Diabetic neuropathy increases stimulation threshold during popliteal sciatic nerve block†

S. Heschl1, B. Hallmann1, T. Zilke1, G. Gemes1, M. Schoerghuber1, M. Auer-Grumbach2, F. Quehenberger3, P. Lirk4, Q. Hogan5 and M. Rigaud1,*

1Department of Anaesthesiology and Intensive Care Medicine, Medical University of Graz, Auenbruggerplatz 29/1, Graz 8036, Austria, 2Department of Internal Medicine, Medical University of Graz, Auenbruggerplatz 15, Graz 8036, Austria, 3Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Auenbruggerplatz 2, Graz 8036, Austria, 4Department of Anaesthesiology, Academic Medical Centre, University of Amsterdam, Meibergdreef 9, Amsterdam 1105AZ, The Netherlands, and 5Department of Anesthesiology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA

*Corresponding author. E-mail: marcelrigaud@gmail.com

Abstract

Background: Peripheral nerve stimulation is commonly used for nerve localization in regional anaesthesia, but recommended stimulation currents of 0.3–0.5 mA do not reliably produce motor activity in the absence of intraneural needle placement. As this may be particularly true in patients with diabetic neuropathy, we examined the stimulation threshold in patients with and without diabetes.

Methods: Preoperative evaluation included a neurological exam and electroneurography. During ultrasound-guided popliteal sciatic nerve block, we measured the current required to produce motor activity for the tibial and common peroneal nerve in diabetic and non-diabetic patients. Proximity to the nerve was evaluated post-hoc using ultrasound imaging.

Results: Average stimulation currents did not differ between diabetic (n=55) and non-diabetic patients (n=52). Although the planned number of patients was not reached, the power goal for the mean stimulation current was met. Subjects with diminished pressure perception showed increased thresholds for the common peroneal nerve (median 1.30 vs. 0.57 mA in subjects with normal perception, P=0.042), as did subjects with decreased pain sensation (1.60 vs. 0.50 mA in subjects with normal sensation, P=0.038). Slowed ulnar nerve conduction velocity predicted elevated mean stimulation current (r=−0.35, P=0.002). Finally, 15 diabetic patients required more than 0.5 mA to evoke a motor response, despite intraneural needle placement (n=4), or required currents ≥2 mA despite needle-nerve contact, vs three such patients (1 intraneural, 2 with ≥2 mA) among non-diabetic patients (P=0.003).

Conclusions: These findings suggest that stimulation thresholds of 0.3–0.5 mA may not reliably determine close needle-nerve contact during popliteal sciatic nerve block, particularly in patients with diabetic neuropathy.

Clinical trial registration: NCT01488474

Key words: diabetic neuropathies; nerve block; peroneal nerve; tibial nerve

†Study registered online Dec 02, 2011 at ClinicalTrials.gov: Identifier NCT01488474, Principal Investigator Marcel Rigaud (https://clinicaltrials.gov/ct2/show/NCT01488474?term=NCT01488474&rank=1).
Accepted: December 21, 2015
© The Author 2016. Published by Oxford University Press on behalf of the British Journal of Anaesthesia.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Electrical peripheral nerve stimulation (PNS) is a common technique for identifying the needle endpoint in regional anaesthesia. However, electrical impedances are not uniform across different body regions and the mix of tissues surrounding a peripheral nerve is not homogeneous, which challenges the use of PNS alone to detect optimal needle position. While the generally recommended stimulation current is 0.3–0.5 mA, this threshold or even higher currents cannot exclude intraneural needle placement. The choice of stimulation current level may be of particular importance when performing PNS in patients with pre-existing neurological deficits, such as diabetic neuropathy. Reports have shown increased stimulation thresholds for diabetic patients, including patients in which no motor response to PNS could be obtained with 2.4 mA, despite clear needle-nerve contact witnessed by ultrasound (US). Animal data also suggest that low-threshold electrical stimulation does not protect against intraneural injection in the presence of diabetes mellitus. Although nerve injury is usually followed by recovery, it remains a major concern and harm can best be avoided by an approach whereby the needle does not enter the nerve. We therefore designed this study to determine the effect of diabetes and diabetic neuropathy on stimulation currents required to elicit motor response during distal sciatic nerve block.

Methods

This study was approved by the institutional review board of the Medical University of Graz (24-064 ex 11/12) and registered online (ClinicalTrials.gov Identifier: NCT01488474, PI Marcel Rigaud, registered Dec 02, 2011). Written informed consent was obtained from all subjects.

