Dissertation

The influence of diabetic neuropathy on current settings during peripheral nerve stimulation for popliteal sciatic nerve block

submitted by

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Declaration

I hereby declare that this dissertation is my own original work and that I have fully acknowledged by name all of those individuals and organizations that have contributed to the research for this dissertation. Due acknowledgement has been made in the text to all other material used. Throughout this dissertation and in all related publications I followed the guidelines of “Good Scientific Practice.

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Abbreviations and Definitions

BMI	Body Mass Index
CDT	Carbohydrate-deficient transferrin
CPN	Common peroneal nerve
CRF	Case report form
CV	Conduction velocity
DM	Diabetes mellitus
DML	Distal motor latency
ENG	Electroneurography
HbA_{1c}	Hemoglobin A_{1C}
IQR	Interquartile range
PNS	Peripheral nerve stimulation
psi	Pounds per square inch
SN	Sciatic nerve
TN	Tibial nerve
RR	Blood pressure (Riva-Rocci)
UN	Ulnar nerve
US	Ultrasound

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Zusammenfassung

Einleitung

Periphere Nervenstimulation (PNS) ist eine häufig angewandte Technik zur Lokalisierung peripherer Nerven im Rahmen regionalanästhesiologischer Verfahren. Die allgemein empfohlenen Stimulationsstromstärken von 0.3-0.5mA führen vor allem bei Patienten mit diabetischer Neuropathie nicht verlässlich zu einer motorischen Antwort. Diese Studie untersucht den Zusammenhang zwischen den Schwellenwerten für eine motorische Aktivität und der Position der Stimulationsnadel im Bezug zu beiden Ästen des Nervus ischiadicus an Patienten mit und ohne diabetischer Neuropathie.

Methoden

Die präoperative Evaluierung umfasste eine detaillierte neurologische Untersuchung, Labortests und Elektroneurographie. Die für eine motorische Antwort notwendige Stromstärke wurde im Rahmen eines ultraschall-gezielten Blocks des Nervus ischiadicus in der Kniekehle für den Nervus tibialis und Nervus peroneus communis an Diabetikern und Nicht-Diabetikern gemessen. Die Nähe der Nadel zum Nerv wurde post-hoc mithilfe von Ultraschallaufnahmen evaluiert.

Ergebnisse

Die mittleren Stimulationsstromstärken unterschieden sich nicht zwischen Diabetikern (n=55) und Nicht-Diabetikern (n=52). Patienten mit abgeschwächter Druckwahrnehmung zeigten einen erhöhten Schwellenwert für den Nervus peroneus communis (median 1.30mA gegenüber 0.57mA bei Patienten mit normaler Druckwahrnehmung, p=0.042), ebenso wie Patienten mit abgeschwächter Schmerzwahrnehmung (1.60mA gegenüber 0.50mA bei Patienten mit normaler Schmerzwahrnehmung, p=0.038). Eine Verlangsamung der Nervenleitgeschwindigkeit am Nervus ulnaris korrelierte mit einer erhöhten mittleren Stimulationsstromstärke (r=-0.35, p=0.002).

15 Diabetiker benötigten mehr als 0.5mA zur Auslösung einer motorischen Antwort obwohl die Stimulationsnadel unbeabsichtigt intraneural platziert wurde (n=4) oder benötigten ≥2mA trotz Nadel-Nerv Kontakt, gegenüber 3 solcher Patienten (1 intraneural, 2 mit ≥2mA) in der Gruppe der Nicht-Diabetiker (p=0.003).

Diskussion

Die Diagnose Diabetes mellitus per se führt zu keiner Erhöhung der erforderlichen Stimulationsstromstärke im Rahmen der PNS. Patienten mit klinischen Zeichen einer Neuropathie benötigten jedoch signifikant höhere Stromstärken zur Auslösung einer motorischen Antwort. Die Stimulationsstromstärken zeigten ein hohes Maß an Variabilität sowohl in der Gruppe der Diabetiker als auch bei gesunden Kontrollpatienten und Stromstärken >0.5mA, dem momentan empfohlenen Schwellenwert, wurden häufig beobachtet. Diabetiker haben ein höheres Risiko einer potentiellen intraneuralen Nadelpositionierung, wenn PNS als alleinige Methode zur Nervenlokalisation verwendet wird. Einfache klinische Tests könnten Patienten, die erhöhte Stimulationsschwellenwerte benötigen, identifizieren.

Schlussfolgerung

Diese Ergebnisse legen nahe, dass Stimulationsstromstärken von 0.3-0.5mA im Rahmen eines poplitealen Ischiaducusblocks eine korrekte Nadelposition direkt am Nerv nicht garantieren. Dies gilt im Besonderen für Patienten mit diabetischen Nervenschäden.

Abstract

Background

Peripheral nerve stimulation (PNS) is a common technique for nerve localization in regional anesthesia, but the generally recommended stimulation threshold of 0.3-0.5mA does not reliably produce distal motor response in the absence of potentially harmful, intraneural needle placement. Since this may be particularly true in patients with diabetic neuropathy, this study examined the relationship of motor activity threshold and needle location at both branches of the sciatic nerve in patients with and without diabetic neuropathy.

Methods

Preoperative evaluation included a detailed neurological exam, laboratory testing and electroneurography. During ultrasound (US) guided popliteal sciatic nerve block, the current required to produce distal motor activity for the tibial nerve (TN) and common peroneal nerve (CPN) in diabetic and non-diabetic patients was measured. Proximity of the needle to the nerve was evaluated post-hoc using US imaging.

Results

Average stimulation currents did not differ between diabetic patients (n=55) and non-diabetic patients (n=52). Subjects with diminished pressure perception showed increased threshold for the CPN (median 1.30mA vs. 0.57mA in subjects with normal perception, p=0.042), as did subjects with decreased pain sensation (1.60mA vs. 0.50mA in subjects with normal pain sensation, p=0.038). Reduced ulnar nerve conduction velocity predicted elevated mean stimulation current (r=-0.35, p=0.002). Finally, 15 diabetic patients required more than 0.5mA to evoke a motor distal response despite unintentional, intraneural needle placement (n=4) or required current ≥2mA despite needle-nerve contact, versus 3 such patients (1 intraneural, 2 with ≥2mA) among non-diabetic patients (p=0.003).

Discussion

The diagnosis of diabetes mellitus per se did not alter the required stimulation thresholds for PNS. Patients with clinically evident signs of neuropathy, however, required substantially increased stimulation currents to elicit a motor response. Stimulation currents showed a high degree of variability for both diabetic patients and healthy controls and stimulation currents >0.5mA, the currently recommended threshold, were frequently observed. Diabetic patients are at significantly higher risk of potential intraneural needle positioning if PNS is used as the sole method of nerve localization. Simple clinical tests could help identifying patients who require increased stimulation thresholds.

Conclusions

These findings suggest that stimulation thresholds of 0.3-0.5mA may not reliably determine close needle-nerve contact during popliteal sciatic nerve block, particularly in patients with neuronal dysfunction due to diabetes mellitus.

1 Introduction

1.1 Peripheral regional anesthesia

1.1.1 Overview

Peripheral regional anesthesia is a growing and still evolving field within anesthesiology and patient safety has always been paramount for anesthetist. Compared to general anesthesia, the various regional anesthetic techniques seem to show significant benefit in multiple areas. The clinically most obvious advantage of regional anesthesia is the superior perioperative pain management compared to the administration of systemic opioids which has been demonstrated in many trials for various different peripheral nerves. (1) This includes not only the reduction in pain, but also reduction of complications like postoperative nausea and vomiting, pruritus which all contribute to significantly improved patient satisfaction. Even though studies regarding surgical outcome depending on anesthetic technique are sparse, there are also reports that regional anesthesia might even improve survival after cancer surgery.(2)

Signal transduction in peripheral nerves in the human body can be blocked by administration of local anesthetics, which act via inhibition of sodium-specific ion channels in the neuronal cell membrane. Sodium influx and therefore generation of an action potential is interrupted which results in analgesia and impairment of the other neurological qualities of the nerve distal to the site of injection. To reach their cytoplasmatic site of action, local anesthetics need to be injected in close vicinity to the peripheral nerve that should be blocked, however injection directly into the nerve should be avoided as this could lead to transient or permanent nerve injury.(3,4) There are currently two methods for identification of the correct position of the injection needle available, peripheral nerve stimulation (PNS) and Ultrasound (US) guidance, which can also be used in combination.

1.1.2 Peripheral nerve stimulation (PNS)

PNS works via stimulation of the nerve with electrical impulses to elicit a motor response of the muscle innervated by the respective nerve. In order to achieve a close needle-nerve relationship, electrical impulses are sent through the tip of an

otherwise insulated needle and the needle is constantly advanced towards the presumed location of the targeted nerve. If a motor response of the respective muscle can be observed, the stimulation current is reduced and the needle position adjusted to achieve maximal motor response. The current is only reduced to a minimal threshold, in order to avoid possibly harmful intraneural injections. This safe lower threshold has long been described and also clinically applied as 0.2-0.5mA.(5)

Our present understanding of the needle-current-nerve relationship is based on Coulomb´s law I_t=K(I/r2), where I_t is the current intensity at a distance r from the electrical source. K is a constant determined by the medium and I is the current intensity of the source. However, this model presumes a homogeneous medium, which does not resemble the situation in the human body with different types of tissue surrounding the nerve. Additionally, it has even been shown, that different body regions have different electrical impedances(6), therefore further challenging the uniform use of PNS to detect optimal needle position.

Additionally, newer studies question the lower threshold of 0.2-0.5mA and especially challenge the concept that stimulation currents in that range can safely rule out intraneural needle placement.(7–11) For example, Bigeleisen et al(7) found that for a supraclavicular block stimulation currents of 0.2-0.5 mA could not preclude an intraneural positioning of the injection needle.

1.1.3 Regional anesthesia and diabetes mellitus

The question about ideal stimulation current becomes even more important when performing PNS in patients with preexisting neurological deficits such as diabetic neuropathy. Sites et al. reported two diabetic patients in which no motor response to PNS could be obtained with 2.4mA even though US showed clear needle-nerve contact(12) and a 7.2 fold increase of required stimulation current has been described for patients undergoing diabetic foot surgery.(13) Animal data also suggest that low-threshold electrical stimulation does not offer satisfactory protection against intraneural injection in the presence of diabetes mellitus.(14) The observed increase in stimulation thresholds might be explained by altered nerve excitability properties which has been shown in established diabetic neuropathy.(15)

With a prevalence of DM in Europe around 10% for patients younger than 60 years and as high as 20% for older patients(16) it is important to ensure this group of patients benefits from regional anesthesia without additional harm, in particular as 50% of diabetic patients develop polyneuropathy.(17) Interestingly, up to 50% of patients with diabetic neuropathy may not experience any symptoms and might therefore be difficult to identify in the preoperative examination.(18) Due to typical cardiovascular comorbidities of diabetic patients, regional anesthesia represents a particular interesting choice of anesthetic for this group of patients as negative effects of general anesthesia can be kept to a minimum.

The widespread use of regional anesthesia in diabetic patients, with or without apparent neuropathy, has always been overshadowed by the fear of additional nerve injury. Patients with preexisting damage to their peripheral nerves may be more susceptible to permanent nerve injury when the nerve is exposed to a secondary traumatic insult. This so called the “double-crush phenomenon” is well described in the literature(19) however evidence in clinical practice is sparse(20) and therefore its relevance for regional anesthesia in humans is not fully understood. Experimental data support the theory that the risk of local anesthetic-induced nerve fiber damage is higher in diabetic animals.(21,22)

Given the possibility of higher neurological complication rates for diabetic patients it is paramount to avoid any additional injury to the peripheral nerve when performing regional anesthetic procedures. However, there are still no established guidelines for PNS guided regional anesthesia in diabetic patients.

1.1.4 Neurologic complications of regional anesthesia

In a recent publication of data from a large clinical registry the prevalence of all-cause neurological sequelae at 60 days postoperatively was 0.89%, while another large review reported the rate of temporary neuropathy at 3%.(23) Neal and Wedel estimated that 4 out of 10.000 patients undergoing peripheral nerve block will have a block related neurological deficit 12 months after the procedure and acknowledge the fact that adequately powered studies to determine the real incidence of neurological complications are statistically challenging.(24)

Three factors may contribute to the mechanism behind regional anesthesia induced nerve injury: mechanical trauma, ischemia and local anesthetic neurotoxicity. If the

block needle enters the nerve, approximately 3% of nerve fascicles in the needle trajectory show direct signs of injury.(25) Additional damage of peri- and endoneural tissue results in edema and a breach of the blood-nerve barrier exposing nerve fibers to the neurotoxic effect of local anesthetics and impairing blood supply to neuronal cells.(26) The neurotoxic effects of local anesthetics are directly proportionate to their concentration and their duration of exposure. Intraneural injection of local anesthetics leads to direct axonal degeneration, vasoconstriction worsens ischemia and induced inflammation causes myelin damage.(3,27)

1.1.5 Distal-lateral sciatic nerve block

The sciatic nerve (SN) was chosen for this study because it can be easily visualized using US, as it is the largest nerve in the human body and has a typical hyperechoic structure. It can be blocked in various regions along its path using several different approaches and techniques. The proximal approaches include posterior, anterior and lateral approaches. Alternatively, approaches can be described as transgluteal, subgluteal/mid-femoral or popliteal, with the two possible access paths in the popliteal region being a lateral or a posterior approach.(28) Popliteal SN blocks are mainly used for foot surgery, however, can also be utilized for knee surgery. Classic landmark-based techniques have largely been replaced by US-guidance which can also be used for various approaches. US has been shown to decrease procedure time(29) and increase success rate for distal-lateral sciatic nerve blocks.(11)

The US-guided distal-lateral sciatic nerve block used in this study was first described by McCartney et al. in 2004.(30) There are two major advantages of that technique compared to the posterior approach in the popliteal fossa. First, using the in-plane US approach, the needle shaft and tip can be visualized in real time during the whole procedure. Second, the patient can remain in the supine position, which is particularly useful if the prone position is either contraindicated or impractical.

1.1.6 Anatomy of the sciatic nerve in the popliteal region

The SN is the largest and thickest nerve of the human body and is formed from the spinal cord segments L4-S3. It travels from its origin in the lumbo-sacral plexus through the sacro-sciatic foramen down the thigh to the popliteal fossa, which is defined by the semimembranosus and semitendinosus muscles medially and the

biceps femoris muscle laterally. Its two branches, the tibial nerve (TN) and the common peroneal nerve (CPN), are typically encompassed by a common layer of connective tissue and diverge in or shortly proximal or distal of the popliteal fossa. The larger tibial nerve then passes between the heads of the gastrocnemius muscles to travel down to the foot in the posterior compartment of the leg. The common peroneal nerve first travels around the fibular head and then down the leg in the lateral and anterior compartment. Except for a small area on the anteromedial aspect of the leg and foot, which is innervated by the saphenous nerve, the two branches of the SN provide innervation for the whole lower leg.(31) Together with the femoral nerve anteriorly and a small area medially, innervated by the obturator nerve, the SN also innervates the knee. The TN and the CPN project their articular branches after their diversion in the popliteal fossa.(32) For that reason the distal-lateral approach for a SN block cannot only be used for surgery below the knee but also for procedures like total knee arthroplasty.

Peripheral nerves in the human body are structured in a typical way. Individual nerve fibers are surrounded by endoneurium that contains primarily collagen to support capillary blood vessels. Multiple axons are surrounded by a thin, but strong sheath of connective tissue, the so-called perineurium and form a fascicle. Finally, the whole nerve, together with its supplying blood vessels is wrapped in the epineurium. This allows free movement of the nerve and protects it from damage.(33,34) The proportion of connective tissue within the nerve increases as the nerve travels more distantly because the number of nerve fibers diminishes. The specific anatomy of the SN, especially at its diversion in the popliteal fossa, however seems to be a bit more complicated. The two branches of the SN travel down the thigh in a common sheath of connective tissue, most commonly referred to as the epineurium. As the two nerves separate, each with its own epineurium, this common wrapping also diverges.

