REGIONAL ANAESTHESIA

Minimal local anaesthetic volumes for sciatic nerve block: evaluation of ED_{99} in volunteers

D. Latzke\textsuperscript{1}, P. Marhofer\textsuperscript{1}\textsuperscript{*}, M. Zeitlinger\textsuperscript{2}, A. Machata\textsuperscript{1}, F. Neumann\textsuperscript{3}, E. Lackner\textsuperscript{2} and S. C. Kettner\textsuperscript{1}

\textsuperscript{1}Department of Anaesthesia, Intensive Care Medicine and Pain Therapy, \textsuperscript{2}Department of Clinical Pharmacology and \textsuperscript{3}Department of Medical Statistics and Informatics, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria

*Corresponding author. E-mail: peter.marhofer@meduniwien.ac.at

\textbf{Background.} This randomized, double-blinded volunteer study was designed to evaluate the ED_{99} volume of local anaesthetic for sciatic nerve blocks using a step-up/step-down methodology.

\textbf{Methods.} A maximum of 20 volunteers were included to receive an ultrasound-guided sciatic nerve block with mepivacaine 1.5\% and a starting volume of 0.2 ml mm\textsuperscript{-2} cross-sectional nerve area. In cases of a complete sensory block, the volume was reduced by 0.02 ml mm\textsuperscript{-2} cross-sectional nerve area until the first block failed. Thereafter, the volume of local anaesthetic was increased by 0.02 ml mm\textsuperscript{-2} cross-sectional nerve area. After three cycles of successful/failed blocks, the ED_{99} volume of local anaesthetic could be calculated by a probability function. The influence of the volumes of local anaesthetics on sensory onset times and duration of sensory block was evaluated by linear regression.

\textbf{Results.} The ED_{99} volume of local anaesthetic for sciatic nerve block was calculated with 0.10 ml mm\textsuperscript{-2} cross-sectional nerve area. The correlation between the volume of local anaesthetic and the sensory onset time was weak (r=0.14), whereas the correlation between the volume of local anaesthetic and the duration of sensory block was moderate (r=0.65).

\textbf{Conclusions.} This is the first study where an ED_{99} volume of local anaesthetic for sciatic nerve block has been evaluated. The resulting local anaesthetic volume of 0.10 ml mm\textsuperscript{-2} cross-sectional nerve area seems to have no impact on sensory onset time, whereas the duration of sensory block is shorter.

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The importance of peripheral regional anaesthesia is rapidly growing.\textsuperscript{1,2} Today, a large spectrum of surgical and pain-related cases are managed with peripheral nerve blocks. The most important prerequisites for the use of peripheral regional anaesthesia in the daily clinical practice are success rates and safety. Both issues are closely related to the administered volumes of local anaesthetics.

During the past decades, large volumes of local anaesthetics have been used for peripheral regional anaesthetic techniques to compensate for morphometric methods of nerve identification. Pure landmark-based, surface nerve mapping or nerve stimulation techniques may serve as examples of indirect methods of identification of peripheral nerves. As a consequence, upper limb blocks have been described with volumes up to 70 ml\textsuperscript{3–5} and lower limb blocks with volumes up to 40 ml of local anaesthetics.\textsuperscript{6–8} Sciatic nerve blocks are also performed with large volumes of local anaesthetics, and descriptions vary from 15 to 35 ml.\textsuperscript{9–14} Despite these large volumes, the overall failure rates for sciatic nerve blocks are described
between 7% and 11% in studies and may be higher in the daily clinical practice.

Direct ultrasonographic visualization of nerve structures enables the performance of blocks with reduced volumes of local anaesthetics. In an early attempt, our study group showed that the ultrasonographic guidance may reduce the volume of local anaesthetic for three-in-one blocks, and Casati and colleagues evaluated an ED95 volume of 22 ml for ultrasonographic-guided femoral nerve blocks. However, the technique of ultrasound-guided regional anaesthesia is rapidly improving, and successful axillary plexus block was recently performed with a volume of 1 ml per nerve. On the basis of a new method to measure the cross-sectional area of nerves by ultrasonography, we described ulnar nerve blocks with local anaesthetic 0.7 ml, which corresponds with an ED95 volume of 0.11 ml mm⁻² cross-sectional nerve area. Thus, the application of these initial results to larger nerves with a broad spectrum of clinical indications should be of particular interest for the regional anaesthetic community. But the ED95 volume for a peripheral nerve implies a failure rate of 5%. The pharmacodynamic model of a dose–response curve does not allow the evaluation of the ED100. However, any point on that curve between ED1 and ED99 can be evaluated. We therefore designed a randomized, double-blinded volunteer study to evaluate the ED99 volume of local anaesthetic for sciatic nerve blocks using a step-up/step-down methodology.