Patients

Surgical lists were screened for patients undergoing lower limb surgery, eligible for popliteal SN block. We included patients aged 18+ and ASA status I to IV. Exclusion criteria were pregnancy, on-going platelet therapy (as dictated by institutional human research panel), allergies to local anaesthetics, and pre-existing neuropathy not attributable to diabetes mellitus. Recruitment followed stratification by age group, sex and diabetes status. Non-diabetic patients were only included to match the number of diabetic patients in the respective group to ensure equal distribution of patients.

Diabetic neuropathy

All included patients were screened preoperatively for signs of neuropathy. A clinical exam of the patient’s foot based on the guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy was performed. Perception of vibration was assessed by a 128 Hz tuning fork on the medial malleolus and the halluc and graded on a scale 0–8. Perception of light touch by cotton wisp, pressure reception by a 10 g monofilament, pain sensation by pin prick test and temperature discrimination by a device that tests the subject’s ability to distinguish two materials of differing thermal conductivity (tip therm®, tip therm GmbH, Brueggen, Germany) were all scored as present or absent. The strength of the Achilles tendon reflex was determined by Achilles tendon percussion using a standard reflex hammer (scale 0–2). The ankle-brachial index (ABI) was calculated using the systolic bp of the respective lower and upper limb. Non-invasive electroneurography (ENG) examinations, including conduction velocity (CV) and distal motor latency (DML), were performed using standardized methods and evaluated by a certified electrophysiologist (M.A.-G.), to quantify diabetic neuropathy and to detect subclinical forms of neuropathy. Preferred side of ENG for tibial nerve (TN) and common peroneal nerve (CPN) was the side of planed surgery. If that was impossible because of patient factors (e.g. casts, pain, previous amputation), the other side was used. The ulnar nerve was measured as a reference.

Sciatic nerve block

For the procedure, patients were placed in a supine position on the operating table. Vital signs were monitored according to current standards of care, which included three-lead-electrocardiogram, automated non-invasive bp, and pulse oximetry monitoring. Oxygen was applied via a non-rebreathing mask and an i.v. line inserted. Analgesia and sedation were achieved by continuous infusion of remifentanil 0.05–0.1 mcg·kg⁻¹·min⁻¹ and a 0.01–0.05 mg·kg⁻¹ bolus of midazolam.

The respective extremity was elevated such that the popliteal region was accessible for the ultrasound probe. The nerve blocks were performed using the standard lateral in-plane ultrasound-guided approach, using a SonoSite S-Nerve ultrasound machine (SonoSite, WA, USA) with a 10–15MHz linear transducer, a 20G, 120mm ultrasound needle (Stimuplex-D, BBraun, Melsungen, Germany) and a Stimuplex HNS 12 nerve stimulator (BBraun, Melsungen, Germany).

Stimulation threshold

The nerve stimulation threshold was determined for both the CPN and TN, with the sequence defined by a pre-determined randomization list generated using an online randomization tool (Randomizer®, available at www.randomizer.at). The point was identified distal to the bifurcation of the SN at which the TN and CPN were clearly separated, the stimulation needle inserted and, under live US-imaging, positioned in close contact with the nerve without penetration of the epineurium (Fig. 1). This endpoint was verified by three signs on ultrasound: (1) the needle tip was localized next to the nerve, (2) when the needle was slightly advanced, the nerve was pushed away, and (3) the nerve moved accordingly to a slight poking movement, but when the needle was moved in an anterior-posterior direction, the nerve did not follow the needle. The nerve stimulator was then turned on with the following settings: stimulus duration 0.1 ms, stimulus frequency of 1Hz and a stimulation current of 0.0 mA. Stimulation current was gradually increased until a visibly obvious motor response of the respective muscles occurred. Thereafter, the minimal stimulation threshold current was verified by reducing the current until the distal motor response vanished. The anaesthetist...
performing the nerve block was blinded to the stimulation current and did not move or reposition the needle during measurements. After this measurement, 1ml of glucose 5% was injected during imaging to facilitate post hoc verification of the exact needle position. Injection pressure was monitored (BSmart, Concert Medical, MA USA) during the injection. The same procedure was then performed on the remaining branch of the SN. All relevant steps were documented using image and video recording.

Nerve block

After completion of measurements, 30ml ropivacaine 0.5% or mepivacaine 1% was injected, depending on the expected duration of surgery, using a multi-injection technique around both branches of the SN.