This complex anatomical situation has led to much confusion and controversy in the literature.(34–36) Almost 20 years ago, Vloka et al. first described a connective tissue sheath that was found to continuously surround the SN and both its branches and called it a "*continuous epineural sheath"*.(31) After further anatomical investigation he describes an inner "*interfasciular epineurium"* and an outer *"epifascicular epineurium"* and found this "*common epineural adventitia"* to

encompass both TN and CPN, which were enveloped by separate epineuria.(33,37) He emphasized that intraepineural needle placement in that region was not equivalent to intraneural or intrafascicular placement. Sala Blanch et al.(38) on the other hand deemed subepineural injections during SN blocks in the popliteal fossa to be intraneural. Other authors acknowledged the fact that intraneural injections can be either extrafascicular or intrafascicular.(9,39) In a recent cadaver study Andersen et al.(40) defined the *"paraneural sheath"* of the SN as a structure clearly separate from the epineurium. It could not reliably be visualized by US but became visible during injection through a catheter. Injection inside the sheath was clearly distinguishable from an intraneural injection as the integrity of the epineurium was preserved. These findings were confirmed by Karmakar et al.(35) in live patients, clearly demonstrating that subparaneural injections shoud not be considered intraneural. This nomenclature has also been adopted in a recent publication.(11) The paraneural sheath is shown on an US image in Figure 1 and on a cadaver in Figure 2.

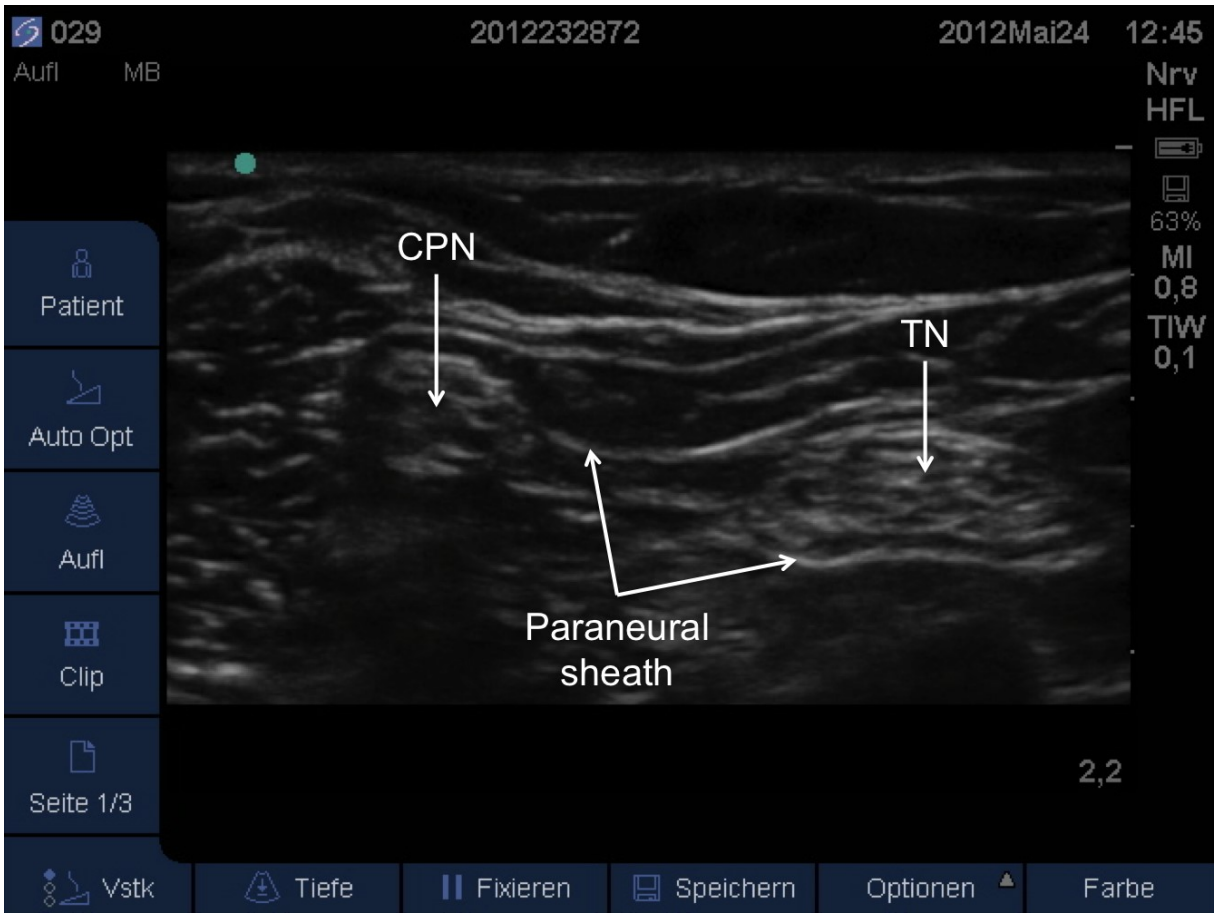

Figure 1: The two branches of the sciatic nerve, common peronel nerve (CPN) and tibial nerve (TN), just after their separation in the popliteal fossa, still surrounded by a common sheath of connective tissue, refered to as the" paraneural sheath" or "paraneurium".

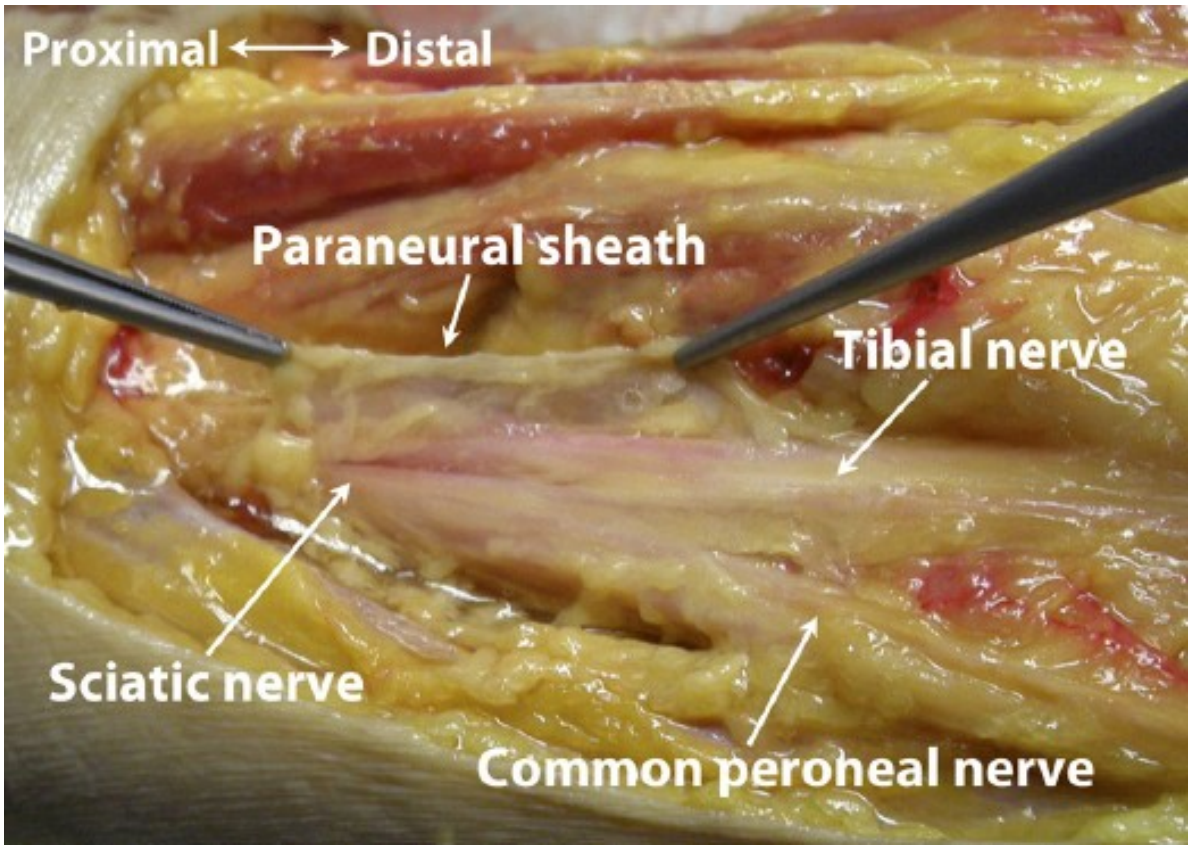

Figure 2: Cadaver dissection of a human popliteal fossa, exposing the bifurcation of the sciatic nerve.(40)

1.2 Aims of the study

Any medical procedure has an inherent risk of complications. In an effort to increase patient safety, research into basic underlying mechanisms of PNS in regional anesthesia can help to improve our knowledge of needle-current-nerve relationships. The proportion of diabetic patients presenting for surgery and possible regional anesthesia is increasing and because of their typical comorbidities, the choice of regional anesthetic techniques over general anesthesia might be of particular benefit in this subgroup. However, anesthetists sometimes refrain from regional anesthesia as this group of patients is thought to be at higher risk of neurological complications and to date there are no specific recommendations regarding PNS in patients with DM.(41) Because of these factors, research in this field is urgently needed and this has also been highlighted in an editorial appeal.(42)

Even though the introduction of US to regional anesthesia brought several advantages, it also has its limitation and a combination of US and PNS is currently regarded the safest approach in regional anesthesia by the majority of anesthetists.(24)

We therefore sought to examine safe stimulation thresholds for PNS in popliteal SN blocks for diabetic and non-diabetic patients. The main hypothesis underlying this project is, that nerves in patients with DM show higher resistance to electrical stimulation and therefore require higher current thresholds for PNS.

The following specific aims were defined for this project:

Specific aim 1: Characterization of the required stimulation current for popliteal SN block in patients with and without DM and correlate it with a comprehensive neurological examination

Specific aim 2: Follow-up patients to examine if a higher rate of neurological complications can be observed in patients with preexisting neuropathies

Specific aim 3: Guided by the results, formulation of recommendations for regional anesthesia in patients with a history of DM

2 Material and Methods

2.1 Registration and institutional review board

The study was approved by the institutional review board of the Medical University of Graz (24-064 ex 11/12) and registered online Dec 20, 2011 at ClinicalTrials.gov: Identifier: NCT01488474, Principal Investigator Marcel Rigaud https://clinicaltrials.gov/ct2/show/NCT01488474?term=NCT01488474&rank=1), before commencement of patient recruitment.

2.2 Patient recruitment

Surgical lists for the next day were screened for patients undergoing lower limb surgery, eligible for popliteal SN block. Procedures included, but were not limited to total knee arthroplasty, hallux valgus repair and forefoot amputation.

Medical records of eligible patients were screened for inclusion and exclusion criteria. Inclusion criteria were patients of both sexes with a minimum age of 18 years and American Society of Anesthesiologists status I to IV. Exclusion criteria were pregnancy, unwillingness or incapability to sign informed consent, ongoing dual anti-platelet therapy, allergies to local anesthetics and preexisting neuropathy not attributable to diabetes mellitus.

Eligible patients were then approached by an anesthetist from the study group. If the patient had not already given their consent to the anesthetic procedure for the surgery then the anesthetist performed a normal patient briefing first, explaining the different possible anesthetic techniques, which was unrelated to the study. If the patient had not given their informed consent to a distal-lateral SN block for the surgical procedure then they were not considered for inclusion in the study. After informed consent to regional anesthesia was given by the patient, information regarding the study was handed out (Appendix 1) and the anesthetist explained the study in detail.

As a lot more non-diabetic than diabetic patients were expected to be eligible and to ensure equal distribution of patients, recruitment followed a stratification by age group (<30 years, 30-60 years and >60 years), gender and diabetes status. Non-

diabetic patients were only included to match the number of diabetic patients in the respective group or if the number of diabetic and non-diabetic patients was the same.

After inclusion in the study, patients were then randomized and assigned to either CPN or TN measurement first (described later).

2.3 Clinical tests

After inclusion all patients were clinically examined for signs of apparent or subclinical neuropathy. Patients were asked to complete a standardized questionnaire regarding their past medical history and a clinical exam (both based on the guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy(18)) was performed. The tests included in the neurological examination of the lower extremity are listed in Table 1.

The presence of a pulse for the dorsal pedis artery was assessed by manual palpation on the back of the foot and for the posterior tibial artery posterior to the medial malleolus. For the calculation of the Ankle-Brachial-Index (ABI) the systolic blood pressure of the dorsal pedis artery and the posterior tibial artery was assessed in the aforementioned locations using a regular blood pressure cuff and an acoustic Doppler probe to detect blood flow in the respective vessel. The respective systolic blood pressure was then divided by systolic blood pressure of the upper limb to yield the ABI. The ability of the patient to sense light touch was assessed using a cotton wisp on the dorsum of the patient's foot. Temperature discrimination was assessed using a device that tests the subject's ability to distinguish two materials of differing thermal conductivity (tip therm©, tip therm GmbH, Brueggen, Germany).(43) A standardized 10g monofilament device was used for pressure perception testing on the sole of the foot. Sensitivity to vibration was assessed on the base of the hallux and on the medial malleolus using a standard 128 Hz tuning fork. Strength of vibration perception was graded between 1/8 and 8/8. The ability to induce a painful sensation using a sharp, yet not penetrating pin on the sole of the foot was assessed with a standard pin prick test. The strength of the Achilles tendon reflex was graded between 0 and 2. The patient was not allowed to watch during any of the sensory tests.

Test	Outcome
Pedal pulses Dorsal pedis artery Posterior tibial artery	Present - Absent
Ankle Brachial Index (ABI) Dorsal pedis artery Posterior tibial artery	$RR_{syst(ankle)}$/ $RR_{syst(arm)}$
Light touch perception	Present - Absent
Temperature discrimination	Present - Absent
Pressure perception	Present - Absent
Vibration perception Hallux Medial malleolus	1/8 – 8/8
Pain sensation	Present - Absent
Achilles tendon reflexes	0= no reflex; 1= weak reflex; 2= normal reflex

Table 1: Clinical tests of preoperative neurological evaluation

2.4 Electroneurography

2.4.1 Overview

There are three different types of nerve conduction studies: motor, sensory and mixed. Motor nerve conduction testing has the advantage of signal amplification by the innervated muscle. This makes it technically the easiest form of electroneurography (ENG) and it therefore also indirectly assesses neuromuscular transmission. Motor nerve conduction studies are capable of separating polyneuropathies from myopathies and motor neuron disease, detecting subclinical neuropathies and differentiating congenital from acquired polyneuropathy.(44) It has also been shown that the results of nerve conduction studies correlate well with diabetic neuropathy.(45)

Sensory nerve conduction studies directly assess sensory axons. Since there is no physiological amplification the detected signal is very small, which leads to various technical and practical problems, ultimately resulting in difficult to obtain and

unreliable test results. Nevertheless they are a valuable part of any ENG and results are typically affected at an earlier stage of neuropathies compared to motor nerve conduction studies.(46)

Mixed nerve conduction studies assess sensory and motor components of mixed nerves simultaneously. Their additional information to motor and sensory nerve conduction studies, except for specific indications, is limited.(47)

Even though ENG appears an easy task, numerous potential pitfalls and sources of error have been identified and make it difficult to obtain clinically reliable results.(44,47)

For all tests, it has to be ensured that the stimulation current is supramaximal, stimulating all neurons, to obtain an accurate signal.

2.4.2 Distal motor latency

The Distal motor latency (DML) is the time interval between the nerve stimulation at the distal stimulation point and the onset of the motor response and is measured in in ms. This interval also includes the time required for neuromuscular transmission and initiation of muscle action potential.(44)

2.4.3 Conduction velocity

Conduction velocity (CV) is a calculated value and measured in m/s. The nerve has to be stimulated at 2 different points along its course, creating a proximal and distal latency. The time difference is then divided by the distance, which is determined by simple surface measurement. This method allows comparison of speed of action potential transmission along different nerves, regardless of the lengths of the nerve segments. CV can be measured for motor and sensory nerves, with sensory CV having the limitations described above.(44)

2.4.4 F-wave

F-wave (following wave) studies use the fact that a stimulation impulse travels both distally and proximally (also referred to as orthodromic and antidromic). The

proximally travelling impulse generates a secondary impulse as soon as it reaches the motor neuron cell bodies, which subsequently results in a small, secondary motor response in the innervated muscle. Several measurements can be done with the F-wave response, the most common ones being amplitude and persistence. Persistence describes the proportion of F-waves obtained per number of stimulations and the normal range is 80-100%.(48)

2.4.5 Performed tests

In this study, non-invasive ENG examinations were performed to quantify diabetic neuropathy and to detect subclinical forms of neuropathies. Preferred side of measurement for tibial nerve (TN) and common peroneal nerve (CPN) was the side of planed surgery, if that was impossible due to patient factors (e.g. casts, pain, previous amputation) the other side was used. The ulnar nerve was measured as a reference. All ENG examinations were performed and analyzed using SystemPLUS Evolution© (Micromed.S.p.A., Mogliano Veneto, Italy). Since PNS for nerve localization in regional anesthesia also uses elicited motor responses and motor nerve conduction studies are easier to perform and offer more reliable results, ENG focused on motor nerve conduction studies.

