each arm was randomized to 1 mL of saline plus 4 mL of ropivacaine at either 7.5 mg/mL(HiRopi) or 5 mg/mL (NoDex). The primary outcome measure was the duration of sensory block assessed by mechanical discrimination.

Results Mean sensory block duration was longer in both the Perineural (14.4 hours, 95% CI 13.1 to 15.6) and Systemic treatments (9.2 hours, 95% CI 8.6 to 9.8) compared with the NoDex treatment (7.1 hours, 95% CI 6.6 to 7.6) (p<0.0001 for both). Systemic dexmedetomidine was inferior (not noninferior) compared with perineural dexmedetomidine, as the 95% CI of the difference (mean difference 5.2 hour, 95% CI 4.2 to 6.1) exceeded the noninferiority limit of 3.6 hour. Onset time did not differ among the groups. The other test modalities demonstrated similar block durations as the primary outcome.

Conclusions Adding dexmedetomidine perineurally to ropivacaine doubles the duration of an UNB. Systemic dexmedetomidine also prolongs the duration of UNB, but has less of an effect compared with the perineural route.

Trial registration number NCT03222323.

INTRODUCTION

Adding perineural dexmedetomidine to local anesthetic consistently prolongs the duration of peripheral nerve blocks.[1] However, since dexmedetomidine is not approved for perineural use and the mechanism for block duration lengthening remains unclear, recent trials have tried to identify the site of action and compare the systemic and perineural routes of administration. In healthy volunteers, a dramatic effect was observed when dexmedetomidine was administered perineurally, but also a lesser result when administered intravenously.[2] In patients, systemic and perineural dexmedetomidine prolonged the duration of interscalene nerve blocks similarly.[3] These trials, however, used a suboptimal dose of dexmedetomidine[4] and lacked control of systemic effects: the extended block duration observed in the perineural groups may have been caused by absorption and re-distribution of the perineural dexmedetomidine triggering systemic effects and not by a perineural mechanism.[2 3]

In contrast, when systemic effects are controlled for, a perineural mechanism of action of dexmedetomidine was demonstrated.[5] It remains unknown, however, if dexmedetomidine in optimal doses increases peripheral nerve block duration to a clinically relevant degree in a controlled setting.

We therefore conducted the present trial to test the joint hypotheses that both perineural and systemic dexmedetomidine prolong the duration of an ulnar nerve block compared with ropivacaine alone and that systemic dexmedetomidine is noninferior compared with perineural dexmedetomidine in prolonging the block.

METHODS

This was a randomized paired noninferiority trial with an active placebo group in healthy volunteers. The study was approved by the Regional Ethics Committee of Region Zealand, Denmark (SJ-595), The Danish Medicine Agency (EudraCT-CT 2016004883–20), and The Danish Data Protection Agency. The trial was prospectively registered at ClinicalTrials.gov (NCT03222323) on July 19, 2017 and monitored by the Good Clinical Practice Unit at Copenhagen University. The manuscript complies with the CONSORT reporting guidelines.[6]

We conducted the trial at Zealand University Hospital (Koege, Denmark) from July through September 2017. Participants were recruited by advertisement in the medical students' bulletin at Copenhagen University and screened prior to trial days. Participants>18 years of age with a body mass index (BMI) of 18–30 kg/m^2 and American Society of Anesthesiologists (*ASA*) physical status score of 1–2 were eligible for inclusion. Female participants of reproductive age were required to be using an effective contraceptive technique and have a negative urine human chorionic gonadotrophin. Exclusion criteria were: inability to speak or read Danish, allergy to study medication, alcohol or drug abuse, daily intake of prescription
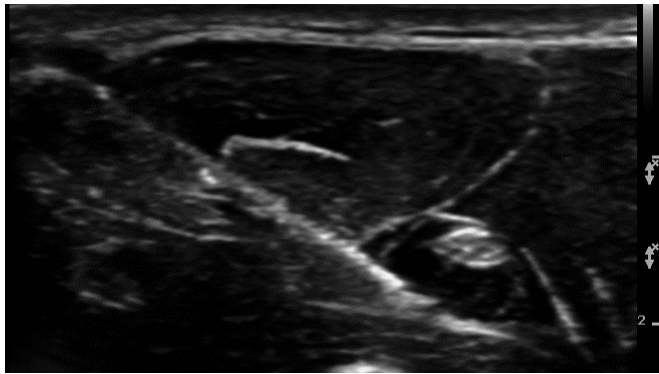
Figure 1 We blocked the ulnar nerve on the proximal forearm in the fascial layers between the flexor carpi ulnaris and flexor digitorum profundus muscles.

analgesics within the previous 4 weeks, use of over-the-counter analgesics during the previous 48 hours, neuromuscular defects or wounds on the upper extremities, diabetes, heart block, and sick sinus node syndrome. Written informed consent was obtained before inclusion in the trial. Participants attended two trial days at least 4 weeks apart.