Post-hoc evaluation of US-imaging

Two blinded investigators evaluated the ultrasound images and videos of the procedure using the same criteria as the investigator performing the block, with the additional information of the spread pattern of 1ml injection of glucose 5%. Needle positions were classified as appropriate (needle-nerve contact), intraneural, or distant (no needle-nerve contact). In accordance with recent studies, we only classified needle positions that led to subepineural spread of the glucose at the two distinct branches (TN, CPN) of the sciatic nerve as intraneural. An injection into the paraneural space was not considered intraneural. If there was dissent between the investigators, another investigator was questioned and a decision was made by consensus.

Follow up

Patients were evaluated on the first postoperative day and again before discharge for any neurological complications. Telephone follow-up was performed after six months and any possible neurological complications were investigated by a neurologist (M.A.-G.).

Statistical analysis

As the stimulation threshold was not normally distributed, non-parametric significance tests were used. Stimulation threshold was analysed both as separate values for the CPN and TN, and as the mean of these for each subject. The association of categorical variables to the stimulation threshold was calculated using the Wilcoxon test. Correlations of numerical variables to the stimulation thresholds were analysed with the Spearman test, and the Ansari-Bradley test was used to compare variances in stimulation currents between groups. For comparison of proportions, Fisher’s exact test was used. Data are presented as median and interquartile ranges. R version 3.1.2 (available online at www.r-project.org) was used for calculations, and P-values below 0.05 are considered significant. A sample size of 70 per group was initially targeted, based on a 0.3 mA difference in stimulation thresholds. The scheduled sample size was not attained during the study period and it was not possible to extend the study period because there was no further funding available. A post hoc power analysis based on the observed standard deviations from analysis of variance (sd CPN 0.80 mA, sd TN 0.53 mA, sd Mean 0.49 mA) yielded a power of 80% to find effect sizes of 0.40 mA for the CPN, 0.26 mA for the TN and 0.24 mA for the mean stimulation current.

Results

A total of 122 patients were initially included in the study. In two patients, the preoperative neurologic evaluation revealed previously undiagnosed polyneuropathies, which were unrelated to DM, and one patient did not tolerate the neurologic evaluation. Surgery was either cancelled or postponed to a time when the study team was unable to perform the stimulation measurements in four patients, and regional anaesthesia was ultimately not performed in two patients. In a further six patients, technical problems occurred, including inability to record or store US imaging. Full data was available for 55 diabetic and 52 non-diabetic patients. Threshold data was not used from subjects in which post-hoc examination of needle position showed either that the needle was distant from the nerve or within the nerve.

Diabetic patients weighed more and had a higher BMI (Table 1). They more often had signs of neurological dysfunction including decreased sensitivity to light touch, pressure, painful stimulus,
Table 1 Patient characteristics. Data are presented as median (interquartile range) unless otherwise specified.

|                        | DM (n=55) | Non-DM (n=52) | P     |
|------------------------|-----------|---------------|-------|
| Male [n (%)]           | 29 (52.7%)| 27 (51.9)     | 1     |
| Weight Mean (sd)       | 87 (14)   | 78 (16)       | 0.002 |
| Height Mean (sd)       | 169 (10)  | 168 (9)       | 0.43  |
| BMI                    | 30 (26-33)| 27 (25-30)    | 0.006 |
| Age Mean (Range)       | 69 (44-90)| 69 (41-88)    | 0.75  |
| History of diabetes [yr]| 9 (4-14)  | -             |       |
| Present light touch perception [n (%)] | 40 (72.7) | 51 (98.1)     | <0.001|
| Present temperature discrimination [n (%)] | 19 (34.5) | 41 (78.8)     | <0.001|
| Present pressure perception [n (%)] | 44 (80.0) | 51 (98.1)     | 0.008 |
| Present pain sensation [n (%)] | 45 (81.8) | 52 (100)      | 0.003 |
| ABI Dorsalis pedis artery | 1.0 (1.0-1.5) | 1.1 (1.0-1.3) | 0.66  |
| ABI Posterior tibial artery | 1 (1.0-1.5) | 1.1 (1.0-1.3) | 0.69  |
| Vibration hallux       | 2 (0-5)   | 6 (4-7)       | <0.001|
| Achilles tendon reflex  | 1 (1-2)   | 2 (2-2)       | <0.001|
| Common peroneal nerve DML [ms] | 13 (12-15) | 12 (11-13) | 0.047 |
| Common peroneal nerve CV [m·s\(^{-1}\)] | 41 (34-44) | 46 (43-49)    | <0.001|
| Tibial nerve DML [ms]  | 15 (14-16)| 15 (13-15)    | 0.31  |
| Tibial nerve CV [m·s\(^{-1}\)] | 40 (36-44) | 44 (39-47)    | 0.009 |
| Ulnar nerve DML [ms]   | 8 (7-9)   | 7 (7-8)       | 0.002 |
| Ulnar nerve CV [m·s\(^{-1}\)] | 53 (47-58) | 58 (54-62) | <0.001|