The following tests were performed and examples of the measurement setups are shown in Figure 3, Figure 4 and Figure 5:

- Distal Motor Latency Common peroneal nerve
- Motor Conduction Velocity Common peroneal nerve
- F-waves amplitude Common peroneal nerve
- F-waves persistence Common peroneal nerve
- Distal Motor Latency Tibial nerve
- Motor Conduction Velocity Tibial nerve
- F-waves amplitude Tibial nerve
- F-waves persistence Tibial nerve
- Sensory Conduction Velocity Sural nerve
- Distal Motor Latency Ulnar nerve
- Motor Conduction Velocity Ulnar nerve
- Sensory Conduction Velocity Ulnar nerve

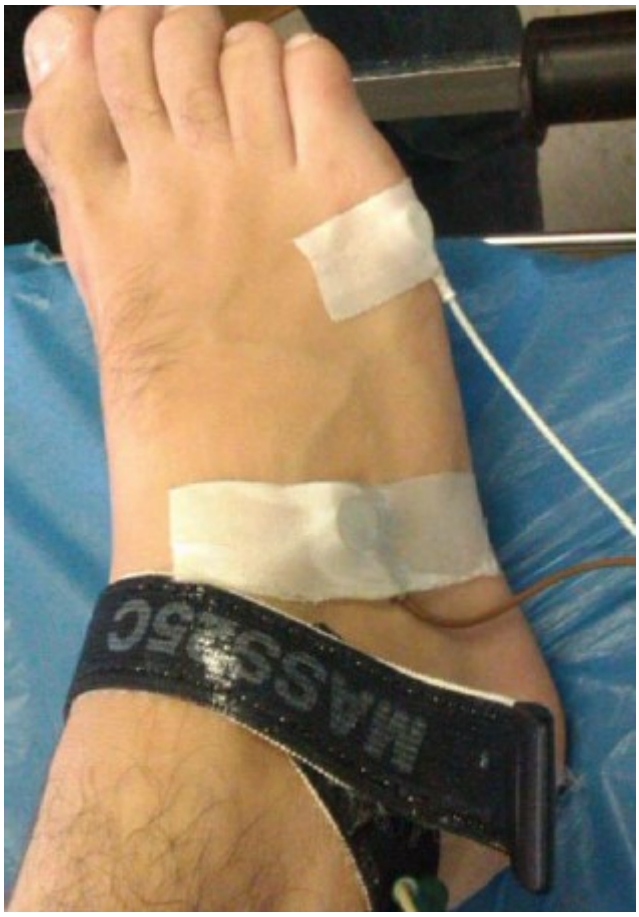

Figure 3: Position of electrodes for motor nerve conduction studies of the common peroneal nerve. Electrodes are positioned over the Extensor digitorum brevis muscle.

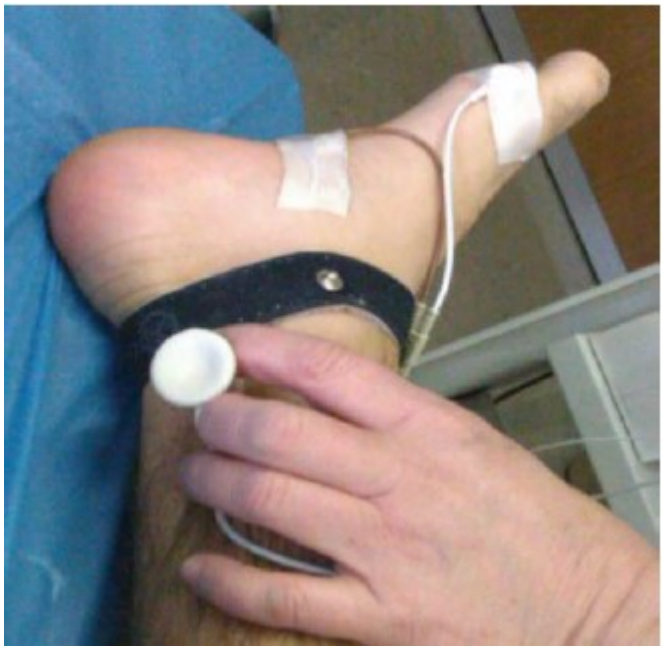

Figure 4: Setup for motor nerve conduction study of the tibial nerve, distal stimulation point

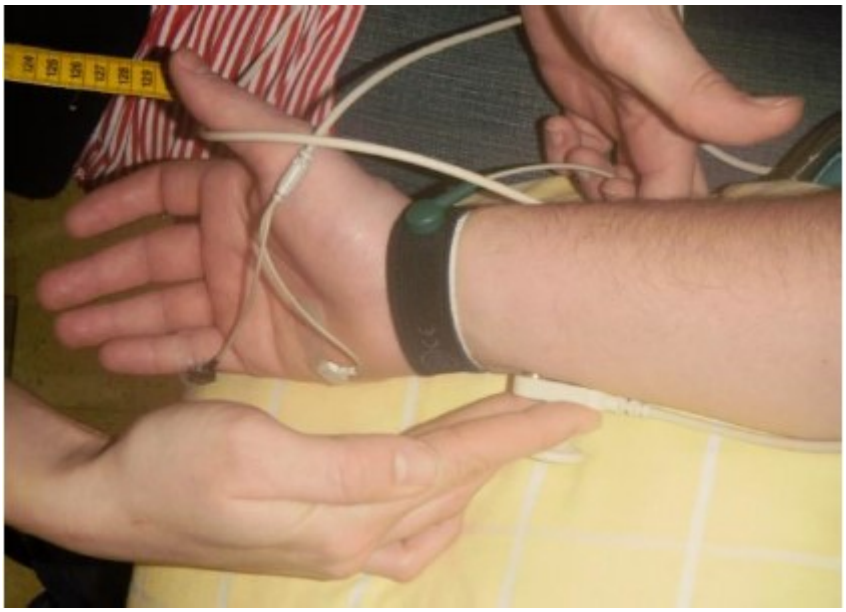

Figure 5: Setup for motor nerve conduction study of the ulnar nerve, distal stimulation point

2.5 Laboratory tests

For further clinical characterization and to exclude possible other forms of neuropathies a series of blood parameters were evaluated preoperatively: Immediately after the patient arrived in the operating theatre two serum and one hematology container (totaling 19 ml of blood) were drawn from the patient and sent to the laboratory for analysis.

Carbohydrate-deficient transferrin (CDT) was analyzed to detect ethanol abuse with possible subsequent alcoholic neuropathy.

To quantify endogenous insulin production, insulin and C-peptide were measured and levels of HbA_{1c} were assessed for long term average plasma glucose concentrations.

Thyroid-stimulating hormone (TSH), unbound thyroxine (fT4) and unbound triiodothyronine (fT3) were measured to asses thyroid function as hypothyroidism is another possible metabolic cause of neuropathy.

Vitamin B12 and folic acid levels were measured to detect deficits which could also lead to peripheral nerve damage.

2.6 Urinalysis

A urine sample from the patient was obtained preoperatively on the ward to determine the amount of proteinuria and therefore degree of DM related kidney damage. It was sent to the laboratory together with the blood samples.

2.7 Procedure recordings

For the procedure, patients were placed in a supine position on the operating table. Vital signs were monitored according to current standards of care(49), which included three-lead-electrocardiogram, automated non-invasive blood pressure and pulse oximetry monitoring. Oxygen was applied via a non-rebreathing mask and an intra-venous line inserted. Analgesia and sedation was achieved by continuous infusion of remifentanil 0,05-0,1 mcg/kg/min and a 0,01-0,05 mg/kg bolus of midazolam.

The respective extremity was elevated in a typical manner such that the popliteal region was accessible for the ultrasound probe (Figure 6). The nerve blocks were performed using the standard lateral in-plane ultrasound-guided approach (30) 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), which is also capable of impedance measurement.

The bifurcation of the SN was identified and the location for the recording was chosen just distally of the bifurcation at the point where the two nerves were clearly separated. The stimulation needle was inserted and, under live imaging, advanced towards the first branch of the SN according to the randomization. The desired final needle position was in contact with the nerve without penetration of the epineurium, because of our underlying hypotheses that needle penetration of the epineurium could be potentially harmful. Now the nerve stimulator was turned on by an assistant with the following settings:

- Stimulus duration 0.1 ms
- Stimulus frequency 1Hz
- Stimulation current 0.0mA.

The assistant increased the stimulation current until an obvious motor response of the respective muscles occurred, while the anesthetist performing the nerve block was blinded to the stimulation current and was not allowed to adapt the needle position. Thereafter, the minimal stimulation threshold current was verified by reducing the current again until the distal motor response vanished. This minimal stimulation current was recorded together with the impedance measured at this point. After this measurement 0.5-1ml of glucose 5% was injected using an injection pressure monitoring device (BSmart, Concert Medical, MA USA) to facilitate definition of the exact needle position. The same procedure was then performed on the remaining branch of the SN. All relevant steps were documented using image and video recording.

After completion of measurements 30ml ropivacain 0.5% or mepivacaine 1%, depending on type and expected length of surgery, were injected in a multi-injection technique around both branches of the SN. If intraneural needle placement was identified during the measurements, the needle was withdrawn and LA was therefore not administered intraneurally.

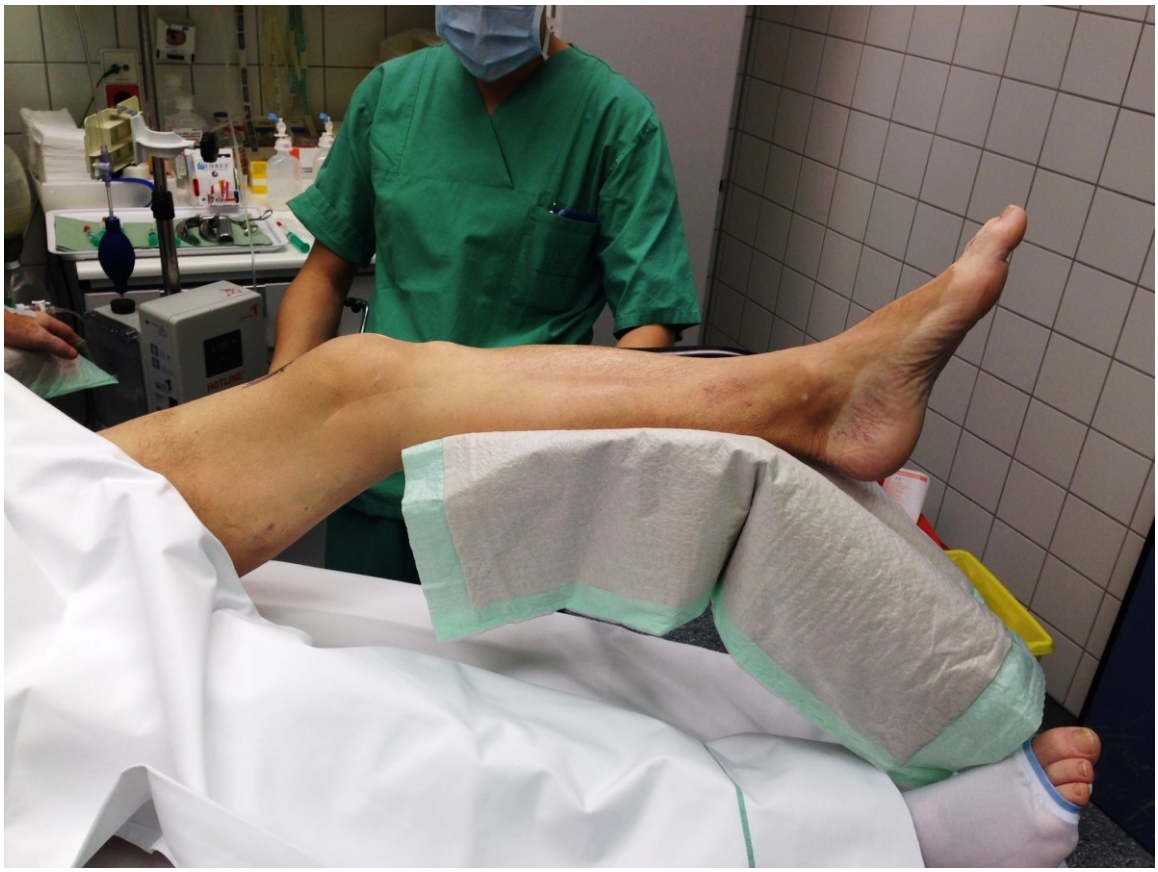

Figure 6: Positioning of the patient's leg for measurements of stimulation current and impedance during popliteal sciatic nerve block via the lateral approach

2.8 Postoperative control visits

There were two postoperative control visits scheduled for each patient, one on the first postoperative day and another one before discharge from hospital. These visits were performed to detect any complication of the peripheral nerve block, in particular neurologic deficits. A neurologic evaluation of the respective extremity included testing of motor function and sensation and a general physical examination was also performed for safety reasons.

2.9 Ultrasound imaging evaluation

US still images and videos of the measurements were saved to the US machine and then exported via USB-drive. Files were stored in a separate folder for every single patient on a password-protected drive in the hospital computer network.

Two independent, blinded investigators evaluated the ultrasound images and videos of the procedure. The final needle position at which the measurement was performed was classified into one of these six categories for both TN and CPN:

1. Intraneural-perifascicular
2. Intraneural-subepineural
3. Extraepineural-subparaneural
4. Extraparaneural
5. Distant (no needle-nerve contact)
6. Position not clearly definable

Factors that were assessed to determine needle position were:

- Needle position on US images and videos
- Movement of the target nerve in relation to the stimulation needle, when the needle was moved up and down (“rolling” of the nerve indicated no penetration of the epineurium, whereas sticking of the nerve to the needle was indicative for penetration of the epineurium)
- Anatomical spread pattern of 0.5-1ml injected glucose 5% (including swelling of the nerve or paraneural sheath)

Figure 7 exemplary shows the classification for the CPN, the same classification was used for the TN.

If there was dissent between the investigators, another investigator was questioned and a consensus decision was made.