Block performance

Subjects received bilateral ultrasound–guided (Philips Sparq ultrasound system, Philips, The Netherlands) ulnar nerve blocks using a linear 12 L ultrasound probe. All nerve blocks were performed by a trained anesthesiologist (JHA) by identifying the ulnar nerve medially on the proximal forearm. A 22 G, 50 mm needle (Pajunk SonoPlex Stim cannula, Germany) was inserted in plane entering the flexor carpi ulnaris muscle. The study medication was injected slowly ensuring circumferential periulnar spread between the fascial layers of flexor carpi ulnaris and flexor digitorum profundus muscles (figure 1). All participants received a left-sided followed immediately by a right-sided ulnar nerve block.

Study medication, randomization, and blinding

On the first day, each arm was randomized to receive 1 mL of either perineural dexmedetomidine (100 µg; Perineural group) or saline (Systemic group) added to the local anesthetic (4 mL ropivacaine 5 mg/mL). The latter constituted the Systemic group as the block was influenced by the absorption and redistribution of the perineurally administered dexmedetomidine in the opposite arm.

On the subsequent treatment day, each arm was randomized to 1 mL of normal saline plus 4 mL of ropivacaine at either 7.5 mg/mL (HiRopi) or 5 mg/mL (NoDex) (figure 2). We included the higher-dose group to secure blinding and to investigate if increasing the dose of ropivacaine by 50% would increase block duration.

Skanderborg Pharmacy, Skanderborg, Denmark prepared a computer-generated randomization list and 22 sequentially numbered sets of two identical boxes, one set for each participant labeled day 1 and day 2. Each box contained two 10 mL plastic ampoules containing ropivacaine (either 5 mg/mL or 7.5 mg/mL) of identical appearance and two 4 mL vials containing dexmedetomidine 100 µg/mL or normal saline according to
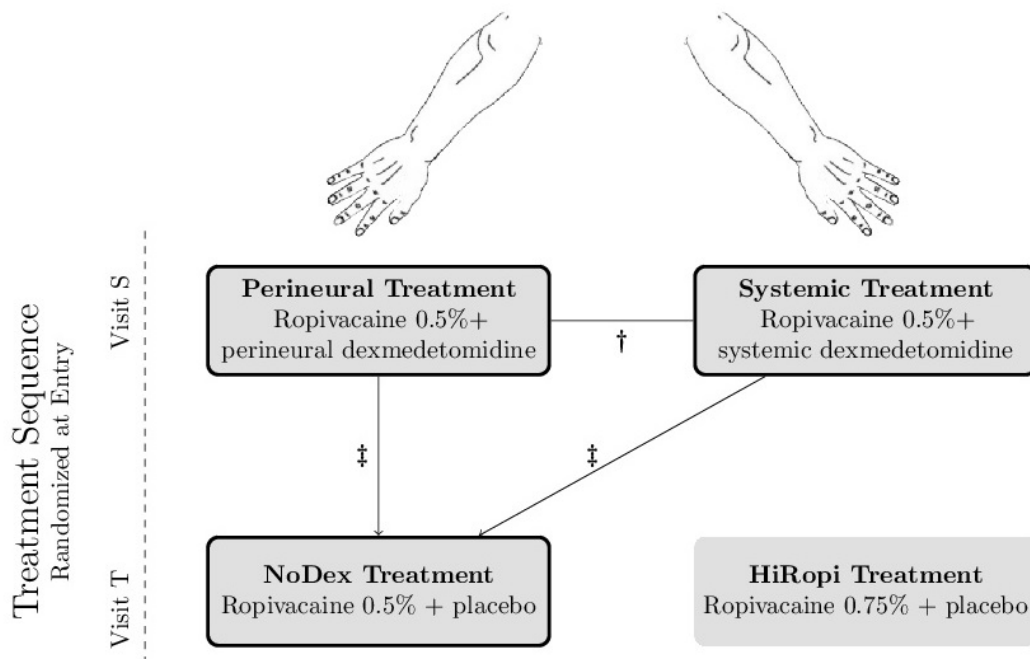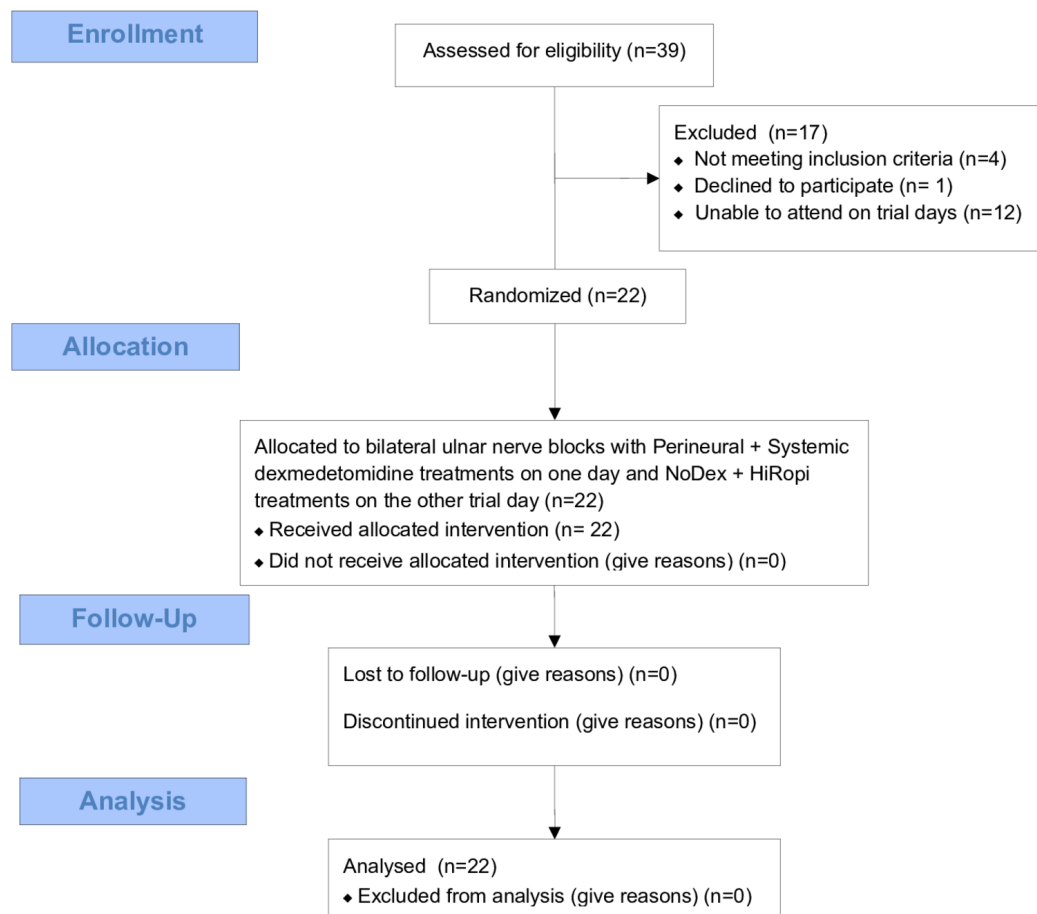

