Dexmedetomidine as an adjuvant to ropivacaine prolongs peripheral nerve block: a volunteer study

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Background. Dexmedetomidine is an α₂-receptor agonist which might be used as an additive to local anaesthetics for various regional anaesthetic techniques. We therefore designed this prospective, double-blinded, controlled volunteer study to investigate the effects of dexmedetomidine as an adjuvant to ropivacaine on peripheral nerve block.

Methods. Ultrasound-guided ulnar nerve block (UNB) was performed in 36 volunteers with either 3 ml ropivacaine 0.75% (R), 3 ml ropivacaine 0.75% plus 20 μg dexmedetomidine (RpD), or 3 ml ropivacaine 0.75% plus systemic 20 μg dexmedetomidine (RsD). UNB-related sensory and motor scores were evaluated.

Results. Sensory onset time of UNB was not different between the study groups, whereas motor onset time was significantly faster in Group RpD when compared with the other study groups [mean (SD)] [21 (15) vs 43 (25) min in Group RsD and 47 (36) min in Group R, P<0.05 Group RpD vs other groups]. The duration of sensory block was 350 (54) min in Group R, 555 (118) min in Group RpD, and 395 (40) min in Group RsD (P<0.01 Group RpD vs other groups, P<0.05 Group RsD vs Group R). Motor block duration was similar to the duration of sensory block.

Conclusions. A profound prolongation of UNB of ~60% was detected with perineural dexmedetomidine when added to 0.75% ropivacaine. The systemic administration of 20 μg dexmedetomidine resulted in a prolongation of ~10% during UNB with 0.75% ropivacaine.

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Peripheral nerve block is a common regional anaesthetic technique and is used for a broad spectrum of surgical, interventional, or diagnostic procedures. Long-acting blocks with local anaesthetics (LAs) such as ropivacaine or bupivacaine are beneficial for improved postoperative pain therapy, but the duration of sensory block is still not sufficient to avoid the postoperative use of opioids.

The aim of prolonging the duration of peripheral nerve blocks to treat postoperative pain is a key issue in regional anaesthesia. Alternative to long-acting LAs, perineural catheters can be used. However, in comparison with single-shot blocks, the insertion of peripheral nerve catheters is more time-consuming, costly, possibly more painful for the patient, has possible higher complication rates (e.g. infection), and needs more postoperative care.¹ ²

Various adjuvants to increase the duration of block are described in the literature and used in the daily clinical practice. Clonidine, an α₂-adrenoceptor agonist, has been shown to prolong the duration of peripheral nerve blocks.³ ⁶ Dexmedetomidine is a selective α₂-adrenoceptor agonist with an eight-fold affinity to the α₂-adrenoceptor compared with clonidine and was recently approved by the European Medication Agency for continuous i.v. sedation in critically ill patients. Animal studies showed that perineural dexmedetomidine added to bupivacaine or ropivacaine prolongs the duration of sensory and motor block.⁵ ⁶ Only two clinical studies investigated the use of dexmedetomidine in patients undergoing axillary brachial and greater palatine nerve block, showing faster onset time and longer duration of block.⁹ ¹⁰ In contrast to animal and clinical studies, studies in volunteers enable a more exact and reliable determination of block parameters.

We therefore designed this prospective, double-blinded, controlled volunteer study to investigate the effects of dexmedetomidine as an adjuvant to ropivacaine in ulnar nerve block (UNB).
**Methods**

The study was approved by the Ethical committee of the Medical University of Vienna (EK 5/2012) and by the Austrian Agency for Health and Food Safety (EudraCT 2012-000030-19). Trial registration was performed via the German Clinical Trials Register (DRKS00003529).

**Screening visit**

Thirty-six healthy, male volunteers between 18 and 45 yr were enrolled in the study. Before inclusion in the study, we informed them about the nature, scope, and the procedures of the study and about the particular study-related risks. Exclusion criteria were defined as follows:

- anatomical abnormalities of the forearm identified by physical examination;
- BMI ≥ 30 kg m⁻²;
- use of non-steroidal anti-inflammatory drug during the last 2 weeks;
- known allergy or hypersensitivity against ropivacaine, other amino-amide LAs, or dexmedetomidine;
- participation in another clinical study within the last 4 weeks before study;
- coagulopathy;
- abnormalities in ECG that are considered clinically relevant like AV block or bradycardia.

After signing the informed consent, each volunteer underwent a general physical examination, including patient’s history and drawing of blood for determination of red and white blood count and standard blood coagulation parameters. In addition, an ECG and also arterial pressure and heart rate measurements were performed.

The screening visit took place within 3 weeks before the study day.