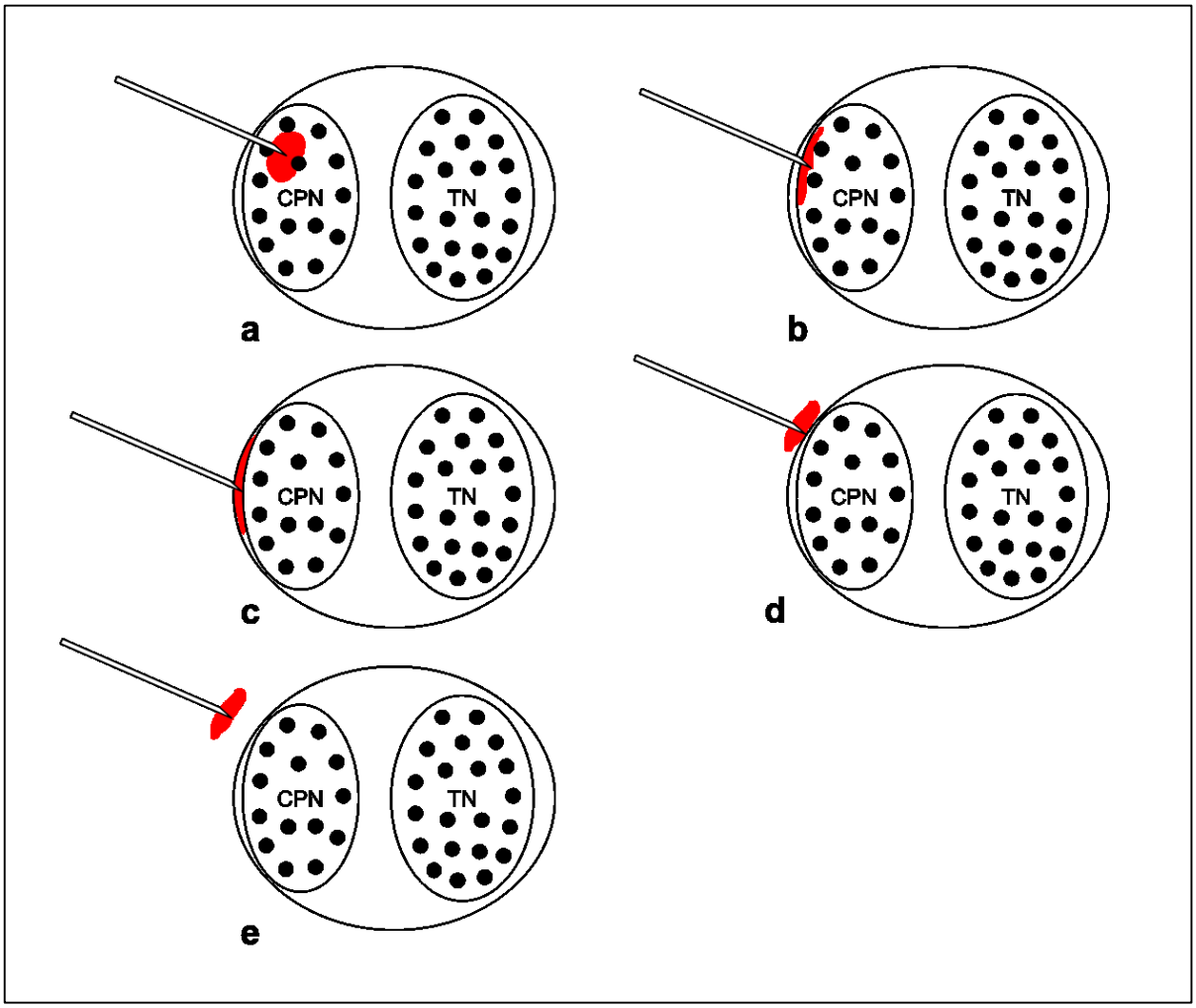

Figure 7: Definition of final needle positions at the common peroneal nerve (CPN) using the spread of 1ml glucose 5%, TN = tibial nerve

a. Intraneural-perifascicular

b. Intraneural-subepineural

c. Extraepineural-subparaneural

d. Extraparaneural

e. Distant (no needle-nerve contact)

2.10 Six-months telephone follow up

Patients were contacted via telephone six months after study measurements. They were questioned for any abnormal sensation or motor deficit in the respective extremity. If a neurological complication of the regional anesthesia could not be ruled out, patients were asked to undergo a thorough examination in hospital.

2.11 Sample size calculations

The difference in minimal stimulation threshold for PNS for the TN and CPN between patients with and without diabetes mellitus was the primary end point and therefore used for sample size calculations. A difference of 0.3mA was considered clinically relevant. As patients were eligible regardless of their duration of diabetes or existing diabetic neuropathy, it was assumed that half of the patients were affected by such a relevant difference. From previous studies it was inferred that the stimulation threshold at the desired needle position had a standard deviation of approximately 0.3mA.(6,7,9) Taking into consideration the diagrams provided by the authors, however it can be concluded, that the distribution is skewed to the right. Sample size calculation was performed with nQuery Advisor v4.0 (available at www.statsols.com) and gave 64 patients in each group to achieve 80% power. The sample size was increased to 70 per group in order to allow for missing values.

The assumptions of the sample size calculations were validated in post hoc power calculations based on the observed standard deviations from analysis of variance (ANOVA).

2.12 Randomization

Stimulation threshold measurements were performed at both branches of the SN, the TN and the CPN, which lie in very close proximity and share a common sheath of connective tissue. To investigate whether the first measurement, in particular the injection of 1ml glucose 5%, altered the conduction properties of the surrounding tissue and therefore the measurements at the second nerve, the order of measurements was randomized and patients were assigned to either “TN first” or

“CPN first”. This randomization also ensured that any possible interference was equally distributed between groups and therefore would affect the results of our main hypothesis in both the diabetic and non-diabetic group in the same way. The web based computer program Randomizer© (available at www.randomizer.at) was used to create a list of procedure orderings for every group (3 age groups:<30 years, 30-60 years, >60 years; gender; diabetes status) Patients were assigned to a measurement order according to their consecutive position in the respective list.

2.13 Data collection

All patient data were written in a paper case report form (CRF) (Appendix 2) as soon as they were obtained. The CRF of each patient was kept by the study team and data was transferred to an electronic version of the CRF immediately after measurements were completed. This electronic CRF was specifically constructed for this study by the Institute for Medical Informatics, Statistics and Documentation of the Medical University of Graz and fed the data to a secure database. All changes of data were tracked to comply with the standards of good scientific practice. This study was monitored by the Coordination Center for Clinical Studies of the Medical University of Graz, and external data monitoring was performed twice during the study period.

To guarantee the study did not negatively interfere with clinical patient care, all staff anesthetists were briefed about the general study algorithm, which was also placed on the official announcement board of the Department of Anesthesiology and Intensive Care Medicen (Appendix 3).

Laminated copies of the exact study algorithm in the operating theatre (Appendix 4) were placed in all areas were regional anesthesia was performed, to allow all staff to familiarize themselves with the procedures of the study and to ensure strict adherence to the study protocol.

2.14 Statistical methods

The main target variable was difference in stimulation threshold for the TN and CPN between diabetic and non-diabetic patients. Both nerves were analyzed separately

and additionally the mean of both stimulation thresholds was also calculated and compared between the two groups to eliminate the problem of multiple testing. As the stimulation threshold was skewed to the right, which is consistent to the findings of other authors(6,7,9), nonparametric significance tests were used. The association of categorical variables to the stimulation threshold and a group comparison between different needle positions was calculated using the Wilcoxon test and for correlations of numerical variables to the stimulation thresholds, the Spearman test was utilized. The Ansari-Bradley test was used to compare variances in stimulation currents between groups. Medians and Interquartile ranges were used in the descriptive statistics. Laboratory results were tested for normality using the Shapiro-Wilk test and compared using an unpaired t-test or independent samples Mann-Whitney-U test accordingly. The computer programs used for calculations and creation of diagrams were R© version 3.1.2 (available online at www.r-project.org) and SPSS version 22 (IBM, Armonk, New York, United States of America). p-values below 0.05 were considered statistically significant.

2.15 Funding and support

This project was funded by the Austrian science fund (FWF), Sensengasse 1, 1090 Vienna, Austria under their KLIF (Klinische Forschung) program. (grant number KLI-135). BBraun (Melsungen, Germany) provided the nerve stimulator (Stimuplex HNS 12) and the injection needles (Stimuplex-D) used in the study free of charge.

3 Results

3.1 Patient recruitment

A total of 124 patients were included in the study, of which 17 had to be excluded prior to data analysis. 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. Four patients had their surgery either cancelled or postponed to a time when the study team was unable to perform the measurements. Because the medical management of two patients was changed to include dual anti platelet therapy after inclusion to the study, they also had to be excluded. Regional anesthesia was ultimately not performed in two patients due to patient factors, why measurements were also not completed. In a further six patients technical problems occurred, including inability to record or store US imaging.

Of the remaining 107 patients where data was available, 55 had a history of DM and 52 were controls. For the main endpoint (stimulation current) only data from nerves where the needle was in close contact with the nerve (needle positions extraepineural-subparaneural and extraparaneural) was used. This left 52 measurements at the CPN and 49 at the TN in the DM group and 46 measurements at the CPN and 45 at the TN in the Non-DM group (see Figure 8).

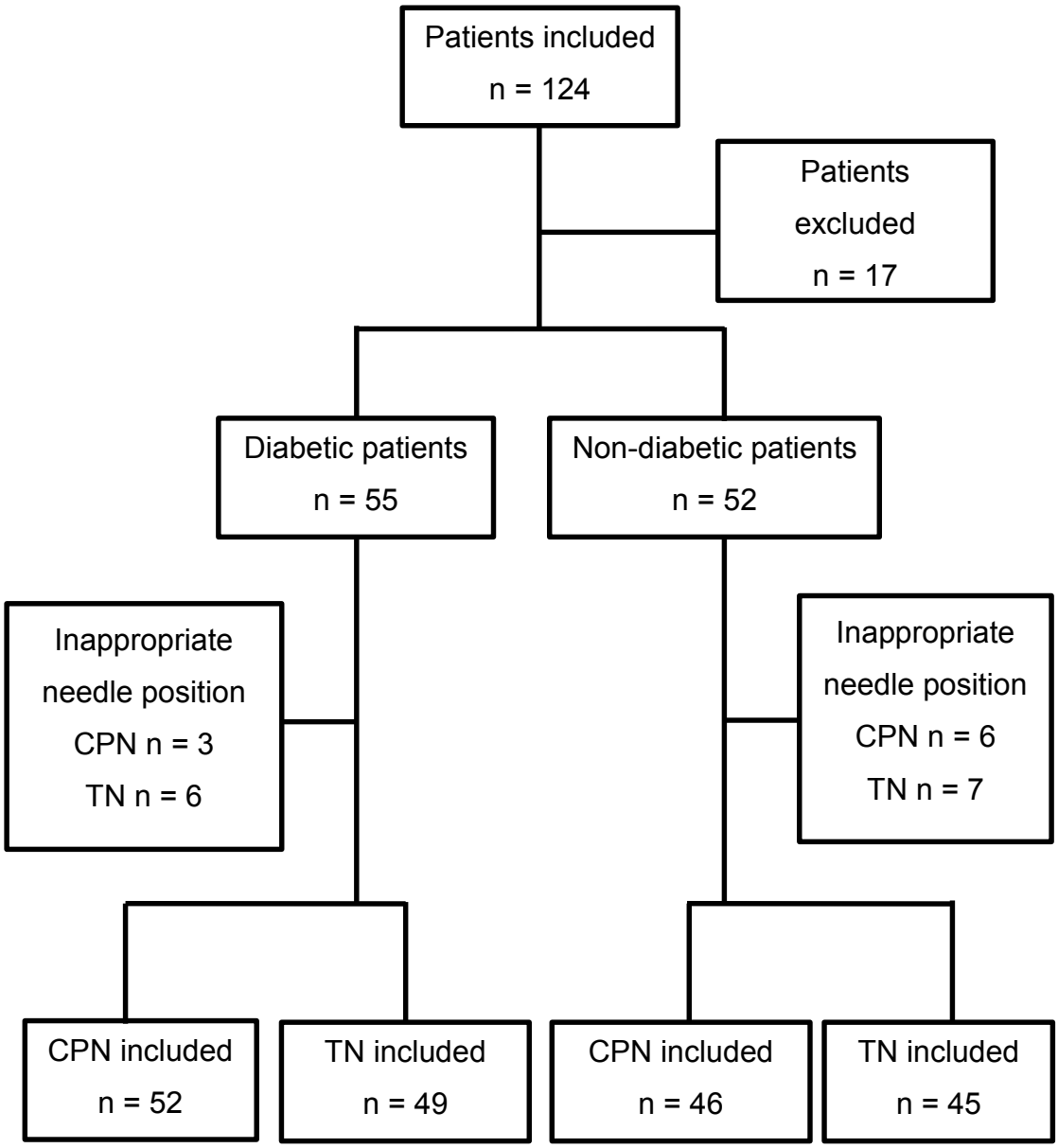

Figure 8: Flowchart of patient recruitment

3.2 Baseline characteristics

General patient demographics and baseline neurological evaluation can be found in Table 2. Diabetic patients had a significantly higher weight and Body Mass Index (BMI). Significantly fewer patients in the DM group had positive results in all clinical sensory tests: light touch perception, temperature discrimination, pressure perception, pain sensation and Vibration perception. The Achilles tendon reflex was also significantly weaker in the DM group. Except for the DML of the TN, all electroneurographic tests revealed significantly worse results in diabetic patients.

	DM	Non-DM	p
Male, n (%)	29 (52.7%)	27 (51.9)	1
Weight [kg]	86 (78-96)	78 (67-86)	**0.002**
Height [cm]	170 (160-180)	170 (160-170)	0.43
BMI	30 (26-33)	27 (25-30)	**0.006**
Age [years]	71 (64-76)	70 (65-74)	0.75
History of diabetes [years]	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 mal. med.	4 (0-5)	6 (5-7)	**<0.001**
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]	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]	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]	53 (47-58)	58 (54-62)	**<0.001**

Table 2: Patient demographics and baseline characteristics. Data are presented as Median (IQR) unless otherwise specified.

3.3 Ultrasound evaluation

The number of final needle positions in each group as verified by the blinded investigators is shown in Table 3. Figure 9 and Figure 10 show exemplary still images of the final needle positions at the CPN and TN, where measurements of stimulation current and impedance were performed.

	Tibial nerve		Common peroneal nerve	
Needle position, n(%)	DM	Non-DM	DM	Non-DM
Intraneural-perifascicular	2 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)
Intraneural-subepineural	3 (5.5)	6 (11.5)	0 (0.0)	1 (1.9)
Extraepineural-subparaneural	42(76.4)	38 (73.1)	35 (63.7)	22 (42.3)
Extraparaneural	7 (12.7)	7 (13.5)	17 (30.9)	24 (46.2)
Distant (no needle-nerve contact)	0 (0.0)	0 (0.0)	2 (3.6)	1 (1.9)
Position not clearly definable	1 (1.8)	1 (1.9)	1 (1.8)	4 (7.7)

Table 3: Needle positions after ultrasound verification

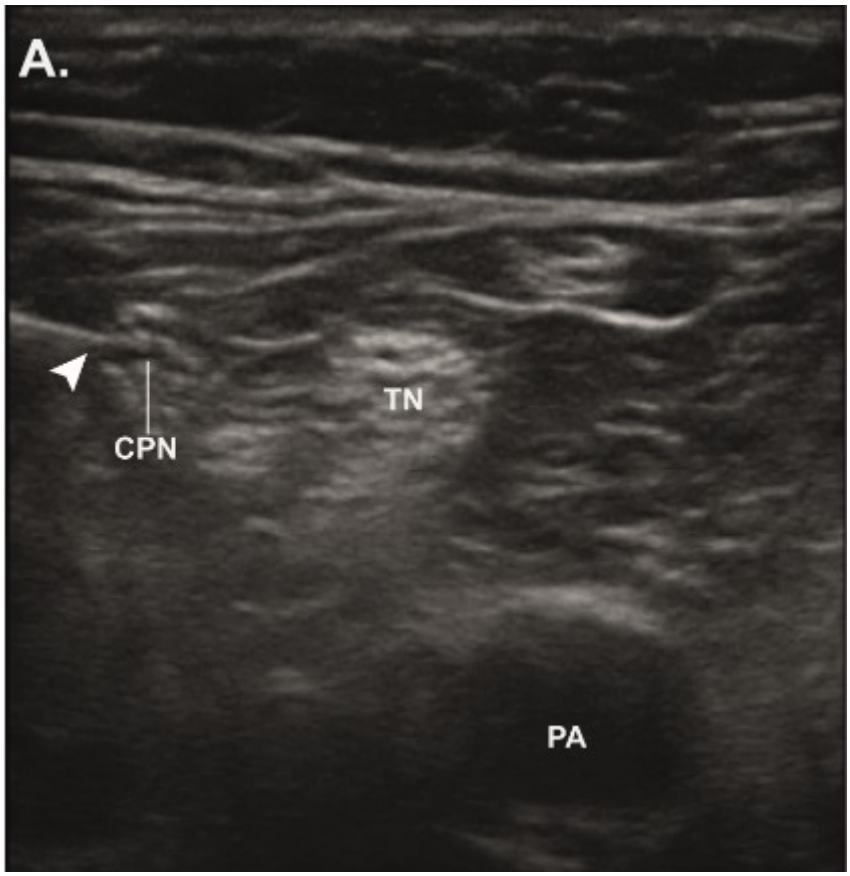

Figure 9: Final needle position at the common peroneal nerve. Arrowhead = needletip, CPN= Common peroneal nerve, TN = Tibial nerve, PA = Popliteal artery