**Methods**

The Ethics Committee of the Medical University of Vienna authorized the investigators to include a maximum of 20 male volunteers between 18 and 50 yr in that study. A physical examination, blood samples (red blood count, white blood count, haemoglobin, haematocrit, platelet count, and blood coagulation parameters), ECG, and non-invasive arterial pressure were performed as a part of the volunteer selection process.

Inclusion criteria were written informed consent after detailed information about the nature, risk, and scope of this clinical study and the desirable and possible adverse effects of the study drug or complications associated with the regional anaesthetic technique. Exclusion criteria were the use of non-steroidal anti-inflammatory drugs during the last 2 weeks prior to the study; known allergy or hypersensitivity against the study drug or the drug class; coagulopathies; abnormalities in the ECG that are considered as clinically relevant, unreliability, lack of cooperation, or both; or other objections in the opinion of the investigators to participate in this study.

In the morning of the study day, the volunteers were admitted to the clinical research ward. A venous access with a switch valve was inserted into an ante-cubital vein, and blood samples, ECG, and non-invasive arterial pressure were again analysed to detect possible differences from the initial values.

With the volunteer in prone position, the sciatic nerve was investigated at the mid-femoral level between the long head of the biceps femoral muscle and the semitendinosus muscle in a cross-sectional view. Transportable ultrasound equipment (SonoSite M-Turbo, SonoSite Inc., Bothell, WA, USA) with an HFL 38 mm 13–6 MHz linear array transducer was used for the primary investigation and the block of the sciatic nerve. The depth (skin—posterior contour in millimetres), the circumference (in millimetres), and the area (in square millimetres) of the sciatic nerve were measured with the internal measurement software tool of the ultrasound machine (Fig. 1). The exact position of the measured nerve was marked on the posterior side of the thigh with a felt pen.

All blocks were performed by one anaesthesiologist with experience in ultrasonographic-guided regional anaesthetic techniques (P.M.). After cross-sectional ultrasonographic visualization of the sciatic nerve exactly at the position of the initial measurement of the nerve area, a skin wheal was performed with mepivacaine 1% (1.0 ml). The sciatic nerve block was performed with a 22 G 70 mm cannula with a facet tip (Polymedic™ by tenema, Z.I. des Amandiers, France) and an injection line under sterile conditions using the immobile needle technique. An in-plane needle guidance technique with the shaft of the needle longitudinal to the ultrasound probe was performed in all cases (Fig. 2). A pre-determined volume of mepivacaine 1.5% (1:1 mixture of 1% and 2% mepivacaine) was administered using a multi-injection technique after a volume reduction protocol (see below) under direct ultrasonographic guidance in order to achieve a circumferential spread of local anaesthetic. Before the administration of local anaesthetic, careful aspiration was performed to detect inadvertent intravascular needle position. The performance of the ultrasonographic-guided nerve block...
Low volume sciatic nerve block

Fig 2 In-line needle guidance technique for the ultrasound-guided block of the sciatic nerve at the mid-femoral level.

The calculated amount of local anaesthetic was prepared in a syringe by another study physician (M.Z.) than the one performing the block (P.M.). The injection of the local anaesthetic was made by the same physician (M.Z.) with the syringe covered, so that the injected volume was neither visible for the physician performing the block nor for the volunteer. The injections were made over an injection line and only the percentage of the total amount of the injected solution was communicated to the physician performing the block. Immediately after the end of the injection, the volunteer was brought into a different room and a third physician who was unaware of the injected amount of local anaesthetic evaluated and recorded the sensory scores to control block success and duration (D.L.).

A pinprick test in comparison with the contralateral area propriae was used to evaluate the sensory block. The following innervation areas were investigated: superficial peroneal nerve, deep peroneal nerve, sural nerve, calcaneal plantar nerve, lateral plantar nerve, and medial plantar nerve. One hundred per cent was graded as no difference in sensitivity (=no sensory block), and 0% was graded as maximum difference in sensitivity (=complete sensory block). Proportions of 10% were evaluated. The definition of a complete sensory block was a pinprick test of 0% in all innervation areas of the sciatic nerve 45 min after block performance. Pinprick testing was performed prior to the block, 2, 4, 6, 10, 15, 20, 30, 45, and 60 min after the block, and thereafter every 30 min until complete recovery from sensory block.

The definition of sensory onset time was the time from performance of the block to pinprick=0 in all innervation areas and the definition of duration of sensory block was the time from performance of the block to pinprick=100 in the first of the six innervation areas of the sciatic nerve.