**Ultrasound-guided UNB**

On the morning of the study day, the volunteers were admitted to the clinical research ward. One plastic cannula (Venflon™) with a switch-valve was inserted into an antecubital vein. The ulnar nerve was investigated via ultrasound in a transverse plane at the area of the proximal non-dominant forearm, where it is embedded between the flexor carpi ulnaris, superficial flexor digitorum (humeroulnar head), and flexor digitorum profundus muscles without any adjacent anatomic structures (e.g. blood vessels). The ultrasound appearance of the ulnar nerve in the described position is usually hyperechoic and triangular. Ultrasound imaging was performed using a SonoSite M-Turbo (SonoSite Inc., Bothell, WA, USA) with an HFL 50 mm 15–6 MHz linear array transducer.

After disinfection of the skin and sterile preparation of the transducer, a 22 G, 50 mm, short-bevel facet tip ultrasound needle (Polymedic; te me na SAS, Carriere's sur Seine, France) was advanced under direct ultrasound visualization in-plane with the transducer, with the ulnar nerve in a short axis. To facilitate the visualization of the needle, SonoSite ENV™ (Enhanced Needle Visualization) software was used. To reach the target of almost circumferential spread of LA around the nerve even with the small volumes of LA, a multiple injection technique was realized with the tip of the needle in several positions around the nerve with consecutive administration of small amounts of LA. The administration of the study drug(s) was performed strictly extra-epineural.

The volunteers were divided into three study groups:
- Ropivacaine group (R): UNB with 3 ml ropivacaine 0.75% plus 0.2 ml saline and i.v. 5 ml saline.
- Ropivacaine plus perineural dexmedetomidine (RpD): UNB with 3 ml ropivacaine 0.75% plus 20 μg dexmedetomidine (Dexdor™, Orion Corporation, Espoo, Finland) and i.v. 5 ml saline.
- Ropivacaine plus systemic dexmedetomidine (RsD): UNB with 3 ml ropivacaine 0.75% and 0.2 ml saline and i.v. 20 μg dexmedetomidine diluted in 4.8 ml saline.

**Systemic administration of dexmedetomidine or saline**

In the RsD group, volunteers received dexmedetomidine 20 μg (diluted in 4.8 ml saline= 5 ml volume) systemically over 60 s after the block. In both other groups, 5 ml saline was administered over 60 s.

**Evaluation of sensory scores**

A pinprick test in comparison with the contra-lateral area propria of the ulnar nerve was performed (100%=no difference to the contra-lateral side; 0%=complete sensory loss). Five areas of sensory supply were defined:

- dorsal side hypothenar muscles;
- ulnar side hypothenar area;
- palmar side hypothenar muscles;
- fifth finger;
- ulnar side fourth finger.

**Evaluation of motor scores**

Ability of thumb adduction in comparison with the contra-lateral side:

- 3, no difference, adduction against contra-force possible;
- 2, slight difference, adduction against slight contra-force hardly possible;
- 1, significant difference, adduction without contra-force hardly possible;
- 0, no active adduction possible, paralysis.

Sensory and motor scores were evaluated as follows: prior to the block, 2, 4, 6, 8, 10, 15, 20, 30, 60 min after the block, and then every 30 min until complete recovery.

**Definition of block success**

Achievement of 0% pinprick testing in the corresponding skin area of the ulnar nerve.
Definitions of time points
Sensory onset time: time from performance of the block to pinprick 0% in all sensory areas.
Duration of sensory block: time during pinprick 0% persisted in all areas.
Complete recovery from sensory block: time from performance of the block to pinprick 100% in all sensory areas.
Motor onset time: time from performance of the block to a motor score 0.
Duration of motor block: time during motor score 0 persisted in all areas.

Monitoring
The volunteers received standard monitoring (ECG, non-invasive arterial pressure, \( \text{SpO}_2 \)) before performance of the UNB until complete resolution of the UNB. Bradycardia was defined when heart rate decreased > 20% from pre-injection values, and hypotension was defined when mean arterial pressure decreased > 20% from pre-injection values. Glycopyrrolate 0.01 mg kg\(^{-1}\) or etilefrine 2 mg was foreseen in cases of bradycardia or hypotension, respectively.
An emergency telephone number was provided in cases of any medical problems until 24 h after performance of PVB.

Blinding
The LA with or without dexmedetomidine was prepared in a syringe by another study physician than the one performing the block. Immediately after the end of the injection, the volunteer was brought into a different room and a third physician, unaware of the injected LA with or without dexmedetomidine, performed and recorded the sensory and motor tests to control block success and duration. The particular volunteers were unaware of the injected LA with or without dexmedetomidine and of the injected systemic drug (dexmedetomidine or saline).

Post-study investigations
Within 1 week after the study day, volunteers underwent a final examination regarding clinical signs of nerve damage (full recovery of the nerve block) and inflammation or infection of the puncture area.