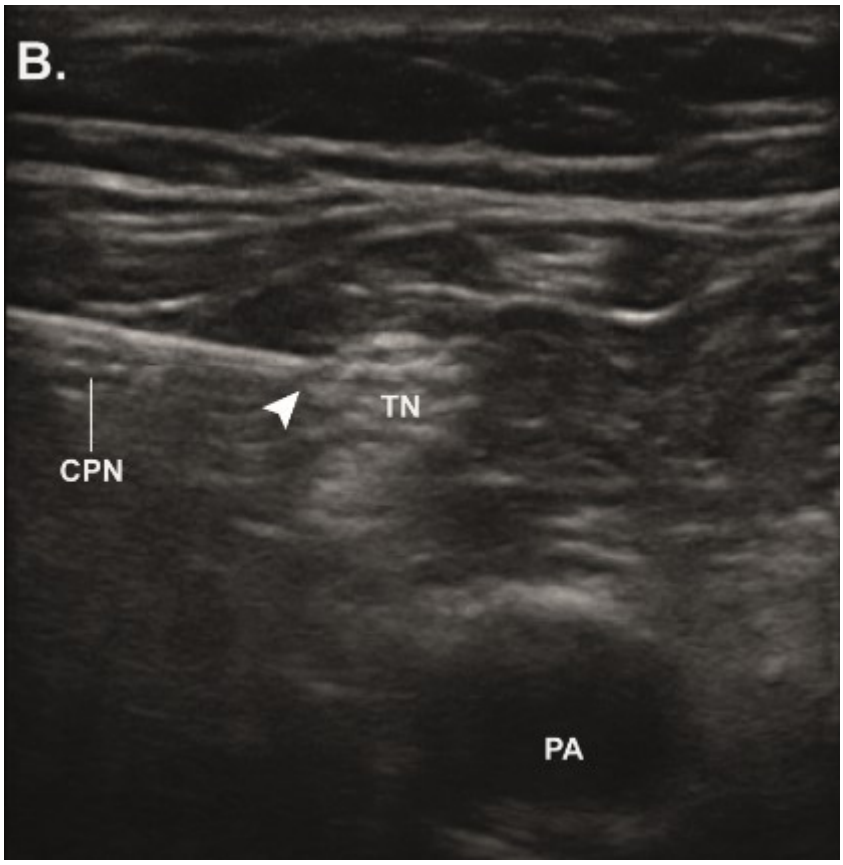

Figure 10: Final needle position at the tibial nerve. Arrowhead = needletip, CPN= Common peroneal nerve, TN = Tibial nerve, PA = Popliteal artery

3.4 Stimulation current

3.4.1 Stimulation current and diabetes mellitus

Results of the evaluation of the stimulation current regarding diabetes status can be found in Table 4. Current thresholds were not significantly different between the two groups. Distribution of the stimulation current for the TN, CPN and mean stimulation current, grouped by diabetes mellitus, is shown in Figure 11, Figure 12 and Figure 13.

	DM	Non-DM	p
Current Common Peroneal nerve [mA]	0.80 (0.37-1.50)	0.50 (0.34-0.97)	0.20
Current Tibial nerve [mA]	0.80 (0.48-1.10)	0.47 (0.40-0.88)	0.05
Mean current [mA]	0.69 (0.44-0.87)	0.58 (0.37-0.63)	0.29

Table 4: Stimulation thresholds at final needle position. Data are presented as Median (IQR).

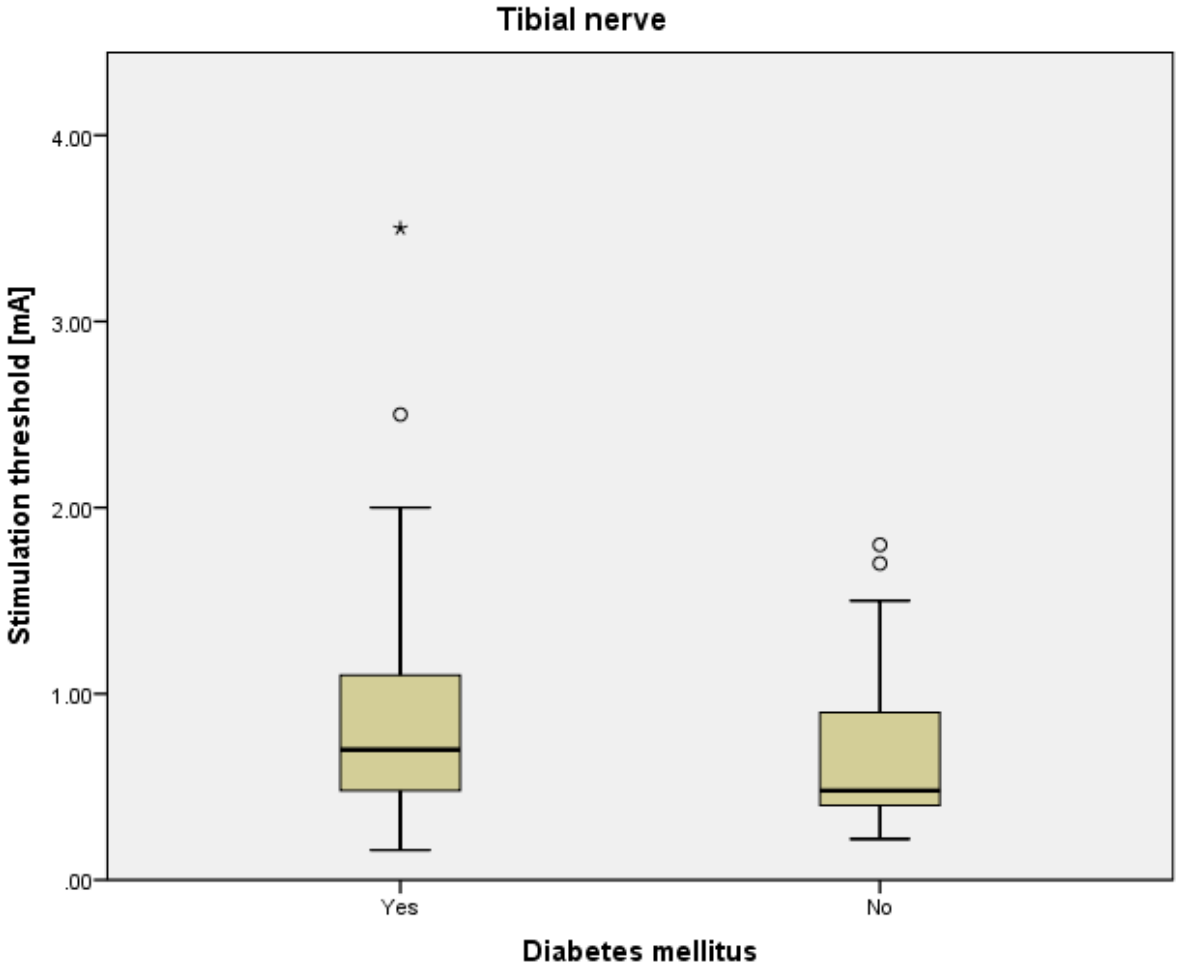

Figure 11: Stimulation threshold for the tibial nerve for diabetic and non-diabetic patients

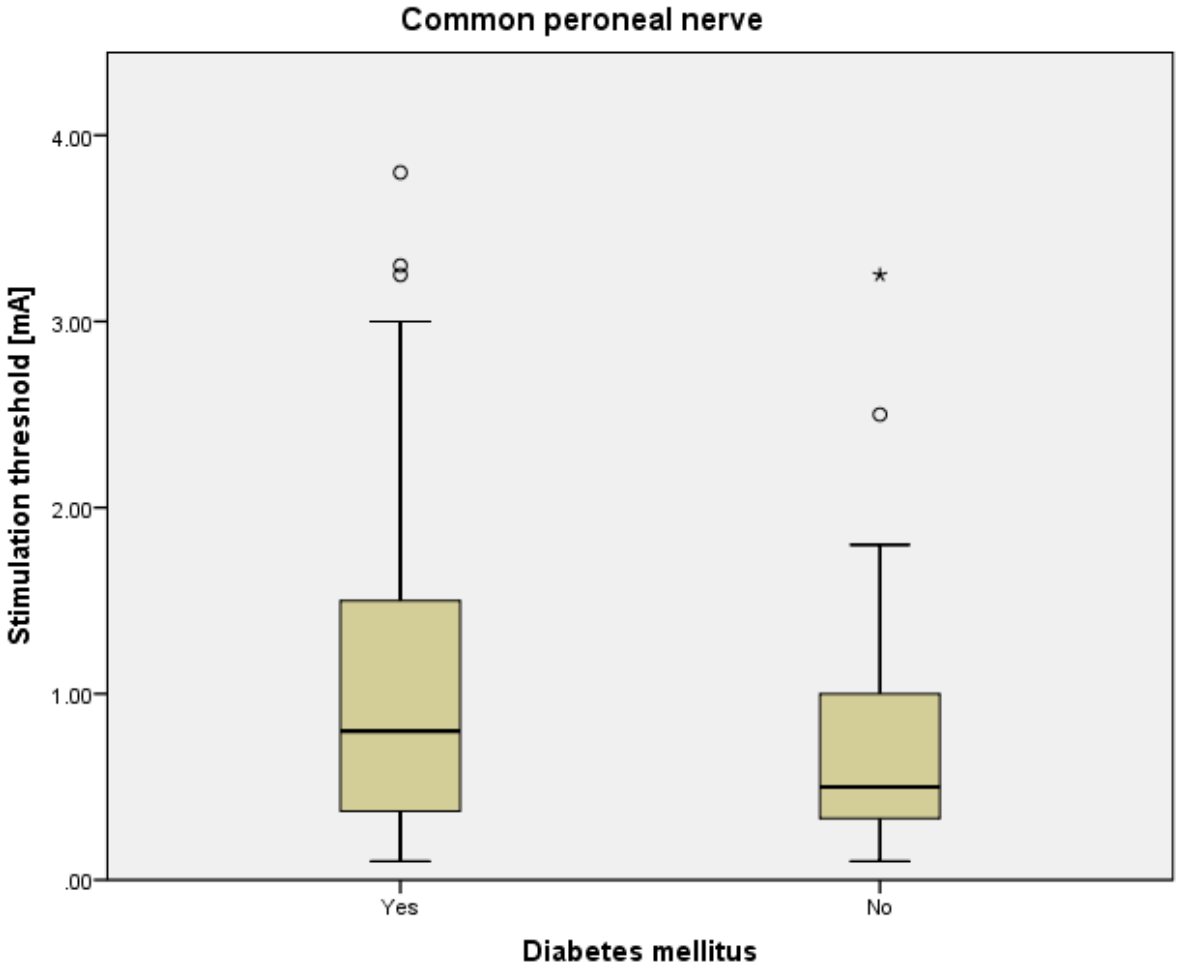

Figure 12: Stimulation threshold for the common peroneal nerve for diabetic and non-diabetic patients

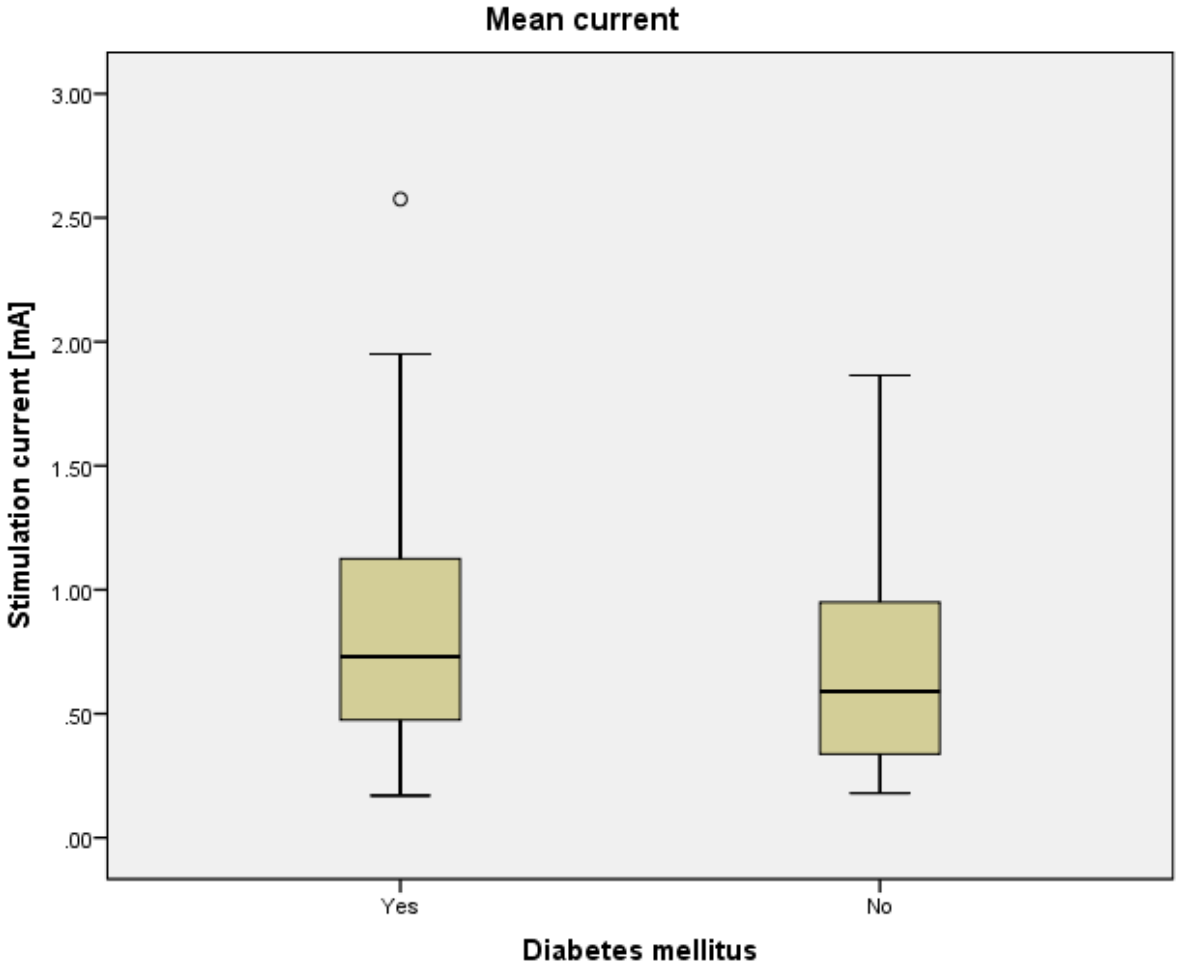

Figure 13: Mean stimulation threshold for diabetic and non-diabetic patients

3.4.2 Stimulation current and needle position

Stimulation current was not significantly different between the two needle positions “Extraepineural-subparaneural” and “Extraparaneural”, which were included in the final data analysis (Table 5, Figure 14, Figure 15).

	Extraepineural-subparaneural	Extraparaneural	p
Current CPN [mA]	0.46 (0.30 – 1.08)	0.80 (0.45 – 0.95)	0.15
Current TN [mA]	0.60 (0.40 – 0.93)	0.65 (0.40 – 1.48)	0.62

Table 5: Stimulation currents at needle positions "Extraepineural-subparaneural" and "Extraparaneural". Data are presented as Median (IQR).