$\mu.$ denotes duration of block. Level of significance $\alpha = 5\%$.

† Non-inferiority test, $\mu_A - \mu_B > -\delta, \delta = \frac{\mu_A}{4}$.
‡ Superiority test. $\mu_A \neq \mu_C, \mu_B \neq \mu_C$.

Figure 2 Trial design with planned statistical analyses. Perineural and Systemic treatments were given on one trial day and NoDex and HiRopi on the other trial day.

CONSORT 2010 Flow Diagram

Figure 3 Consolidated Standards of Reporting Trials (CONSORT 2010) flow diagram summarizing enrollment, allocation, follow-up, and analysis of participants in the trial.

randomization. Ropivacaine, dexmedetomidine, and saline are all clear, colorless fluids of identical appearance. According to the randomization, the vials and ampoules were labeled "left" and "right" arm. The medication was drawn in syringes labeled "left" and "right" by the principal investigator supervised by a sub-investigator. Participants were assigned consecutively on enrolment. The principal investigator, outcome assessors, participants, statistician, and all other personnel were blinded until completion of data analysis.

According to protocol, we intended to randomize both to which day the participants received either treatment Perineural+Systemic or NoDex+HiRopi, and to which arms the participants would receive these treatments. Due to a misinterpretation by the pharmacy, all participants were randomized to receive Perineural+Systemic treatments on day 1 and NoDex+HiRopi on day 2, instead of individual randomization

of study days. This error was revealed when the trial was unblinded on receiving the randomization list from the pharmacy. Importantly, the randomization of treatments to either left or right arm on both study days was done correctly. Thus, the blinding on each study day was not compromised.

Outcome measures

We evaluated sensory block in the hypothenar area using three modalities:

Mechanical discrimination (pinprick)

The ability to distinguish blunt from sharp when indenting the skin with a needle (pinprick). The onset of nerve block was defined as time from block performance until pinprick ceased to feel sharp. The primary outcome, the duration of

Table 1 Duration (hours) and onset (min) of ulnar nerve block for perineural (4 mL ropivacaine 5 mg/mL+100 µg dexmedetomidine), systemic (4 mL ropivacaine 5 mg/mL+100 µg dexmedetomidine systemically), NoDex (4 mL ropivacaine 5 mg/mL+saline) and HiRopi (4 mL ropivacaine 7.5 mg/mL+saline) treatments