Fig 2 Comparison of minimal stimulation current required to elicit a motor response with close needle-nerve contact between patients with and without diabetes mellitus for the common peroneal nerve (A) and tibial nerve (B).

vibration, and temperature, and deficits in Achilles tendon reflex and neural conduction.

Stimulation currents did not differ between diabetic and non-diabetic patients for the CPN [0.80 (0.37–1.50) vs. 0.50 (0.34–0.97), P=0.20], the TN [0.80 (0.48–1.10) vs. 0.45 (0.40–0.88), P=0.05] and the mean of both nerves [0.69 (0.44–1.06) vs. 0.58 (0.37–0.88), P=0.29] (Fig. 2). A high degree of variability was found in both diabetic and non-diabetic patients, but variances were not significantly different between the groups (CPN: P=0.35; TN: P=0.53 mean current: P=0.14). With close needle-nerve contact, 29 diabetic (57%) and 22 (48%) non-diabetic patients required stimulation currents >0.5 mA for the CPN (P=0.42), and for the TN, >0.5 mA was required for 31 (63%) diabetics and for 19 (42%) non-diabetics (P=0.06). There was also a positive correlation between the duration of diabetes and the stimulation current for the CPN (Table 2), and absence of pressure perception and pain sensation predicted elevated stimulation threshold of the CPN (Table 3), as did reduced strength of the Achilles tendon reflex.

Neuronal dysfunction revealed by electroneurography was also variably associated with elevated stimulation current. For the CPN, conduction velocity negatively correlated with stimulation current, while elevated distal motor latency predicted increased TN current threshold. Nerve conduction properties of the ulnar nerve showed the most robust correlations to stimulation currents for the CPN and TN (Table 2). The ulnar nerve conduction velocity showed a highly significant negative correlation to stimulation current for both the CPN and the TN (Fig. 3), and the mean stimulation current. The ulnar nerve distal motor latency correlated with the stimulation current of the CPN and the mean current. The correlations however were only moderate.

The order of measurements (CPN or TN first) had no effect on stimulation current (data not shown).

We note that intraneural needle placement (four diabetic, one non-diabetic) occurred despite stimulation currents >0.5 mA. Additionally, stimulation currents ≥2 mA were necessary to evoke motor response in 14 patients (12 diabetic of which one patient had intraneural needle placement at the TN and required ≥2 mA with close needle-nerve contact for the CPN and two non-diabetic) despite close needle-nerve contact. Considering these patients at particular risk for nerve damage, they constitute 27% of the total diabetic group, which is substantially elevated compared with the non-diabetic group (6%, P=0.003).

No injection of 1ml of glucose 5% for needle position verification required an injection pressure greater than 15psi, and no patient reported any pain or paraesthesia during the procedure. After six months, there were no permanent nerve injuries attributable to peripheral regional anaesthesia.

**Discussion**

In this study, we aimed to determine the effect of diabetic neuropathy on the current threshold for nerve stimulation during popliteal sciatic nerve block. We found that not only did a
substantial number of healthy subjects fail to exhibit motor response at 0.3–0.5 mA, but also that subjects with manifestations of diabetic neuropathy required substantially elevated currents to produce motor responses.

**Motor response threshold**

Our first observation was a wide variation in the nerve stimulation threshold of the TN and CPN, even in healthy subjects. Whether the sciatic nerve can be reliably detected using the conventionally accepted threshold of 0.3–0.5 mA has been the subject of debate. On one hand, Dufour and Keyl observed almost no variability in stimulation threshold during popliteal nerve block in patients without neuropathy, and these findings are in accordance with very small variation in stimulation thresholds in healthy volunteers. On the other hand, recent clinical evidence suggests that even when using 0.5 mA as the upper limit of accepted nerve stimulation threshold, intraneural injection of the popliteal sciatic nerve frequently occurs, suggesting that this threshold may be inappropriate for some patients during popliteal nerve block. The anatomy of the sciatic nerve in the popliteal fossa is unique, composed of two constituent nerves (common peroneal, tibial) within a common connective tissue sheath. Here, the sciatic nerve consists of more than 50% non-neuronal tissue, which forms a barrier to local anaesthetic penetration and nerve stimulation.