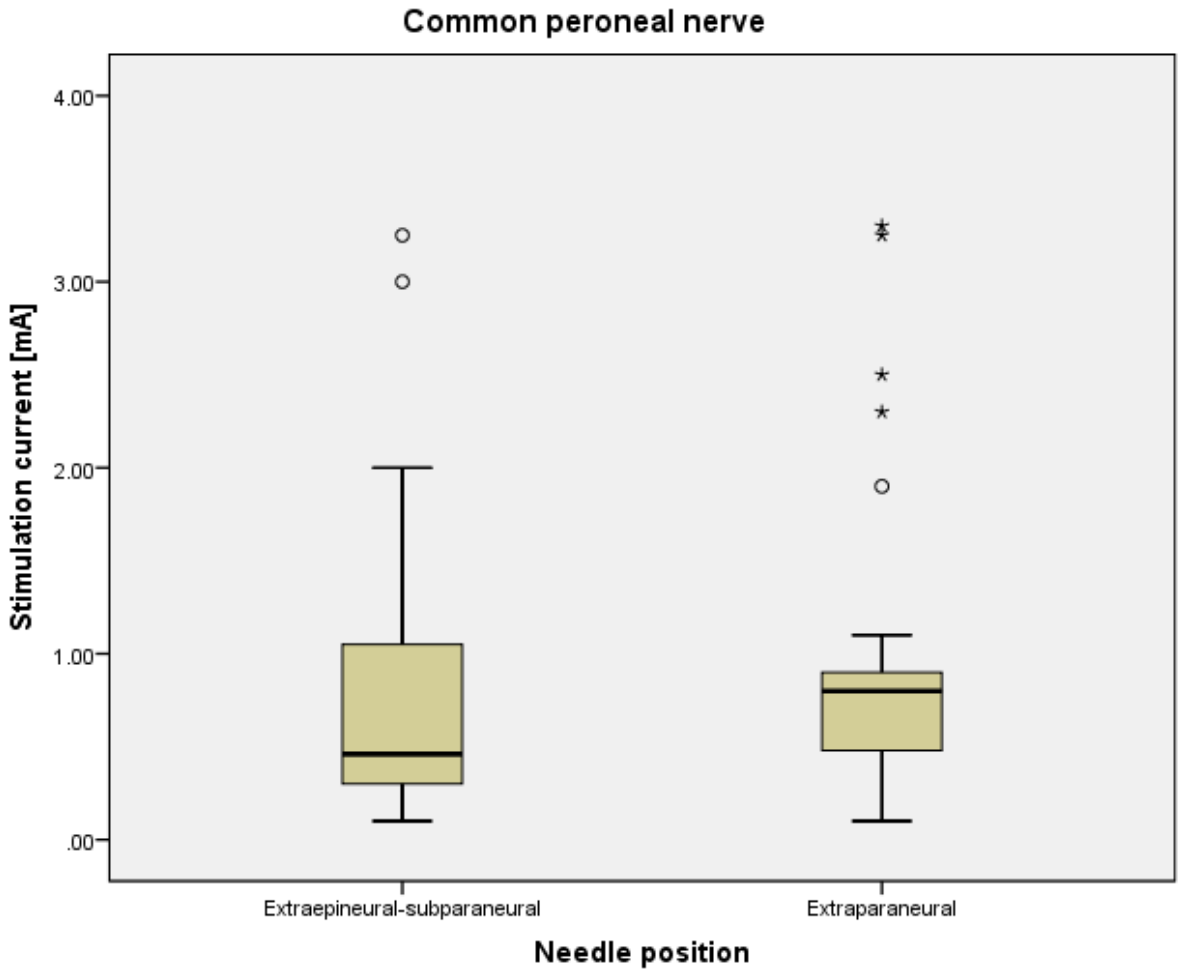

Figure 14: Stimulation current of the CPN at needle positions "Extraepineural-subparaneural" and "Extraparaneural"

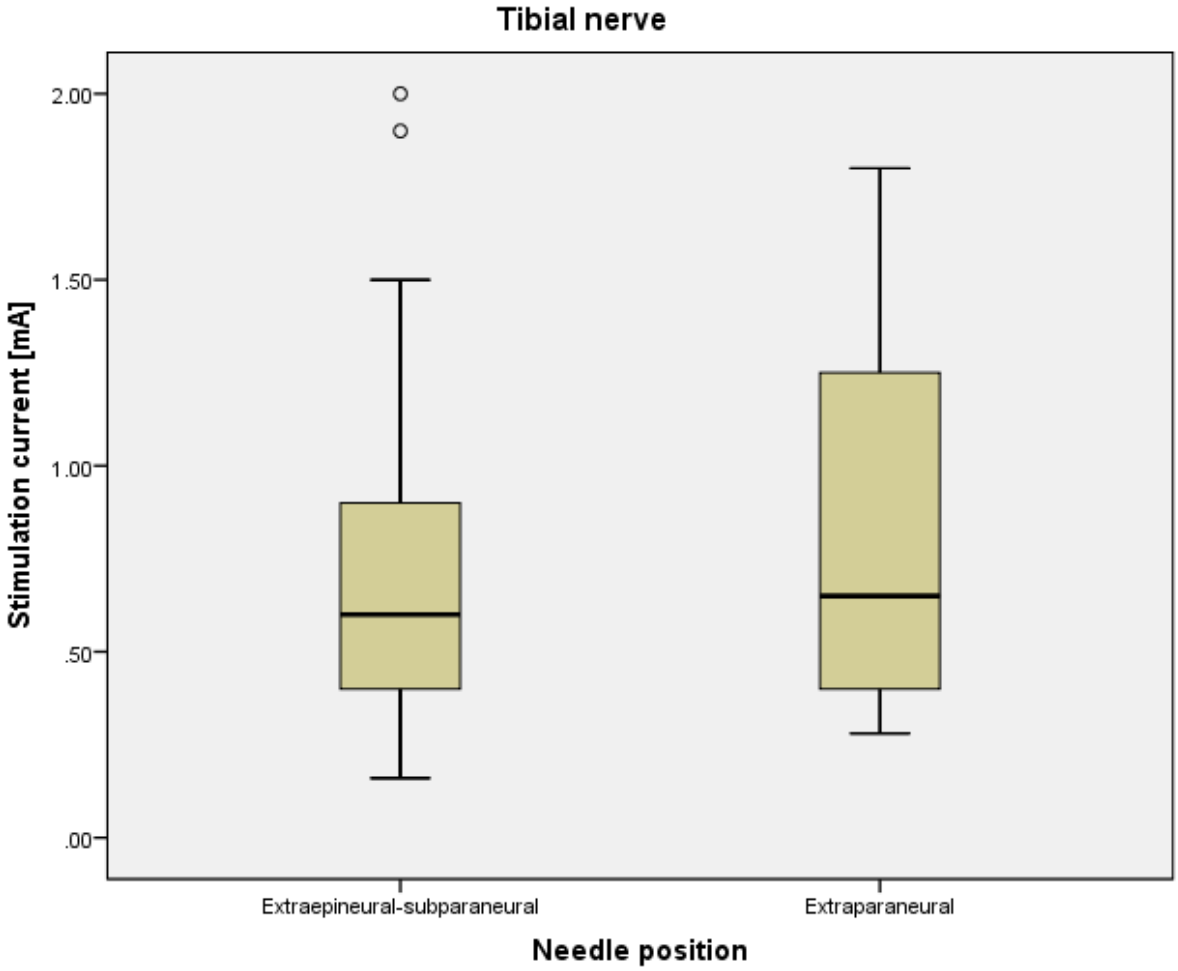

Figure 15: Stimulation current of the TN at needle positions "Extraepineural-subparaneural" and "Extraparaneural"

3.4.3 Clinical thresholds for stimulation current

With close needle-nerve contact (needle positions, "Extraepineural-subparaneural" and "Extraparaneural") 29 diabetic (57%) and 22 (48%) non-diabetic patients required stimulation currents >0.5mA for the CPN (p=0.42), and for the TN, >0.5mA was required for 31 (63%) diabetics and for 19 (42%) non-diabetics (p=0.06).

Despite intraneural needle placement, stimulation currents >0.5mA were measured in four diabetic and one non-diabetic patient. Additionally, stimulation currents ≥2 mA were necessary to evoke motor response despite close needle-nerve contact in 12 diabetic patients (of which 1 patient had intraneural needle placement at the TN and required ≥2 mA with close needle-nerve contact for the CPN) and 2 non diabetic

patients. Considering these patients at particular risk for nerve damage, they constitute 27% of the total diabetic group, which is substantially elevated compared to three such patients in the non-diabetic group (6%, p=0.003).

3.4.4 Order effect

Separate analysis of the randomization groups revealed no difference in stimulation currents and therefore an order effect was excluded (Table 6).

	CPN first	TN first	p
Current CPN [mA]	0.60 (0.37 – 1.10)	0.70 (0.33 – 1.00)	0.87
Current TN [mA]	0.50 (0.40 – 0.85)	0.80 (0.40 – 1.10)	0.37
Mean current [mA]	0.66 (0.42 – 1.05)	0.70 (0.43 – 1.10)	0.70

Table 6: Stimulation current and regarding to randomization order. Data are presented as Median (IQR).

3.4.5 Comparison of variability

Stimulation current showed a high degree of variability in both diabetic and non-diabetic patients, which was not significantly different between the groups (Table 7).

	DM	Non-DM	p
Current CPN [mA]	0.37 – 1.50	0.34 – 0.97	0.35
Current TN [mA]	0.48 – 1.10	0.40 – 0.88	0.53
Mean current [mA]	0.44 – 1.06	0.37 – 0.88	0.47

Table 7: Comparison of distribution for stimulation thresholds between diabetic and non-diabetic patients, Data are presented as IQR.

3.5 Impedance

3.5.1 Impedance and diabetes mellitus

Results of the impedance measurements were not significantly different between the groups (Table 8). Distribution of impedance at the TN, CPN and mean impedance is shown in Figure 16, Figure 17 and Figure 18, respectively.

	DM	Non-DM	p
Impedance Common peroneal nerve [kΩ]	12.20 (10.15-15.80)	11.15 (9.65-12.85)	0.25
Impedance Tibial nerve [kΩ]	12.00 (9.30-14.65)	11.30 (9.45-13.55)	0.71
Mean Impedance [kΩ]	12.34 (9.55-12.52)	10.59 (9.68-11.44)	0.22

Table 8: Impedance measurements at final needle position, Data are presented as Median (IQR).