Outcomes	Perineural	Systemic	NoDex	HiRopi	Difference in duration/onset between groups	P value
Duration of block (mechanical discrimination) (hours)	14.4 (13.1 to 15.6)	9.2 (8.6 to 9.8)	7.1 (6.6 to 7.6)	7.8 (7.3 to 8.3)	A>B: 5.2 (4.2 to 6.1) A>C: 7.2 (5.9 to 8.6) B>C: 2.1 (1.3 to 2.9) A>D: 6.6 (5.4 to 7.7) B>D: 1.4 (0.7 to 2.2) D>C: 0.7 (0.2 to 1.1)	P<0.0001 P<0.0001 P<0.0001 P<0.0001 P=0.001 P=0.01
Onset of block (mechanical discrimination) (min)	13 (10 to 16)	12 (10 to 15)	13 (10 to 15)	12 (8 to 16)	A>B: 1 (−3 to 4) A>C: 1 (−3 to 5) B>C: 0 (−4 to 4)	P=0.61 P=0.61 P=0.98
Duration of block (temperature discrimination) (hours)	14.0 (13.1 to 15.0)	9.1 (8.6 to 9.7)	7.5 (6.9 to 8.1)	8.1 (7.5 to 8.6)	A>B: 4.9 (4.0 to 5.9) A>C: 6.5 (5.5 to 7.6) B>C: 1.6 (0.8 to 2.4)	P<0.0001 P<0.0001 P=0.0006
Duration of block-analgesia (Pain during tonic heat stimulation (hours)	13.6 (12.7 to 14.6)	9.3 (8.5 to 10.0)	7.6 (7.1 to 8.1)	8.0 (7.5 to 8.5)	A>B: 4.4 (3.5 to 5.3) A>C: 6.1 (5.0 to 7.1) B>C: 1.7 (0.8 to 2.6)	P<0.0001 P<0.0001 P=0.0009
Duration of motor block (MVIC) (h)	15.4 (14.2 to 16.6)	9.8 (9.1 to 10.5)	7.4 (6.9 to 8.0)	8.1 (7.5–8.7)	A>B: 5.6 (4.7 to 6.4) A>C: 8.0 (6.7 to 9.3) B>C: 2.4 (1.5 to 3.3)	P<0.0001 P<0.0001 P<0.0001

Values are mean (95% CI).

MVIC, maximal voluntary isometric contraction.

sensory nerve block, was the time from block completion until pinprick again was perceived as sharp.

Temperature discrimination
The ability to feel a cold sensation when stimulated with an alcohol swab. The duration of the nerve block was time from block performance until stimulation of the skin with an alcohol swab felt cold again.

Pain during tonic heat stimulation
A computer-controlled thermode (2.5 cm^2, Thermotest, Somedic A/B, Hörby, Sweden) was heated to 45°C for 30 s to mimic clinical pain. The duration of analgesia assessed by tonic heat stimulation was the time from block performance until tonic heat stimulation again elicited a painful response on a visual analog scale score (VAS>0).

We assessed motor block by an average of three measurements of maximal voluntary isometric contraction (MVIC) of abductor digiti minimi muscle using a dynamometer (Lafayette Manual Muscle Testing System, Lafayette Instrument Company, Lafayette, Indiana, USA). The fingers I to IV were fixed thereby isolating fifth finger abduction. Duration of motor block was defined as time from block performance until MVIC>75% of baseline values. On the first day of the trial, two participants were unable to reach MVIC>75% of baseline values, although reporting normalized function of motor skills subjectively. They stated fatigue from the multiple motor tests as the cause. We therefore changed the secondary outcome,