Statistical analysis
Sample size calculation was based on the assumption that dexmedetomidine prolongs sensory block of the ulnar nerve by \( \sim 30\% \). We used the data published by Esmaoglu and colleagues,\textsuperscript{9} who showed prolongation of sensory block from 670 (70) to 880 (70) min in humans receiving axillary plexus block. Anyway, the SD of 70 min seems to be optimistic regarding our clinical observation of peripheral nerve blocks. We therefore assumed an SD of 120 min, resulting in a sample size of 12 volunteers per group and a total of 36 volunteers with a power of 80% with \( P < 0.05 \).
Differences in the duration of sensory and motor block were tested using an analysis of variance. The incidence of incomplete sensory or motor blocks was compared using a Fisher’s exact test. Data are presented as mean (SD).

Results
We randomized 36 volunteers into three groups of this study. Every volunteer received an ultrasound-guided UNB, resulting in a complete sensory block of the ulnar nerve in all cases. Patient characteristic data of the volunteers are presented in Table 1.

Sensory onset time of the UNB was not statistically different between the study groups, whereas motor onset time was statistically faster in the RpD group when compared with the other study groups (Table 2). The dose of 20 \( \mu \)g dexmedetomidine prolonged the duration of sensory and motor block when administered perineurally and systemically compared with ropivacaine alone (Table 2).
Incomplete motor block occurred in two volunteers in the R group, in three volunteers in the RpD group, and in two volunteers in the RsD group (n.s.).
Bradycardia (heart rate decrease > 20% from pre-injection values) or hypotension (arterial pressure decrease > 20% from pre-injection values) did not occur throughout the study period.
No block-related side-effects occurred during the study period or at the follow-up examination.

Discussion
To our knowledge, this is the first volunteer study investigating the use of dexmedetomidine as an adjuvant to LAs for peripheral nerve blocks. We found a profound prolongation of UNB with perineural dexmedetomidine, added to 0.75% \( \text{Ropivacaine} \) (Table 2).

**Table 1** Pertinent patient data; values are mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>RpD</th>
<th>RpS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>180 (7)</td>
<td>180 (9)</td>
<td>187 (7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77 (10)</td>
<td>77 (13)</td>
<td>84 (11)</td>
</tr>
<tr>
<td>BMI (kg m(^{-2}))</td>
<td>24 (2)</td>
<td>24 (3)</td>
<td>24 (3)</td>
</tr>
</tbody>
</table>

**Table 2** Block characteristics; values are mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>RpD</th>
<th>RpS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory onset time (min)</td>
<td>19 (14)</td>
<td>13 (18)</td>
<td>16 (18)</td>
</tr>
<tr>
<td>Duration of sensory block (min)</td>
<td>350 (54)</td>
<td>555 (118)\textsuperscript{12}</td>
<td>395 (40)\textsuperscript{1}</td>
</tr>
<tr>
<td>Time until pinprick testing 100%</td>
<td>455 (70)</td>
<td>743 (152)\textsuperscript{3,5}</td>
<td>518 (59)\textsuperscript{6}</td>
</tr>
<tr>
<td>Motor onset time (min)</td>
<td>47 (36)</td>
<td>21 (15)\textsuperscript{7}</td>
<td>43 (25)</td>
</tr>
<tr>
<td>Duration of motor block (min)</td>
<td>348 (74)</td>
<td>590 (92)\textsuperscript{8,9}</td>
<td>438 (54)\textsuperscript{10}</td>
</tr>
</tbody>
</table>
Dexmedetomidine for peripheral nerve block

ropivacaine, of ~60%. Even with the systemic administration of 20 μg dexmedetomidine, a prolongation of ~10% was detected for UNB.

So far, the clinical evidence for the use of dexmedetomidine as an adjuvant to LA for peripheral nerve blocks is limited to animal studies and two off-label studies in patients undergoing hand surgery and cleft palate repair. In the clinically more relevant study by Esmaoglu and colleagues, nerve stimulation was used as the guidance method and 40 ml LA plus 100 μg dexmedetomidine were administered for axillary brachial plexus block. Nowadays, ultrasound guidance is described as the ‘golden standard’ in peripheral regional anaesthesia and enables the reduction in LAs. Therefore, the study by Esmaoglu and colleagues does not reflect the current clinical standard in this field. Consequently, we used ultrasound guidance and low volumes of ropivacaine 0.75% for peripheral nerve block.

We powered the present study to find a clinically meaningful prolongation of UNB of 30%. Of note, we found twice the effect that we assumed. This is especially interesting as there are no dose–response data available, and the dose of 20 μg dexmedetomidine was based on earlier animal studies and the assumption that sedation will not occur with this dose.