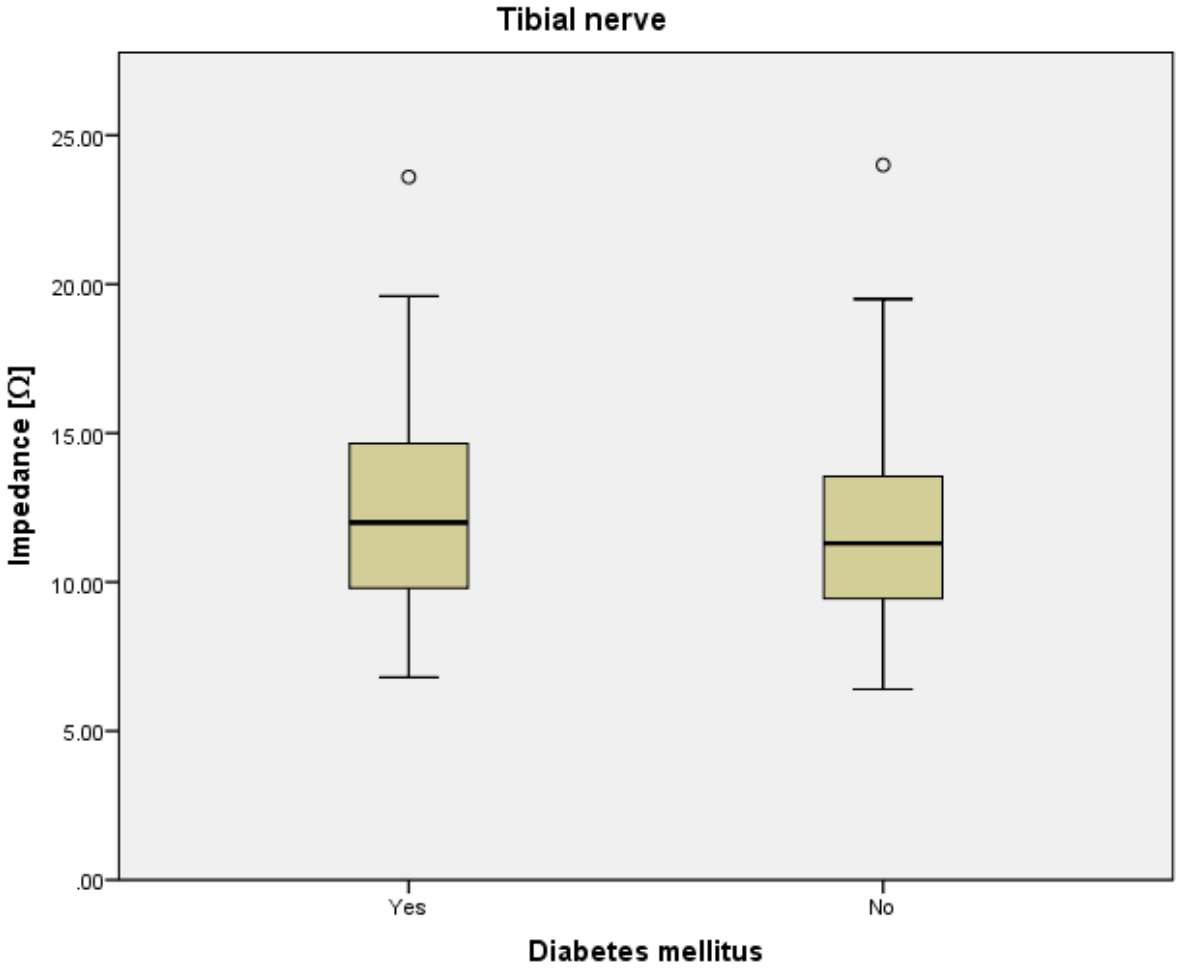

Figure 16: Impedance for the tibial nerve for diabetic and non-diabetic patients

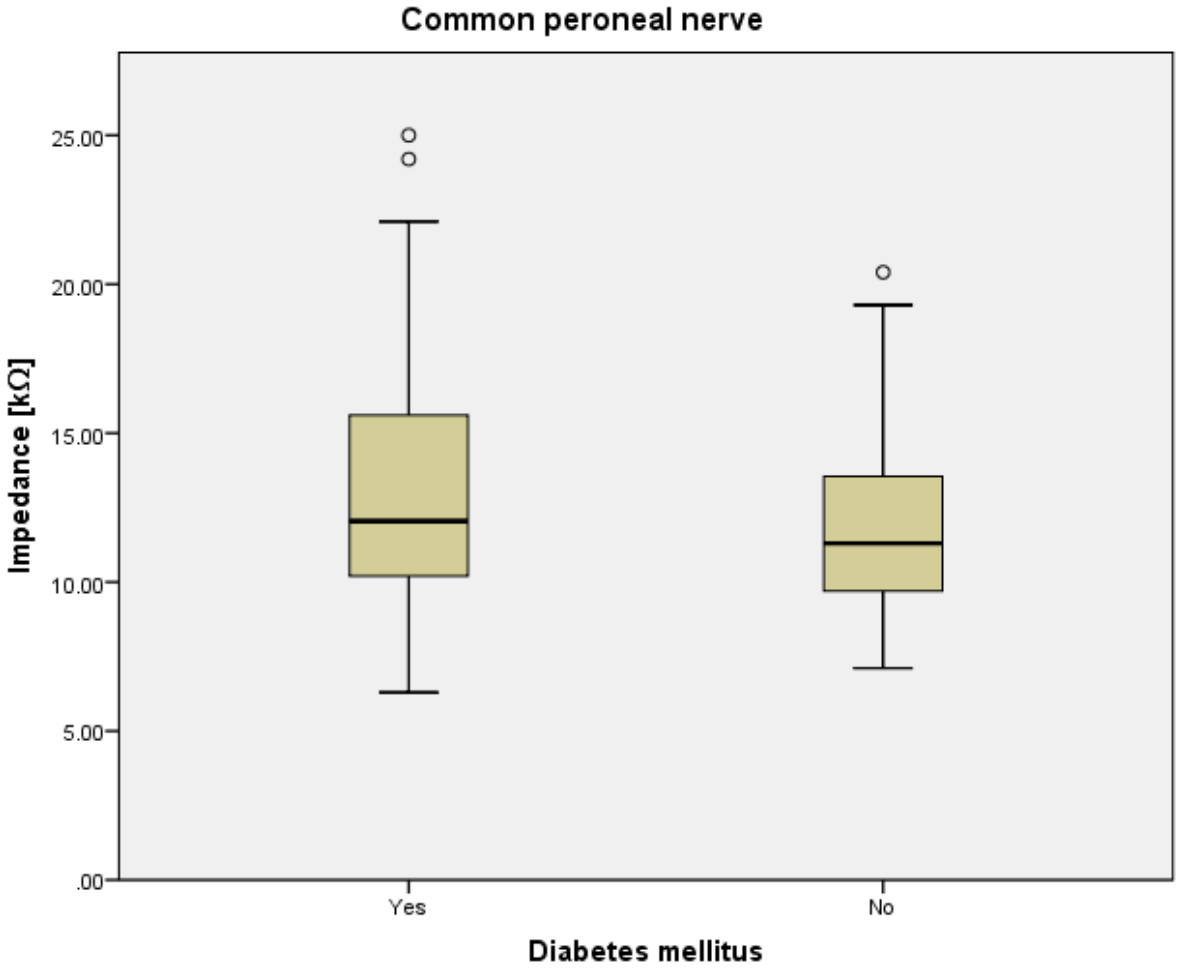

Figure 17: Impedance for the CPN for diabetic and non-diabetic patients

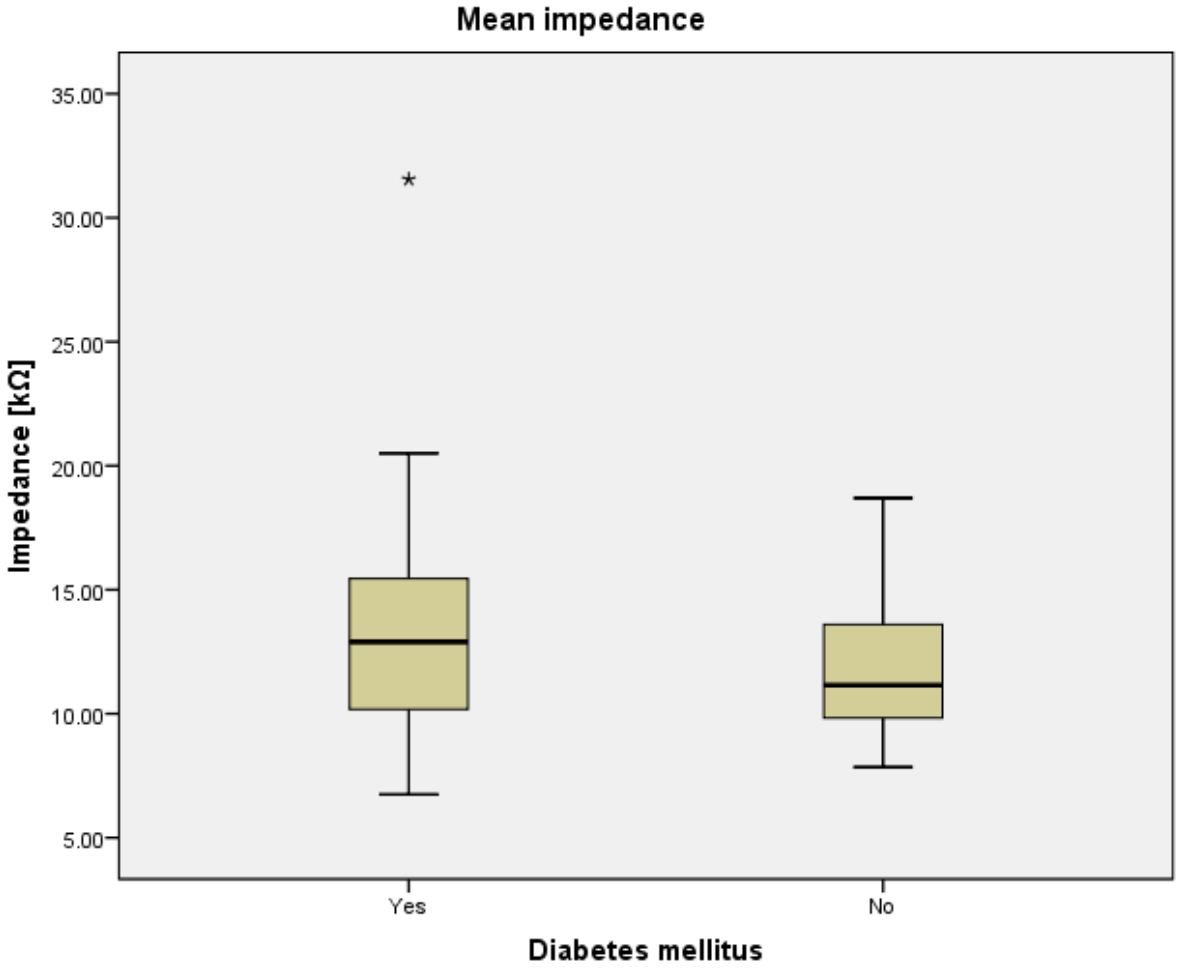

Figure 18: Mean impedance for diabetic and non-diabetic patients

3.5.2 Order effect

Separate analysis of the randomization groups revealed no difference in impedance measurement and therefore an order effect was excluded for impedance (Table 9).

	CPN first	TN first	p
Impedance CPN [kΩ]	11.80 (10.10 – 15.85)	12.00 (10.05 – 15.25)	1.00
Impedance TN [kΩ]	11.80 (9.90 – 14.15)	12.00 (9.20 – 14.75)	0.47
Mean Impedance [kΩ]	11.80 (9.65 – 14.55)	12.45 (10.00 – 14.35)	0.75

Table 9: Impedance measurements regarding to randomization order. Data are presented as Median (IQR).

3.5.3 Comparison of variability

Variability of impedance was not significantly different between diabetic and non-diabetic patients (Table 10).

	DM	Non-DM	p
Impedance CPN [kΩ]	10.15 – 15.80	9.65 – 12.85	0.53
Impedance TN [kΩ]	9.30 – 14.65	9.45 – 13.55	0.42
Mean Impedance [kΩ]	9.55 – 12.52	9.68 – 11.92	0.28

Table 10: Comparison of distribution for impedance between diabetic and non-diabetic patients, Data are presented as IQR.

3.5.4 Correlation stimulation current and impedance

There was a significant negative correlation between stimulation current and impedance for the CPN (r= -0.27, p=0.009; Figure 19) but not for the TN (r= -0.14, p=0.18; Figure 20).

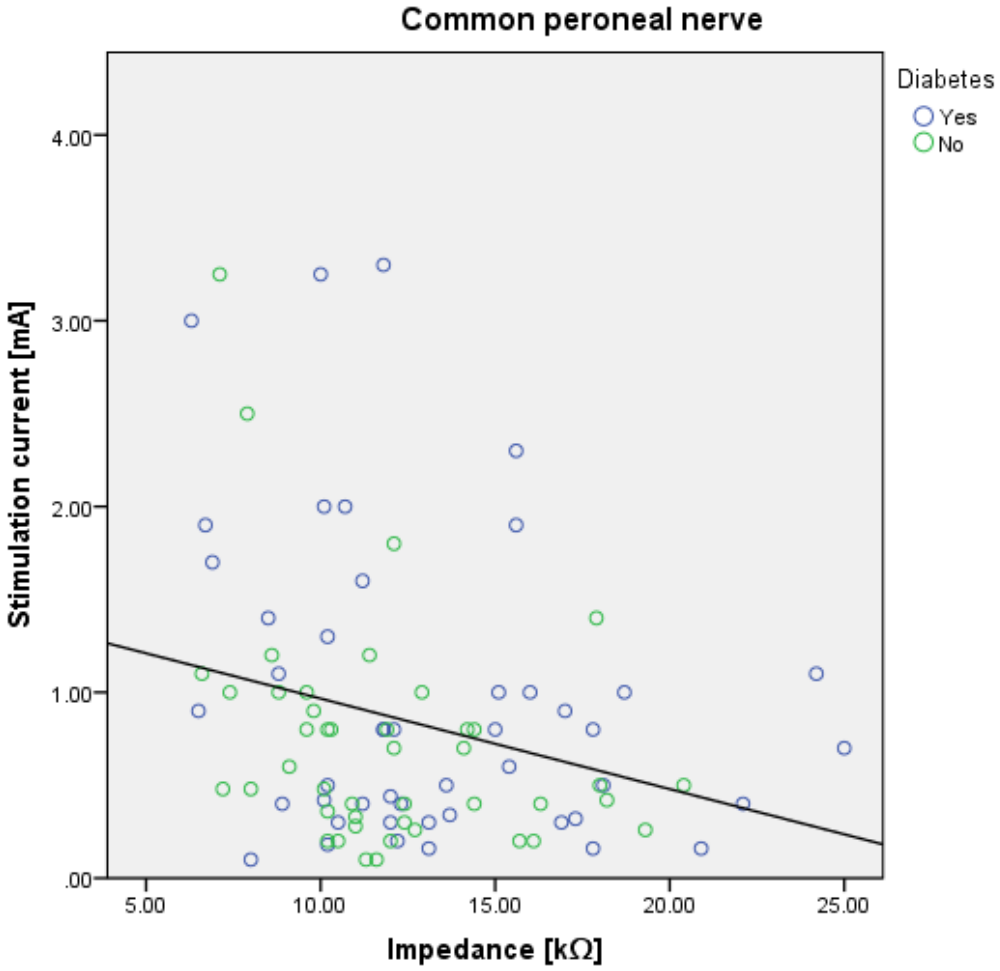

Figure 19: Correlation between Impedance and stimulation current for the CPN

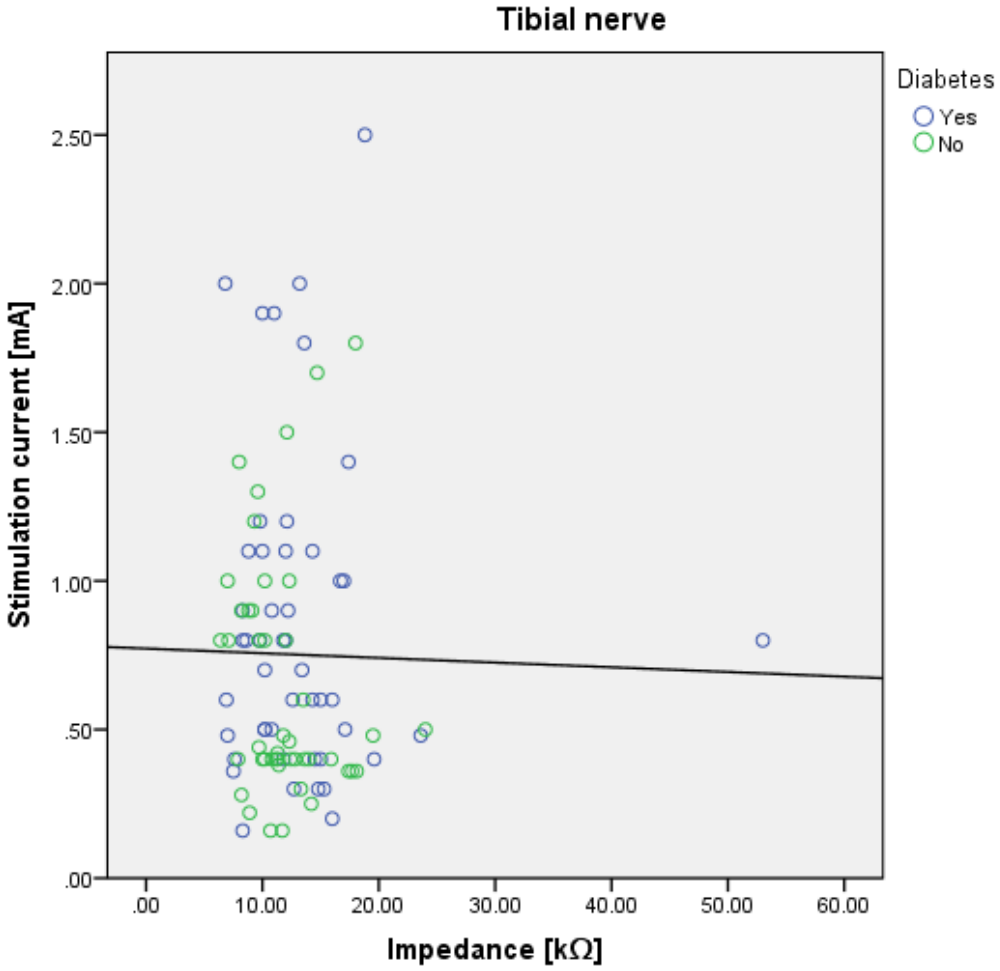

Figure 20: Correlation between Impedance and stimulation current for the TN

3.5.5 Impedance and needle position

Impedance was not significantly different between the two needle positions "Extraepineural-subparaneural" and "Extraparaneural", which were included in the final data analysis (Table 11, Figure 21, Figure 22).

	Extraepineural-subparaneural	Extraparaneural	p
Impedance CPN [kΩ]	12.00 (10.13 – 16.55)	11.80 (9.35 – 15.20)	0.47
Impedance TN [kΩ]	11.35 (9.53 – 14.23)	13.80 (8.60 – 14.65)	0.67

Table 11: Impedance at needle positions "Extraepineural-subparaneural" and "Extraparaneural". Data are presented as Median (IQR).

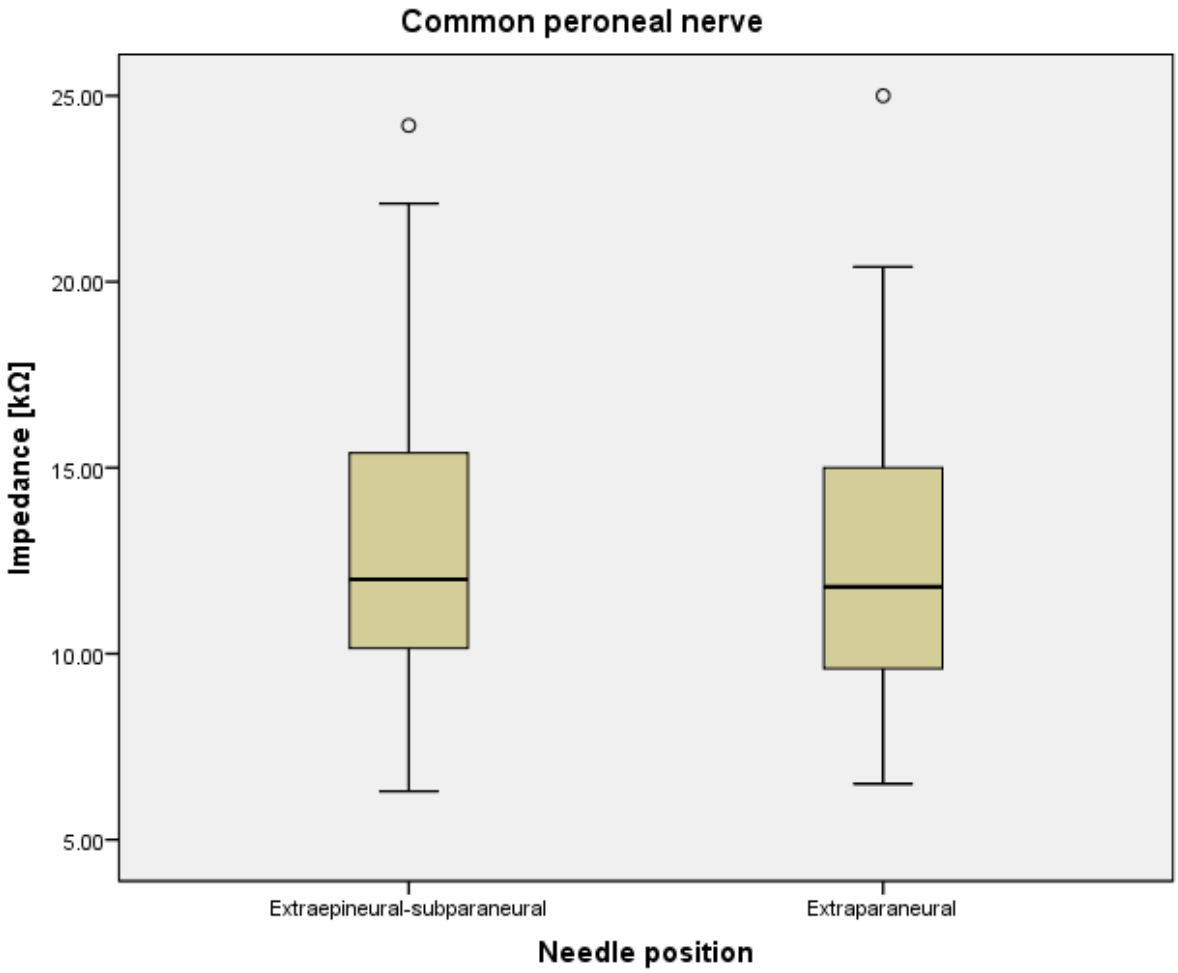

Figure 21: Impedance of the CPN at needle positions "Extraepineural-subparaneural" and "Extraparaneural"