**Diabetes mellitus and nerve stimulation threshold**

We note that a diagnosis of diabetes mellitus per se was not associated with an increase in mean nerve stimulation threshold as compared with non-diabetic control patients. Only when analysed separately did diabetic patients exhibit higher stimulation currents at the TN compared with non-diabetic control patients. Only when analysed separately did diabetic patients exhibit higher stimulation currents at the TN compared with non-diabetic control patients.

**Table 2** Correlation between preoperative neurologic exams and stimulation currents

|                          | Current Common peroneal nerve | Current Tibial nerve | Mean current |
|--------------------------|-------------------------------|----------------------|--------------|
|                          | P   | r     | P   | r     | P   | r     |
| Duration of diabetes     | 0.022 | 0.34 | 0.73 | – | 0.15 | – |
| ABI Dorsalis pedis artery| 0.81 | –     | 0.15 | – | 0.66 | – |
| ABI Posterior tibial artery| 0.98 | –     | 0.10 | – | 0.49 | – |
| Vibration mal. med.       | 0.45 | –     | 0.09 | – | 0.34 | – |
| Vibration hallux          | 0.94 | –     | 0.69 | – | 0.82 | – |
| Achilles tendon reflex    | 0.044 | –0.21 | 0.22 | – | 0.07 | – |
| Common Peroneal nerve DML| 0.07 | –     | 0.06 | – | 0.10 | – |
| Common Peroneal nerve CV  | 0.013 | –0.27 | 0.05 | – | 0.045 | –0.24 |
| Tibial nerve DML          | 0.12 | –     | 0.029 | 0.25 | 0.049 | 0.24 |
| Tibial nerve CV           | 0.46 | –     | 0.13 | – | 0.35 | – |
| Ulnar nerve DML           | 0.003 | 0.30 | 0.11 | – | 0.049 | 0.22 |
| Ulnar nerve CV            | <0.001 | –0.36 | 0.010 | –0.27 | 0.002 | –0.35 |

**Table 3** Association of preoperative neurologic exams with stimulation currents. Data are presented as median (interquartile range)

|                          | Present                  | Absent                  | P     |
|--------------------------|--------------------------|-------------------------|-------|
| Current Common peroneal nerve | Light touch perception | 0.52 (0.32–1.00) | 0.80 (0.41–1.80) | 0.11 |
|                          | Temperature discrimination | 0.50 (0.35–1.00) | 0.80 (0.34–1.10) | 0.55 |
|                          | Pressure perception      | 0.57 (0.30–1.00) | 1.30 (0.50–1.60) | 0.042 |
|                          | Pain sensation           | 0.50 (0.32–1.00) | 1.60 (0.70–2.00) | 0.038 |
| Current Tibial nerve     | Light touch perception   | 0.50 (0.40–0.90) | 0.75 (0.57–1.20) | 0.14 |
|                          | Temperature discrimination | 0.50 (0.40–0.90) | 0.70 (0.45–1.10) | 0.26 |
|                          | Pressure perception      | 0.55 (0.40–1.00) | 0.65 (0.60–0.88) | 0.30 |
|                          | Pain sensation           | 0.55 (0.40–1.00) | 0.60 (0.60–0.70) | 0.90 |
| Mean current             | Light touch perception   | 0.63 (0.42–0.96) | 0.89 (0.48–1.20) | 0.19 |
|                          | Temperature discrimination | 0.66 (0.45–0.98) | 0.66 (0.37–0.98) | 0.87 |
|                          | Pressure perception      | 0.63 (0.4–0.98) | 0.76 (0.60–1.00) | 0.17 |
|                          | Pain sensation           | 0.63 (0.42–0.94) | 0.98 (0.53–1.10) | 0.18 |
observations indicate that neuropathy, rather than the diagnosis of diabetes mellitus per se, is the critical predictor of altered nerve responses to regional anaesthesia.