We included only the clinical relevant sensory scores, and not motor scores, in the statistical analysis. The primary endpoint was the block success; secondary endpoints were sensory onset time and duration of sensory block. Twenty-four hours after performance of the sciatic nerve block, the sensory innervation areas of the sciatic nerve were re-investigated by pinprick testing and the puncture area was investigated to detect a local infection or haematoma.

Statistical analysis

From binary response data (response, complete sensory block; no response, insufficient block), response probabilities were estimated for each volume level (dosage) of mepivacaine 1.5% and fit to a probit model function. The resulting probability function yields continuous estimates of the response probabilities over the full range of dosage volumes. From this curve, the 1.5% mepivacaine volume can be obtained which produces a complete sensory block in 50% (ED50), 95% (ED95), and 99% (ED99) of the subjects.

Correlation of the volume of 1.5% mepivacaine mm⁻² cross-sectional nerve area relative to the sensory onset time and duration of sensory block was done by linear regression (Origin Pro7, OriginLab Cooperation, MA, USA).

The SAS System V9.2 (SAS Institute Inc., Cary, NC, USA) was used for computational procedures.
Results

Nineteen volunteers were required to evaluate the ED$_{99}$ volume of local anaesthetic for sciatic nerve block. The ultrasonographic visualization of the sciatic nerve and the subsequent measurements were possible in all volunteers. We performed 13 blocks on the right and 6 blocks on the left side.

The patient characteristic data and morphometric data of the sciatic nerves are presented in Table 1. The volume of local anaesthetic in ml mm$^{-2}$ cross-sectional nerve area for each individual volunteer is illustrated in Figure 3, with 14 successful blocks and 5 block failures. The probit analysis resulted in an ED$_{50}$, ED$_{95}$, and ED$_{99}$ of 0.04, 0.08, and 0.10 ml mm$^{-2}$ cross-sectional nerve area, respectively (Fig. 4).

We found no correlation between the volume of local anaesthetic and the sensory onset time ($r=0.14$), whereas the correlation between the volume of local anaesthetic and the duration of sensory block was moderate ($r=0.65$). Figures 5 and 6 illustrate these data.

We did not find any study-related side-effects at the post-study investigation.

Discussion

An ED$_{99}$ local anaesthetic volume of 0.10 ml mm$^{-2}$ cross-sectional nerve area was evaluated for ultrasonographic-guided sciatic nerve blocks by using the step-up/step-down

Table 1 Patient characteristics and sciatic nerve measurements at the mid-femoral level

<table>
<thead>
<tr>
<th>Median (range) measurements</th>
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<tr>
<td>Height (cm)</td>
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<tr>
<td>Weight (kg)</td>
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<tr>
<td>BMI (kg m$^{-2}$)</td>
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<tr>
<td>Depth of the sciatic nerve (mm)</td>
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<td>Circumference of the sciatic nerve (mm)</td>
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<td>Cross-sectional nerve area (mm$^2$)</td>
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Fig 3 The up-and-down sequence of volumes of mepivacaine 1.5% to achieve a sensory block of the sciatic nerve. The injected volume of local anaesthetic in ml mm$^{-2}$ cross-sectional nerve area is shown in each volunteer.

Fig 4 Correlation of the volume of 1.5% mepivacaine mm$^{-2}$ cross-sectional nerve area vs probability for complete sensory blocks within 45 min. Squares represent observed cases; size of squares indicates the number of cases for the respective volume (between 1 and 5). The line indicates fit by a probit model function.

Fig 5 Correlation of the volume of 1.5% mepivacaine mm$^{-2}$ cross-sectional nerve area and time to a complete sensory block. The line represents fit by linear regression ($r=0.14$, $P=0.63$). Only subjects with successful blocks are shown.

Fig 6 Correlation of the volume of 1.5% mepivacaine mm$^{-2}$ cross-sectional nerve area and duration of sensory block. The line represents fit by linear regression ($r=0.65$, $P=0.003$).
One of the main advantages of ultrasonographic guidance for nerve blocks is the possibility to reduce the volumes of local anaesthetics, which is mainly due to the direct observation of the spread of local anaesthetic. In a number of earlier attempts, significant lower volumes of local anaesthetics have been described for ultrasound-guided nerve identification techniques when compared with nerve stimulation. Marhofer and colleagues showed similar block qualities of nerve stimulator-guided three-in-one blocks with 20 and 30 ml, where faster sensory onset times have been observed with 20 ml when ultrasonographic guidance was used. Casati and colleagues described an ED95 local anaesthetic volume of 22 ml for ultrasonographic-guided femoral nerve block, and Oberndorfer and colleagues showed that ultrasonographic-guided femoral and sciatic nerve blocks can be successfully performed with low volumes in children.