There are some investigations of dexmedetomidine as an adjuvant to LAs in animals. Brummett and colleagues reported that large doses of dexmedetomidine prolong the duration of sciatic nerve block with the use of bupivacaine in rats. In addition, histopathological examinations showed that the nerve axon and myelin were unaffected after perineural application of dexmedetomidine at 24 h and at 14 days. In the same model, these authors showed that dexmedetomidine prolonged nerve blocks when added to ropivacaine in a dose-dependent manner. The doses of dexmedetomidine used in this study were 0.5, 2, 6, and 20 μg kg⁻¹. Even in the low-dose group, Brummett and colleagues used approximately double the dose per kilogram bodyweight we used in the present study. Further studies have to elucidate a dose-responsiveness of dexmedetomidine as adjuvative for LA in humans.

Besides the profound prolongation of UNB when administered perineurally, we also found a prolongation with systemic administration. The mechanism by which α-2-adrenergic receptor agonists produce analgesia and sedation is not fully understood but is likely to be multifactorial. Peripherally, α-2 agonists produce analgesia by reducing release of norepinephrine and causing α-2 receptor-independent inhibitory effects on nerve fibre action potentials. Centrally, α-2 agonists cause analgesia and sedation by inhibition of substance P release in the nociceptive pathway at the level of the dorsal root neurone and by activation of α-2 adrenoceptors in the locus coeruleus.

Moreover, experiments on dexmedetomidine as an adjuvant for nerve blocks have shown that the duration of analgesia is prolonged by block of the hyperpolarization-activated cation current (Ih current). The Ih current is important to bring a peripheral nerve back to the resting potential. The action potential will result in a hyperpolarized state, and the nerve will hardly be able to produce a new action potential. Therefore, the nerve is refractory to further stimulation. To produce another action potential, the nerve needs to get back to the resting potential. This process occurs in the late phase of the repolarization period. Blocking the Ih current will result in prolonged hyperpolarization of the nerve, which seems to be more distinct in the unmyelinated C fibres (pain) than in A α fibres (motor). Therefore, blocking the Ih current may have a more pronounced effect on pain than on motor response.

The central effects of dexmedetomidine seem to be that relevant, that even the small dose of 20 μg prolonged UNB in our study. However, further studies are warranted to investigate the mechanisms of how α-2 agonists, and especially dexmedetomidine, prolong the action of LA in peripheral nerve blocks.

Dexmedetomidine did not decrease the sensory onset time of UNB in our study, which is in contrast to the study by Esmaoglu and colleagues investigating the effects of dexmedetomidine as an adjuvant for brachial plexus block. This may be explained by the fact that we used ultrasound guidance, which reduces the onset time of peripheral nerve blocks in comparison with nerve stimulation as used by Esmaoglu and colleagues.

Dexmedetomidine can cause dose-dependent side-effects such as bradycardia and hypotension. We used 20 μg perineural and systemic dexmedetomidine and did not find haemodynamic side-effects, which supports the safety profile of our study medication regime. However, our haemodynamic data do not allow a conclusion regarding the safety in cardiovascular compromised patients.

The use of dexmedetomidine as an adjuvant to LA for peripheral nerve blocks has not been approved by the US Food and Drug Administration or by the European Medicines Agency. Currently, it is too early to support the use of dexmedetomidine as an adjuvant to LA for perineural use in humans. Further studies are required to determine the dose–response and the effects on complex nerve structures such as brachial plexus block. These studies should test systemic administration of dexmedetomidine in a control arm. However, the available data from experimental studies and the data from the present volunteer study are promising.

In conclusion, the present volunteer study shows a profound prolongation of UNB with perineurally administered 20 μg dexmedetomidine as an adjuvant to 0.75% ropivacaine. Our data encourage further studies in patients undergoing peripheral nerve block.

Declaration of interest
None declared.

References


5 Brummett CM, Amodeo FS, Janda AM, Padda AK, Lydic R. Perineural dexmedetomidine provides an increased duration of analgesia to a thermal stimulus when compared with a systemic control in a rat sciatic nerve block. Reg Anesth Pain Med 2010; 35: 427–31

6 Brummett CM, Hong EK, Janda AM, Amodeo FS, Lydic R. Perineural dexmedetomidine added to ropivacaine for sciatic nerve block in rats prolongs the duration of analgesia by blocking the hyperpolarization-activated cation current. Anesthesiology 2011; 115: 836–43


8 Brummett CM, Padda AK, Amodeo FS, Welch KB, Lydic R. Perineural dexmedetomidine added to ropivacaine causes a dose-dependent increase in the duration of thermal antinociception in sciatic nerve block in rat. Anesthesiology 2009; 111: 1111–9


15 Lönqvist P. Alpha-2 adrenoceptor agonists as adjuncts to peripheral nerve blocks in children—is there a mechanism of action and should we use them? Paediatr Anaesth 2012; 22: 421–4


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