In considering risk however, it may not be sufficient to evaluate group averages alone, as outlier events may represent significant risk. In our study, even when the needle was unintentionally placed intraneurally, as assessed by post-hoc US image evaluation, we found four patients who required stimulating currents exceeding 0.5 mA, even reaching a stimulation threshold of 2.5 mA in one diabetic patient. Despite having the needle in close contact with the nerve, we observed frequent outliers regarding motor stimulation threshold. Fourteen patients showed a motor response only with stimulation currents $\geq 2$ mA (12 diabetic and two non diabetic) and six of those patients even required stimulation currents $\geq 3$ mA (five diabetic and one non diabetic). These patients are at high risk for intraneural needle placement if PNS is used as the sole tool to identify correct needle position. The significantly higher proportion of these patients in the diabetic group warrants particular caution when performing regional anaesthesia without the additional aid of ultrasound.

Together with a generally high variability of stimulation thresholds both in diabetic and non-diabetic patients, our findings challenge the concept that stimulation thresholds of 0.3–0.5 mA reliably preclude possibly harmful intraneural needle placement during popliteal nerve block. Our results may therefore, in part, explain the phenomenon of popliteal intraneural injection despite the use of conventionally adequate nerve stimulator settings.6 21

**Diabetic neuropathy and nerve stimulation threshold**

Finally, we show that diabetic neuropathy, when assessed by electroneurography, is associated with increased nerve stimulation thresholds, as has been described in a case report.26 In dogs with long-standing diabetes, using conventional stimulation thresholds during sciatic nerve block was associated with a high risk of intraneural injection.10 A study that systematically looked at stimulation thresholds during supraclavicular nerve block revealed a subset of 18% of patients with diabetes mellitus in whom the threshold was increased by more than twofold as compared with healthy controls, with a large interindividual variability in the diabetic group.4 In patients with diabetic gangrene, stimulation thresholds were increased seven-fold compared with non-diabetic controls, again with substantial interindividual variability among diabetic patients.5 Our findings similarly indicate that the nerve stimulation threshold in diabetic neuropathy is increased, and we confirm the large interindividual variability. In our diabetic patients, we observed a direct correlation between the duration of diabetes mellitus and the stimulation threshold for the CPN, the nerve that is typically more affected by diabetic neuropathy than the TN.27 We conclude that diabetes alone does not change the way a nerve reacts to stimulation, but that diabetic neuropathy is associated with a profound change in nerve physiology, resulting in such changes as increased block duration28–30 and altered nerve excitability.23 24

**Clinical consequences**

Our study shows that the nerve stimulation threshold is increased in diabetic neuropathy. However, the exact evaluation of a diabetic neuropathic state is difficult in daily clinical practice and diabetic neuropathy cannot be easily correlated to expected stimulation thresholds for peripheral nerve stimulation. It also shows that nerve stimulation is not as reliable as previously thought and even more so in patients with diabetic neuropathy. It is therefore advisable to use additional tools such as ultrasound to decrease the risk of potentially harmful intraneural injections.

**Limitations**

Even in experienced hands, sonographic identification of the exact position of the needle tip can be challenging. We addressed this limitation with post-hoc analysis of stored images and video
interpretation by two blinded investigators. Further, the injection of a small amount of glucose after the first measurement to facilitate needle position verification however might have altered conduction characteristics of the tissue for the consecutive measurements. Therefore the sequence of investigation was randomized and we limited the injection volume to 1ml of glucose 5%, which is thought not to impair nerve conduction.\(^\text{31}\) Next, preoperative ENG was not always possible on the same side as the measurement because of various reasons (cast, previous amputation). However, as diabetic neuropathy is symmetrical\(^\text{27}\) this should not alter our results and resemble clinical practice. This study evaluated stimulation thresholds at a point where the two branches of the sciatic nerve were clearly separated. It remains unclear whether our results can be extrapolated to the sciatic nerve as a whole or even other peripheral nerves. Conversely, most previous studies have been performed on the sciatic nerve before its division and the validity of their results for the separate branches of the sciatic nerve cannot be determined. Finally, as permanent needle-placement related nerve injury is rare,\(^\text{25}\) this study, together with most studies in this field, was not powered to determine whether patients with pre-existing diabetic neuropathy were at higher risk of nerve injury. We note that six months after nerve blocks, with a small number of unintentional, intraneural needle placements, we observed no clinically apparent permanent nerve damage.