Duration of sensory nerve block measured by mechanical discrimination
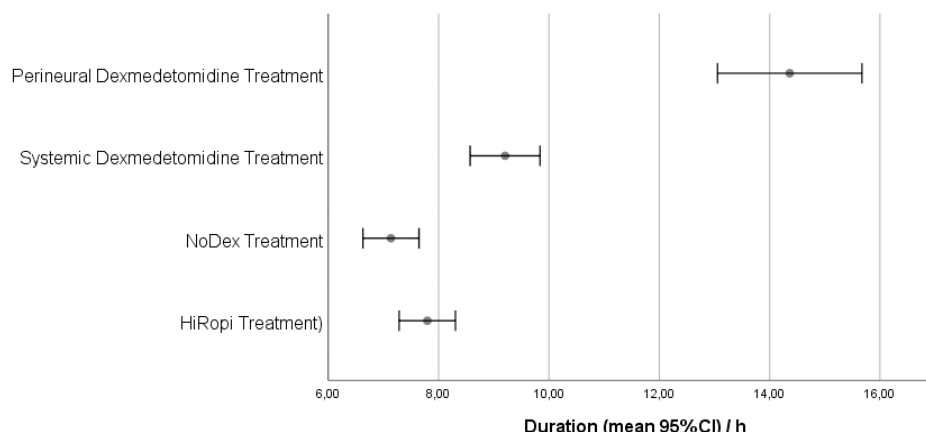
Figure 4 Duration of block measured by mechanical discrimination/hour for Perineural, Systemic, NoDex and HiRopi treatments, mean (95% CI).
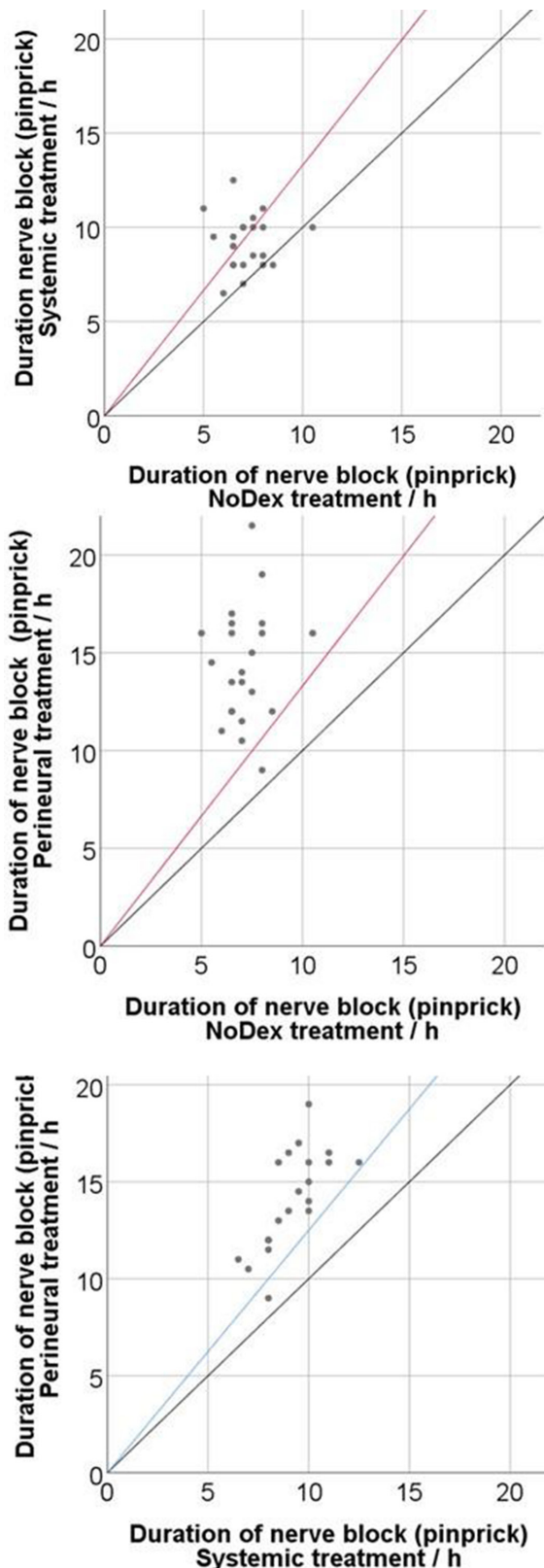
Figure 5 Individual participant data of duration of sensory nerve block measured by mechanical discrimination (pinprick). Each dot represents duration of two ulnar nerve blocks for one participant. Top graph: Systemic vs NoDex treatment. Middle graph: Perineural vs NoDex treatment. Bottom graph: Perineural vs Systemic treatment. The black reference lines indicate no difference in duration of nerve blocks. The red reference line indicates the clinically relevant difference of 33%. The blue line is the noninferiority margin of 25%.

duration of motor block, to either time until MVIC>75% of baseline values or the participant indicated a subjective return of normal motor function.

We measured baseline values of all tests before block performance. The onset of nerve block was assessed every 5 min and duration of nerve block every 30 min after block administration. Block success was defined as a complete lack of mechanical discrimination and MVIC<50% of the baseline value at 1 hour following block administration.

During the first 4 hours of the trial, we monitored blood pressure, electrocardiography, and assessed sedation using a verbal rating scale from 0 to 3 (0: none, 1: light, 2: moderate, 3: pronounced).

The primary outcome measure was the duration of nerve block assessed by mechanical discrimination among the Perineural, Systemic, and NoDex treatments. Secondary outcome measures included the duration of sensory nerve block assessed by mechanical discrimination in the high-dose ropivacaine treatment; duration of sensory nerve block assessed by temperature discrimination; duration of sensory nerve block assessed by pain during tonic heat stimulation; duration of motor nerve block assessed by maximum voluntary isometric contraction; and onset of sensory nerve block assessed by mechanical discrimination.

Statistical analysis and sample size calculation

We aimed to test the joint hypotheses that both perineural and systemic dexmedetomidine prolong the duration of an ulnar nerve block compared with ropivacaine alone and that systemic dexmedetomidine is noninferior compared with perineural dexmedetomidine in prolonging the block (figure 2). Two previous trials in healthy volunteers investigated ulnar nerve blocks and found a mean (SD) duration of 350 (54) min when using ropivacaine alone[2] and 546 (198) min when adding 100 µg dexmedetomidine to ropivacaine.[4] We have previously found that the duration of a saphenous nerve block with systemic dexmedetomidine was 10% shorter than a block with perineural dexmedetomidine using a similar protocol as the current trial.[5] Given the sedative and hemodynamic side-effects of dexmedetomidine we would demand at least a 33% difference in duration of the nerve block between the Perineural and NoDex treatments and between the Systemic and NoDex treatments to consider it clinically relevant. According to our statistical plan, we would only proceed to noninferiority testing if both the duration of the Perineural and Systemic treatments were superior to the NoDex treatment. As dexmedetomidine is only registered for systemic and not perineural use, we set the noninferiority margin of the Perineural versus Systemic treatments to 25%. The clinical relevant differences in superiority comparisons and noninferiority limit are in agreement with a recent clinical trial.[3]

With a significance level of 5% and a power of 90%, we determined a sample size of 19 participants through simulation of 10 000 sample populations from independent multivariate Gaussian distributions on which we performed multiple testing (Microsoft R Open 3.3.1, Redmond, Washington, USA) using superiority between Perineural versus NoDex and Systemic versus NoDex treatments and noninferiority between Systemic and Perineural treatments. To account for dropouts, we included 22 participants.