Recently, extreme low volumes of local anaesthetics have been used by O’Donnell and Iohom and by our group, either still resulting in successful nerve blocks or describing the ED95 of local anaesthetic volumes for a specific block. O’Donnell and Iohom used the usual approach by investigating patients undergoing elective surgery. The up-and-down method for determining the dose–response curve of local anaesthetics has the drawback that a number of blocks have to fail. When used in a clinical setting, this might lead to significant pain in some patients and to ethical issues. O’Donnell and Iohom prevented these block failures by implementing a rule that the study will be stopped, if five consecutive blocks are successful with the arbitrary volume of local anaesthetic 1 ml per nerve. However, this stopping rule also prevented the estimation of the dose–response curve. The authors postulate that reducing the volume beyond 1 ml per nerve is of little clinical significance. Although not of clinical significance, the scientific importance of ED50 volumes is given. It is a prerequisite for the determination of safe and effective dosages of drugs to evaluate dose–response curves.

By investigating volunteers in a laboratory setting, we avoided the ethical issues of failed blocks and consecutive pain. Moreover, we had the better controlled setting in a laboratory to investigate healthy volunteers, compared with the setting in an operating theatre investigating patients undergoing surgery, which might lead to a higher variability of the results.

The present study is the first which provides the ED99 volume of local anaesthetic for peripheral nerve blocks. Several ‘ED’ volumes have been evaluated in the past for different regional anaesthetic techniques. Mainly, the ED50 and ED95 have been described in this context. The definition of both values is a failure rate of 50% and 5%, respectively. Failure rates due to insufficient volumes of local anaesthetic are inappropriate for regional anaesthesia. Therefore, we provide the ED99, which is associated with a failure rate of only 1%. An ED100 cannot be evaluated by the pharmacodynamic model of a dose–response curve, as the curve asymptotically approaches a 100% success rate.

The ED99 volume for the block of the sciatic nerve in the current study is 0.10 ml mm⁻² cross-sectional nerve area, which is equivalent to 5.7 ml for a sciatic nerve with a cross-sectional area of 57 mm² (the mean value in this study), 2.8 ml for the smallest and 10.2 ml for the largest nerve. In fact, the successful sciatic nerve block with the lowest volume of local anaesthetic was performed with 1.7 ml (Case 17, 42 mm² cross-sectional nerve area, 0.04 ml mm⁻² local anaesthetic per cross-sectional nerve area). In this case, the probability of a successful block would be 50% (Fig. 4). A complete surrounding of the nerve with local anaesthetic is not possible with such a low volume (Fig. 7), but nonetheless the block was sufficient. Therefore, the popular hypothesis for successful performance of peripheral nerve block, that the local anaesthetic has to surround the nerve completely (‘donut sign’), should be reconsidered.

Whether the volume of local anaesthetic influences the onset or duration of a particular regional anaesthetic technique remains unclear. The literature regarding that topic is heterogenic. Although some publications report shorter onset times and duration of block when lower volumes are used, others do not. We observed a moderate correlation between volumes of local anaesthetics and duration of blocks (r=0.65), whereas the sensory onset time remained unaffected by the volume of local anaesthetic.

Fig 7 Cross-sectional view of the sciatic nerve at the mid-femoral level with the local anaesthetic covering the posterior aspect of the nerve. The local anaesthetic solution is indicated with the arrows. The successful block was performed with 0.1 ml mm⁻² cross-sectional nerve area (=5.1 ml total volume of local anaesthetic).
The results of this study have to be confirmed in a larger number of cases. The evaluated ED99 is the individual value of an experienced user and maybe less experienced practitioners need larger volumes for successful sciatic nerve blocks. Anyway, if the calculated volume of local anaesthetic is injected directly adjacent to the nerve under real-time ultrasonographic visualization, the ED99 volume of local anaesthetic provides a successful block. Thus, the routine calculation of the volume of local anaesthetic based on the cross-sectional nerve area could be useful to avoid inappropriate large volumes of local anaesthetic. The prerequisite for the successful performance of blocks with this ED99 volume of local anaesthetic is an exact needle guidance technique.

In summary, this is the first study where an ED99 volume of local anaesthetic for sciatic nerve block has been evaluated. The resulting local anaesthetic volume of 0.10 ml mm⁻² cross-sectional nerve area seems to have no impact on sensory onset time, but the duration of sensory block is shorter with such low volumes of local anaesthetics. The evaluated ED99 is the individual value of an experienced user and subsequent studies will show if the results of that study can be transferred to the daily clinical practice.

References

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