Conclusion
The variability of stimulation currents encountered suggests that the generally accepted target stimulation threshold of 0.3–0.5 mA may not lead to reliable nerve stimulation during popliteal sciatic nerve block, even in healthy patients and necessary stimulation currents exceeding 0.5 mA despite close needle-nerve contact are frequent. Whereas diabetic patients as such did not exhibit different stimulation thresholds, they were at significantly higher risk of possible intraneural needle injection if PNS had been used without ultrasound. In contrast, patients with diabetic neuropathy require significantly increased nerve stimulation thresholds. The use of simple clinical tests may allow for the detection of neuropathic patients, but given the substantial variability observed, the optimal threshold for any individual diabetic neuropathic patient may be impossible to predict \textit{a priori}.

Authors’ contributions
Study design: S.H., G.G., M.A.-G., F.Q., Q.H., M.R.
Study conduct: S.H., B.H., T.Z., G.G., M.S., M.A.-G., M.R.
Data analysis: S.H., M.A.-G., F.Q., P.L., Q.H., M.R.
Writing paper: S.H., P.L.
Revising paper: all authors

Acknowledgements
The authors would like to acknowledge the assistance of Thomas Boessner M.D and Maria Gries M.D., Department of Anaesthesiology and Intensive Care Medicine, University Hospital Graz, Austria, in the operating theatre in the process leading to the study and Gerd Koehler M.D, and Ulrike Leb-Stoeeger M.D., Department of Internal Medicine, University Hospital Graz, Austria, for their support with the evaluation of diabetic patients.

Declaration of interests
None declared.

Funding
This work was supported by the Austrian Science Fund (FWF), Sensengasse 1, 1090 Vienna, Austria [grant KLI 135-B00]. BBraun\(^\circ\), Carl-Braun-Straße 1, 34212 Melsungen, Germany provided a nerve stimulator and the stimulation needles free of charge.