The secondary outcome comparisons served only to support or weaken the result of the primary outcome. Accordingly, we did not correct for multiple testing.

The principal investigator used SPSS V.19.0 (SPSS, Chicago, Illinois, USA) and the statistician (GHL) SAS V.9.4 (SAS, Cary,
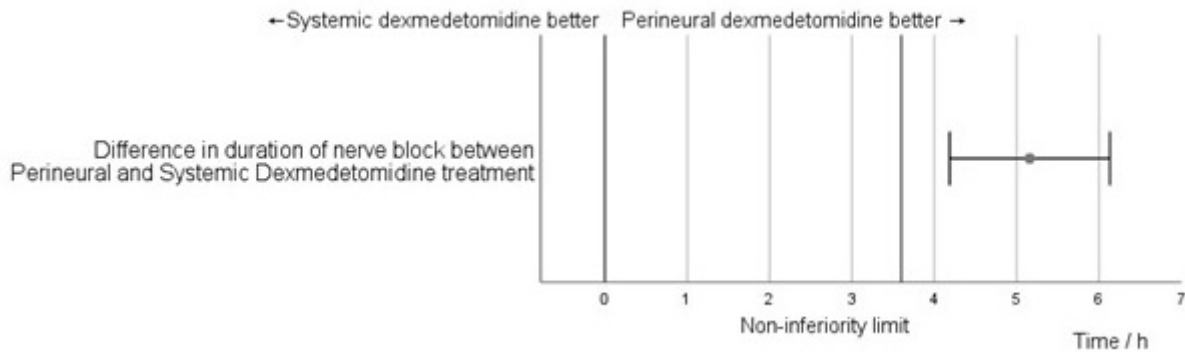
Figure 6 Difference in duration of sensory nerve block between Perineural and Systemic dexmedetomidine treatments (mean (95% CI). The noninferiority limit is 25% of the duration of sensory nerve block measured by mechanical discrimination in the perineural treatment.

North Carolina, USA), for data analysis. On agreement of results, the trial was unmasked. The pairwise differences between treatments did not show systematic deviations from the assumption of normal distribution of data when inspecting box plots, histograms, and Q-Q plots. We tested if the systemic route was noninferior to the perineural route using a 25% noninferiority limit. The rest of the comparisons were done using paired t-tests.

RESULTS

From July to September 2017, we screened 39 individuals and included 22 healthy volunteers, 10 females and 12 males, with a mean (SD) age of 24 (2) years; height of 177 (12) cm; weight of 70 (15) kg, and BMI of 22 (2) kg/m^2. All participants received the assigned treatment and completed the trial. There were no failed blocks per protocol. There were no missing data points, and all participants were analyzed for all outcome measures (figure 3).

Primary outcome

The duration of sensory nerve block measured by mechanical discrimination was longer in participants receiving dexmedetomidine perineurally with a mean 14.4 hour (95% CI 13.1 to 15.6) compared with ropivacaine alone (NoDex treatment) mean 7.1 hour (95% CI 6.6 to 7.6) with a mean difference of 7.2 hour (95% CI 5.9 to 8.6; p<0.0001). The duration of nerve block was also significantly longer when dexmedetomidine was added systemically with a mean 9.2 hours (95% CI 8.6 to 9.8) compared with ropivacaine alone (NoDex treatment) with a mean difference of 2.1 hours (95% CI 1.3 to 2.9; p<0.0001; table 1 and figures 4 and 5). The noninferiority limit was 25% of the nerve block duration of the Perineural treatment (14.4 hours), or 3.6 hours. Systemic dexmedetomidine was inferior (not noninferior) compared with perineural dexmedetomidine, as the entire 95% CI of the 5.2 hour difference (4.2 to 6.1) exceeded the noninferiority limit of 3.6 hours (figure 6).
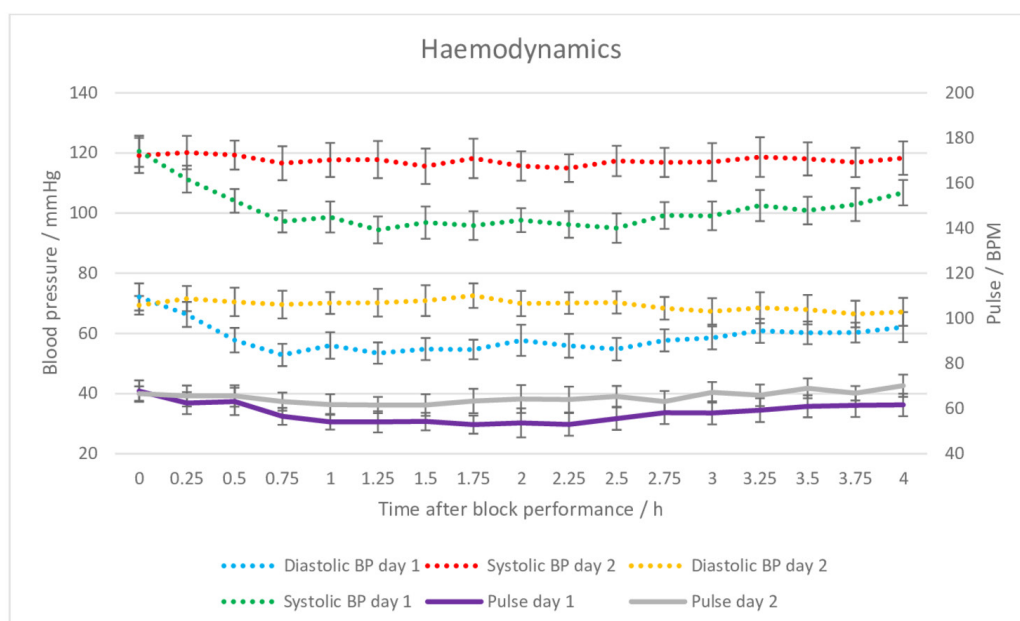
Figure 7 Hemodynamics the first 4 hours post block on day 1 (dexmedetomidine day) and day 2 (placebo day) mean (95% CI).
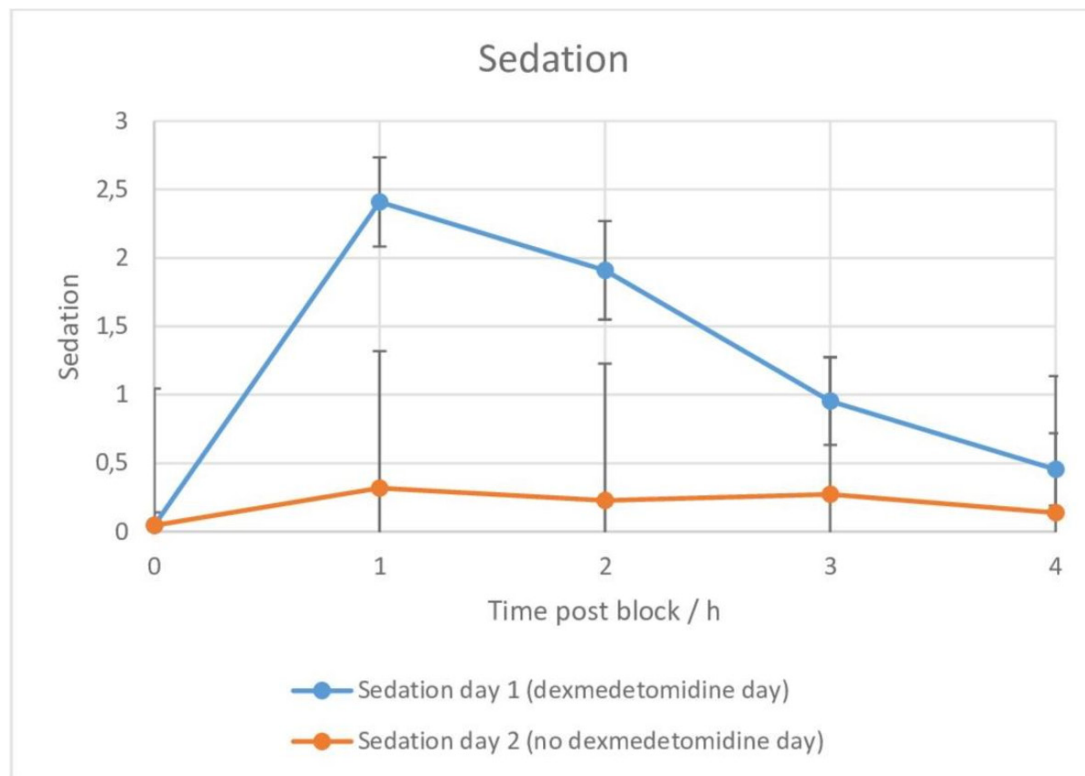
Figure 8 VRS from 0 to 3 (0: no sedation, 1: light sedation, 2: moderate sedation, 3: pronounced sedation) mean (95% CI) during the first 4 hours of the trial. VRS, Verbal Rating Scale.

Secondary outcome measures

The comparisons of nerve block durations were similar when assessed by the other sensory and motor modalities supporting our primary outcome (table 1). In the absence of dexmedetomidine, increasing the dose of ropivacaine by 50% prolonged the duration of nerve block with a mean difference of 0.7 hours (95% CI 0.2 to 1.1; p=0.01). Onset time did not differ between any of the treatments (table 1).

Hemodynamic parameters and adverse events

Blood pressure and pulse rate were lower during the first 4 hours of the trial for all treatments (figure 7). Sedation levels were higher on the day the participants received dexmedetomidine compared with the day without (figure 8). On getting up from bed 1 hour after receiving perineural dexmedetomidine, one participant experienced dizziness and a pulse rate of 40 and blood pressure 77/40 mm Hg. The symptoms resolved before intravenous treatment could be administered. We identified no nerve injuries or other adverse events.