References
1. Brull R, Wijayatilake DS, Perlas A, et al. Practice Patterns Related to Block Selection, Nerve Localization and Risk Disclosure: A Survey of the American Society of Regional Anesthesia and Pain Medicine. \textit{Reg Anesth Pain Med} 2008; 33: 395–403
2. Sauter AR, Dodgson MS, Kalvé H, Grimnes S, Stubhaug A, Klaastad O. Current threshold for nerve stimulation depends on electrical impedance of the tissue: a study of ultrasound-guided electrical nerve stimulation of the median nerve. \textit{Anesth Analg} 2009; 108: 1338–43
3. Dufour E, Quennesson P, Van Robais AL, et al. Combined ultrasound and neurostimulation guidance for popliteal sciatic nerve block: a prospective, randomized comparison with neurostimulation alone. \textit{Anesth Analg} 2008; 106: 1553–8
4. Bigeleisen PE, Moayeri N, Groen GJ. Extraneural versus intraneural stimulation thresholds during ultrasound-guided subpraclovicular block. \textit{Anesthesiology} 2009; 110: 1235–43
5. Chan VWS, Brull R, McCartney CJL, Xu D, Abbas S, Shannon F. An ultrasonographic and histological study of intraneural injection and electrical stimulation in pigs. \textit{Anesth Analg} 2007; 104: 1281–4
6. Robards C, Hadzic A, Somasundaram L, et al. Intraneural injection with low-current stimulation during popliteal sciatic nerve block. \textit{Anesth Analg} 2009; 109: 673–7
7. Sala-Blanch X, López AM, Pomés J, Valls-Sole J, García AI, Hadzic A. No clinical or electrophysiologic evidence of nerve injury after intraneural injection during sciatic popliteal block. \textit{Anesthesiology} 2011; 115: 89–95
8. Seidel R, Natge U, Schulz J. Distal sciatic nerve blocks: randomized comparison of nerve stimulation and ultrasound guided intraneural block. \textit{Anaesthesist} 2013; 62: 183–92
9. Keyl C, Held T, Albiez G, Schmack A, Wiesenack C. Increased electrical nerve stimulation threshold of the sciatic nerve in patients with diabetic foot gangrene: a prospective parallel cohort study. \textit{Eur J Anaesthesiol} 2013; 30: 435–40
10. Rigaud M, Filip P, Lirk P, Fuchs A, Gemes G, Hogan Q. Guidance of block needle insertion by electrical nerve stimulation: a pilot study of the resulting distribution of injected solution in dogs. \textit{Anesthesiology} 2008; 109: 473–8
11. Hogan QH. Pathophysiology of peripheral nerve injury during regional anesthesia. \textit{Reg Anesth Pain Med} 2008; 33: 435–41
12. Lirk P, Birmingham B, Hogan Q. Regional anesthesia in patients with preexisting neuropathy. \textit{Int Anesthesiol Clin} 2011; 49: 144–65
13. Boulton AJ, Gries FA, Jervell JA. Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy. \textit{Diabet Med} 1998; 15: 508–14
14. Viswanathan V, Snehalatha C, Seena R, Ramachandran A. Early recognition of diabetic neuropathy: evaluation of a simple outpatient procedure using thermal perception. \textit{Postgrad Med J} 2002; 78: 541–2
15. Wilbourn AJ. Nerve conduction studies: Types, components, abnormalities, and value in localization. \textit{Neurol Clin} 2002; 20: 305–38
16. ASA Standards Guidelines and Statements: Standards for basic anesthetic monitoring. Methods. 2011. Available at http://www.asahq.org/~/media/sites/asahq/files/public/resources/standards-guidelines/standards-for-basic-anesthetic-monitoring.pdf (accessed 7 March 2016)
17. McCartney CJL, Brauner I, Chan VWS. Ultrasound guidance for a lateral approach to the sciatic nerve in the popliteal fossa. Anaesthesia 2004; 59: 1023–5
18. Karmakar MK, Shariat AN, Pangthipampai P, Chen J. High-definition ultrasound imaging defines the paraneural sheath and the fascial compartments surrounding the sciatic nerve at the popliteal fossa. Reg Anesth Pain Med 2013; 38: 447–51
19. Andersen HL, Andersen SL, Tranum-Jensen J. Injection inside the paraneural sheath of the sciatic nerve: direct comparison among ultrasound imaging, macroscopic anatomy, and histologic analysis. Reg Anesth Pain Med 2012; 37: 410–4
20. Chan VWS, Nova H, Abbas S, McCartney CJL, Perlas A, Xu DQ. Ultrasound examination and localization of the sciatic nerve: a volunteer study. Anesthesiology 2006; 104: 309–14
21. Sala Blanch X, López AM, Carazo J, et al. Intraneural injection during nerve stimulator-guided sciatic nerve block at the popliteal fossa. Br J Anaesth 2009; 102: 855–61
22. Moayeri N, Groen GJ. Differences in quantitative architecture of sciatic nerve may explain differences in potential vulnerability to nerve injury, onset time, and minimum effective anesthetic volume. Anesthesiology 2009; 111: 1128–34
23. Krishnan AV, Kierman MC. Altered nerve excitability properties in established diabetic neuropathy. Brain 2005; 128: 1178–87
24. Nodera H, Kaji R. Nerve excitability testing and its clinical application to neuromuscular diseases. Clin Neurophysiol 2006; 117: 1902–16
25. Kroin JS, Buvanendran A, Tuman KJ, Kerns JM. Effect of acute versus continuous glycemic control on duration of local anesthetic sciatic nerve block in diabetic rats. Reg Anesth Pain Med 2012; 37: 595–600
26. Sites B. Ultrasound-guided popliteal block demonstrates an atypical motor response to nerve stimulation in 2 patients with diabetes mellitus. Reg Anesth Pain Med 2003; 28: 479–82
27. Halar EM, Graf RJ, Halter JB, Brozovich FV, Soine TL. Diabetic neuropathy: a clinical, laboratory and electrodiagnostic study. Arch Phys Med Rehabil 1982; 63: 298–303
28. Sertoz N, Deniz MN, Ayanoglu HO. Relationship between glycosylated hemoglobin level and sciatic nerve block performance in diabetic patients. Foot Ankle Int 2013; 34: 85–90
29. Cuvillon P, Reubrecht V, Zoric L, et al. Comparison of subgluteal sciatic nerve block duration in type 2 diabetic and non-diabetic patients. Br J Anaesth 2013; 110: 823–30
30. Lirk P, Verhamme C, Boeckh R, et al. Effects of early and late diabetic neuropathy on sciatic nerve block duration and neurotoxicity in Zucker diabetic fatty rats. Br J Anaesth 2014; 114: 319–26
31. Tsui BCH, Kropelin B. The electrophysiological effect of dextrose 5% in water on single-shot peripheral nerve stimulation. Anesth Analg 2005; 100: 1837–9
32. Brull R, McCartney CJL, Chan VWS, El-Beheiry H. Neurological complications after regional anesthesia: contemporary estimates of risk. Anesth Analg 2007; 104: 965–74

Handling editor: L. Colvin