DISCUSSION

In this trial, we observed a doubling in the duration of a ropivacaine ulnar nerve block when adding dexmedetomidine perineurally compared with the same dose of ropivacaine alone. Systemic dexmedetomidine also prolonged the duration of nerve block, but to a lesser degree than when administered perineurally.

Trials investigating dexmedetomidine administered perineurally and intravenously compared with placebo in a three-group design does not permit firm conclusion of the site where dexmedetomidine actually exhibits its block prolonging effects.[2 3] When dexmedetomidine is administered perineurally, it is absorbed and redistributed systemically, leading to plasma-concentration that resembles those seen when using dexmedetomidine intravenously

for sedation in the intensive care unit.[7] The prolonged duration of block in the perineural group in these trials[2 3] could therefore be caused by the systemic effects of dexmedetomidine and not necessarily by a perineural mechanism. In this bilateral trial, the dexmedetomidine administered in the perineural treatment was absorbed and redistributed, and the systemic effect of dexmedetomidine on the two nerve blocks in the perineural and systemic treatments was the same. Consequently, the longer duration of the nerve block in the perineural group was solely conditioned by a perineural effect.

This perineural effect is in agreement with a study employing a similar design investigating bilateral saphenous nerve blocks with dexmedetomidine added on one side.[5] The magnitude of the effect, however, was far more pronounced in the current trial examining the ulnar nerve. The evidence of a perineural effect of dexmedetomidine is further strengthened when looking at the individual participant data (figure 5): all subjects had a longer duration of nerve block on the side receiving perineural dexmedetomidine compared with the contralateral side influenced by systemic dexmedetomidine. Only one participant had a duration of nerve block in the Systemic treatment that would be noninferior compared with the Perineural treatment using the 25% noninferiority limit. Additionally, all participants had a longer duration of block when receiving dexmedetomidine perineurally, and 21 of 22 had a prolongation that exceeded the clinically relevant difference of 33% when compared with ropivacaine alone.

Another trial in healthy volunteers investigated the effects of adding 20 µg of dexmedetomidine either intravenously or perineurally on the duration of a ropivacaine ulnar nerve block when compared with ropivacaine alone. The ulnar nerve blocks were prolonged by 10% and 60% in the groups receiving intravenous and perineural dexmedetomidine, respectively, compared with ropivacaine alone.[2] In comparison, the current study found a

nerve block prolongation of 30% and 100% with the Systemic and Perineural treatments, respectively, compared with the same dose of ropivacaine alone. The difference in magnitude may be explained by the five times higher dose of dexmedetomidine used in the current study.

It is challenging to determine the relative importance of dexmedetomidine dose and concentration in determining block prolongation. In the previously mentioned trial with bilateral saphenous nerve blocks, an identical dose of dexmedetomidine was used as the current study (100 µg), but this was added to 20 mL ropivacaine yielding a concentration of dexmedetomidine of four times less than the current trial.[5] There was a 2 hour (10%) difference in duration between the perineural and the systemic groups in the previous trial, whereas the difference in the current trial between the same groups was 5 hours (56%). This larger difference could be explained by the difference in concentration, and perineural dexmedetomidine may be more applicable in low volume blocks.

A clinical trial investigated the perineural and intravenous addition of dexmedetomidine 0.5 µg/kg vs placebo to an interscalene nerve block using 15 mL ropivacaine.[3] They reported that both perineural and systemic dexmedetomidine prolonged the duration of the nerve block significantly, which is in support of our results. However, the systemic route was noninferior to the perineural route when applying the same noninferiority margin of 25% as the current study. This difference may be explained by the concentration of perineural dexmedetomidine used in the current study, which was more than three times higher compared with their trial.

Our trial has several limitations. As bilateral surgery is rare, we conducted the trial in healthy volunteers, and it is uncertain how these results will transfer to clinical practice. Although 100 µg of dexmedetomidine seems optimal for prolonging nerve blocks,[4] we observed sedative and hemodynamic side effects that may limit the clinical usefulness in such a high dose, including ambulatory settings. A subgroup analysis from a recent systematic review suggested that a lower dose of dexmedetomidine of 50–60 µg maximized block prolongation while minimizing hemodynamic side-effects.[1] Even though the trial was triple blinded, the marked sedation and hemodynamic side effects may have influenced the assessment of the nerve blocks. Further, the flawed randomization of trial days by the pharmacy also increases the risk of bias. However, as participants were markedly more sedated on the day they received dexmedetomidine, this would have presumably been the case regardless of randomization. Importantly, the blinding between treatments within each study day (intravenous versus perineural dexmedetomidine and high versus low concentration of ropivacaine) was not compromised. Finally, we did not correct for multiple comparisons which increases the risk of Type 1 error, and findings in secondary outcomes should be viewed as suggestive.

CONCLUSION
Both perineural and systemic dexmedetomidine prolong the duration of an ulnar nerve block compared with an equivalent dose of ropivacaine alone, but only the perineural route to a clinically relevant extent. Systemic dexmedetomidine is inferior (not noninferior) compared with perineural dexmedetomidine in prolonging the block.

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