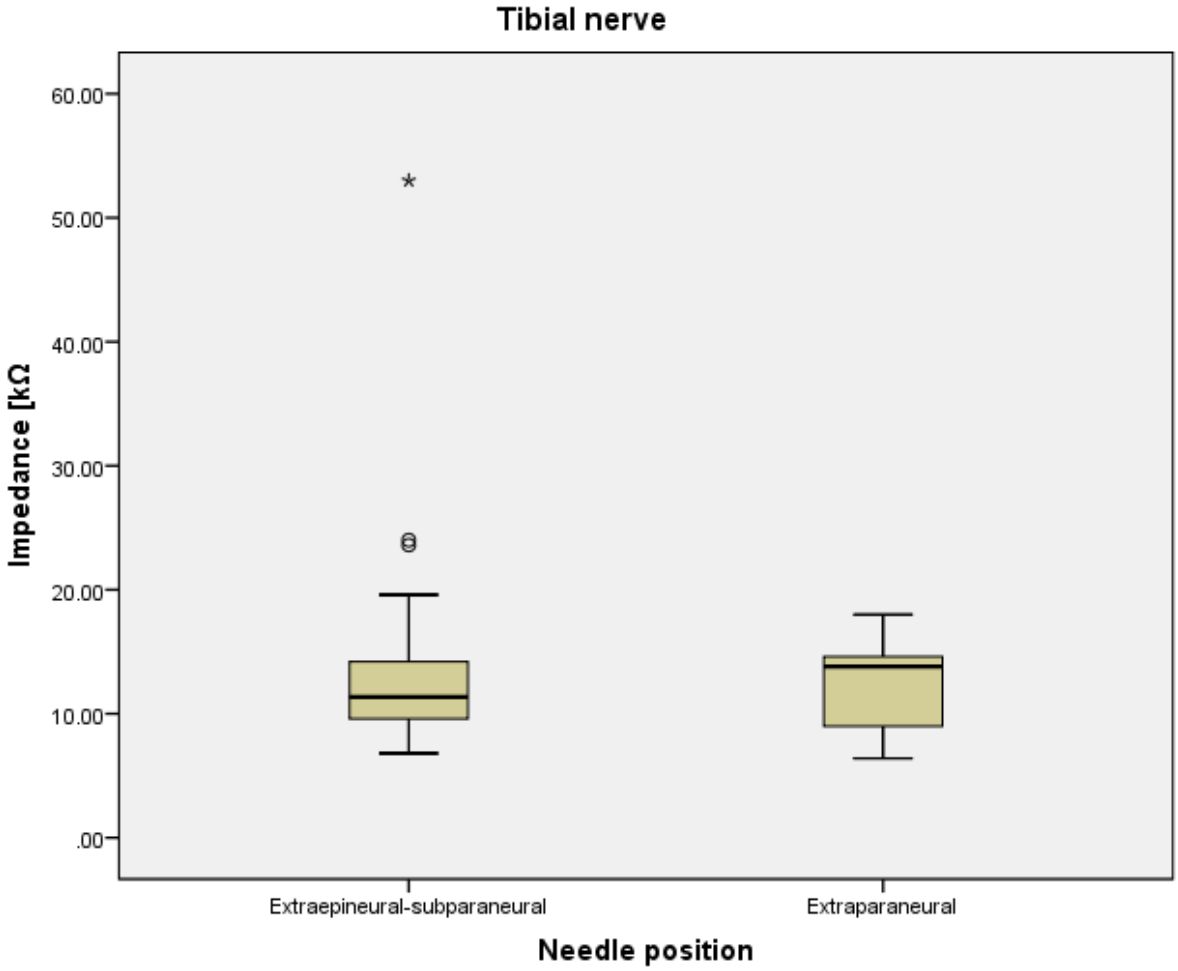

Figure 22: Impedance of the TN at needle positions "Extraepineural-subparaneural" and "Extraparaneural"

3.6 Clinical tests

The correlation of the preoperative clinical tests and the stimulation currents are shown in Table 12. There was no significant correlation of any clinical test to the mean stimulation current. The stimulation current of the CPN significantly correlated with the duration of DM (Figure 23). A diminished achilles tendon reflex as well as absence of pressure perception and pain sensation predicted increased stimulation currents for the CPN. For the dichotomous variables no correlation coefficient was calculated and the median stimulation currents are presented in Table 13 for the CPN, Table 14 for the TN and Table 15 for the Mean stimulation current, respectively.

	Current Common peroneal nerve		Current Tibial nerve		Mean current	
	p	r	p	r	p	r
Duration of diabetes	**0.02**	0.34	0.74	-	0.15	-
ABI Dorsalis pedis artery	0.80	-	0.14	-	0.66	-
ABI Posterior tibial artery	0.98	-	0.11	-	0.50	-
Vibration mal. med.	0.46	-	0.09	-	0.35	-
Vibration hallux	0.94	-	0.69	-	0.82	-
Achilles tendon reflex	**0.04**	-0.21	0.22	-	0.07	-

Table 12: Correlation of clinical tests to stimulation thresholds

	Present	Absent	p
Claudication	0.70 (0.31 – 1.00)	0.55 (0.40 – 1.90)	0.31
Foot deformities	0.70 (0.36 – 1.10)	0.46 (0.30 – 1.23)	0.61
Family history of DM	0.66 (0.37 – 1.10)	0.50 (0.26 – 1.70)	0.54
Family history of foot ulcera	0.55 (0.33 – 1.08)	0.80 (0.32 – 1.78)	0.50
Dorsal pedis artery pulse	0.60 (0.31 – 1.00)	1.00 (0.40 – 1.00)	0.70
Posterior tibial artery pulse	0.55 (0.30 -1.00)	1.00 (0.60 (1.50)	0.24
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)	**0.04**
Pain sensation	0.50 (0.32 – 1.00)	1.60 (0.70 – 2.00)	**0.04**

Table 13: Association of stimulation current at the common peroneal nerve to preoperative neurologic exams. Data are presented as Median (IQR).

	Present	Absent	p
Claudication	0.50 (0.40 – 0.83)	0.90 (0.50 – 1.40)	**<0.001**
Foot deformities	0.60 (0.40 – 1.00)	0.800.40 – 0.95)	0.90
Family history of DM	0.50 (0.40 – 0.90)	0.80 (0.44 – 1.40)	0.14
Family history of foot ulcera	0.60 ((0.40 – 0.93)	0.60 (0.40 – 1.10)	0.63
Pulse dorsal pedis artery	0.60 (0.40 – 0.90)	0.60 (0.48 – 0.90)	0.72
Pulse posterior tibial artery	0.60 (040 – 0.88)	0.60 (0.49 – 0.90)	0.80
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

Table 14: Association of stimulation current at the tibial nerve to preoperative neurologic exams. Data are presented as Median (IQR).

	Present	Absent	p
Claudication	0.70 (0.40 – 0.95)	0.72 (0.53 – 1.56)	0.05
Foot deformities	0.73 (0.45 – 1.10)	0.60 (0.36 – 0.98)	0.42
Family history of DM	0.74 (0.45 – 1.01)	0.58 (0.44 – 1.40)	0.9
Family history of foot ulcera	0.70 (0.45 – 1.05)	0.95 (0.37 – 1.44)	0.42
Pulse dorsal pedis artery	0.66 (0.37 – 0.90)	0.98 (0.44 – 1.10)	0.57
Pulse posterior tibial artery	0.63 0.45 – 0.97)	0.84 (0.57 – 1.10)	0.44
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

Table 15: Association of mean stimulation current to preoperative neurologic exams. Data are presented as Median (IQR).

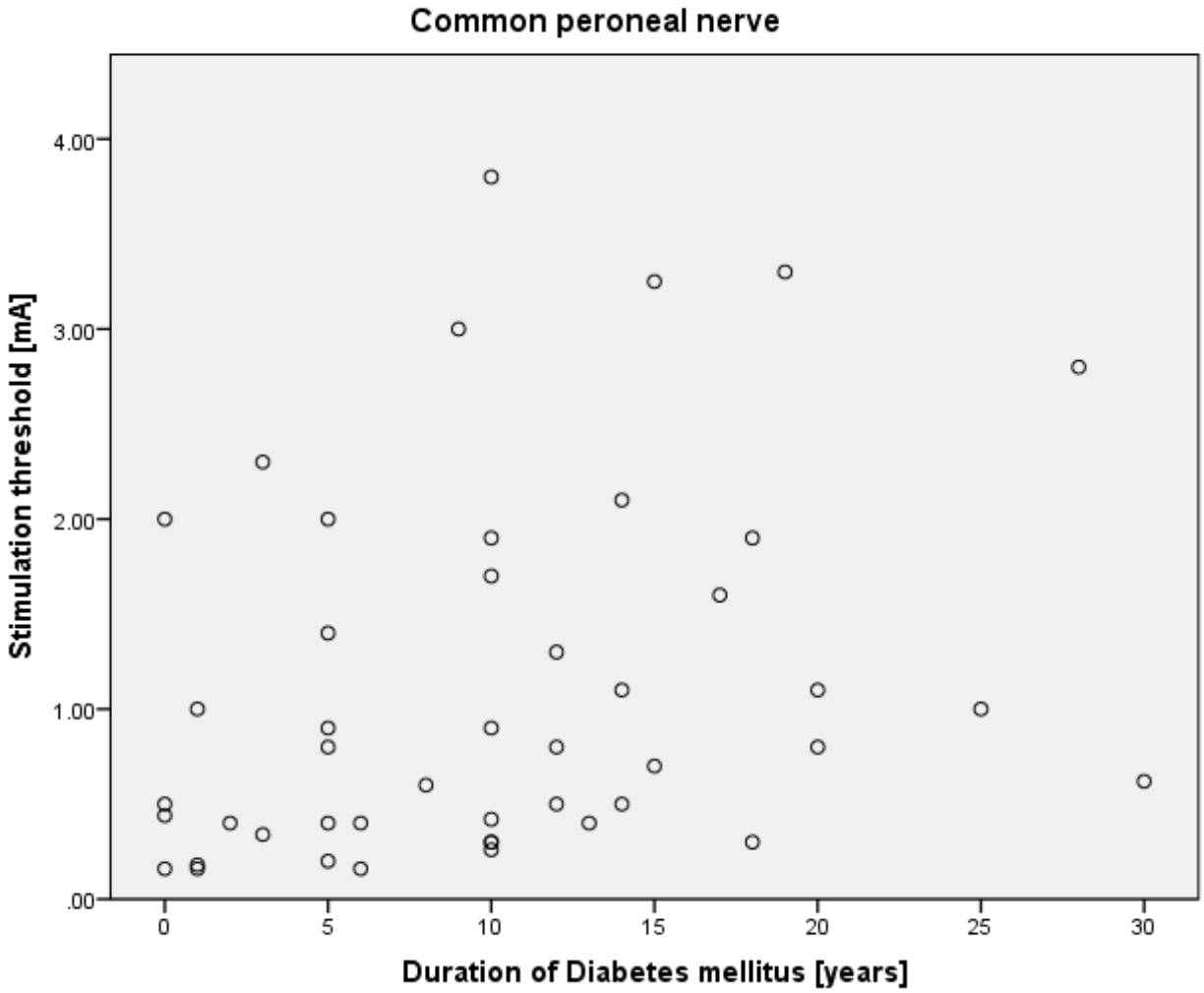

Figure 23: Correlation of duration of diabetes and stimulation threshold for the common peroneal nerve

3.7 Electroneurography

ENG revealed significant correlation of nerve conduction properties to stimulation currents (Table 16). For the CPN it was its CV, which showed a significant negative correlation to stimulation current (Figure 24), whereas for the TN its DML showed a significant correlation to the stimulation current (Figure 25). The CV of the ulnar nerve showed a highly significant negative correlation to stimulation current for both CPN (Figure 26) and TN (Figure 27) and the DML of the ulnar nerve had a correlation to the stimulation current of the CPN only (Figure 28). The mean

stimulation current was correlated to the CPN CV (Figure 29), TN DML (Figure 30), UN DML (Figure 31) and UN CV (Figure 32).

	Current Common peroneal nerve		Current Tibial nerve		Mean current	
	p	r	p	r	p	r
Common Peroneal nerve DML [ms]	0.07	-	0.05	-	0.10	-
Common Peroneal nerve CV [$m \cdot s^{-1}$]	**0.014**	-0.27	0.06	-	**0.045**	-0.24
Tibial nerve DML [ms]	0.11	-	**0.029**	0.25	**0.048**	0.24
Tibial nerve CV [$m \cdot s^{-1}$]	0.45	-	0.13	-	0.35	-
Ulnar nerve DML [ms]	**0.004**	0.30	0.11	-	**0.049**	0.22
Ulnar nerve CV [$m \cdot s^{-1}$]	**<0.001**	-0.36	**0.009**	-0.27	**0.002**	-0.35

Table 16: Correlation of electroneurography results to stimulation thresholds

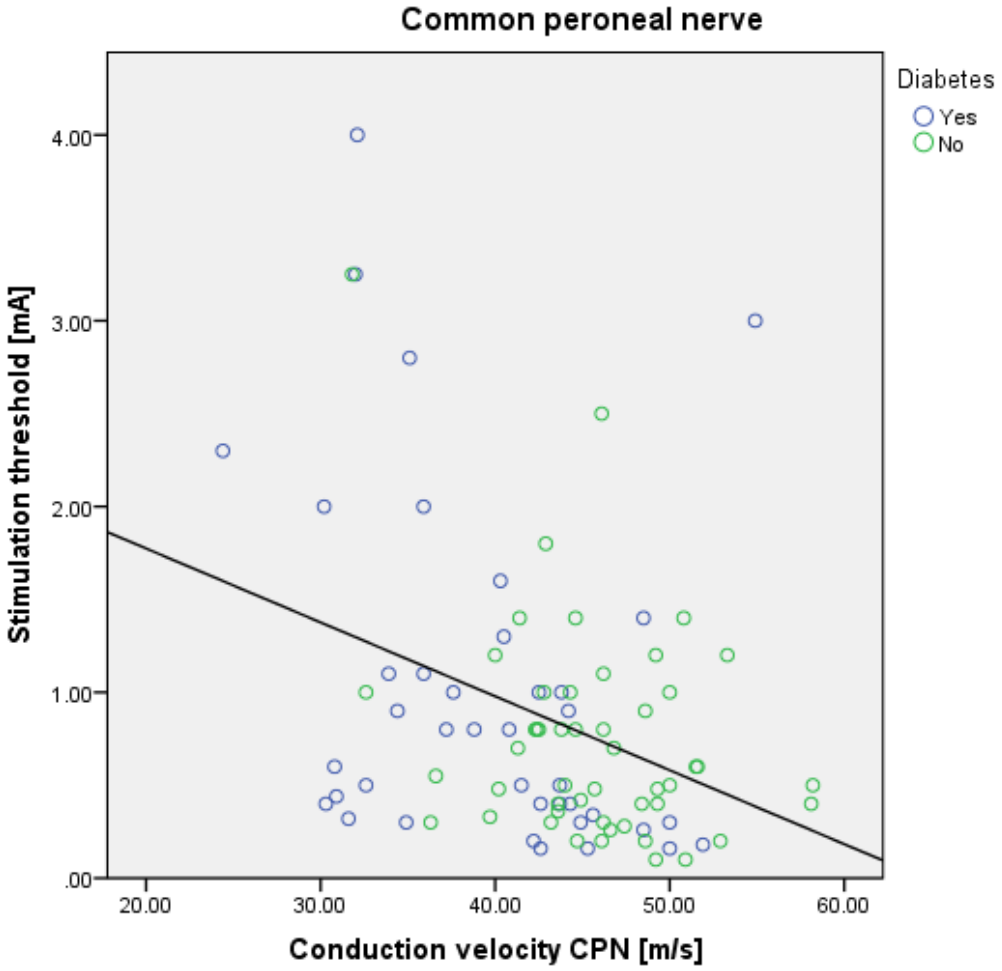

Figure 24: Correlation of the conduction velocity of the CPN and the stimulation threshold for the CPN

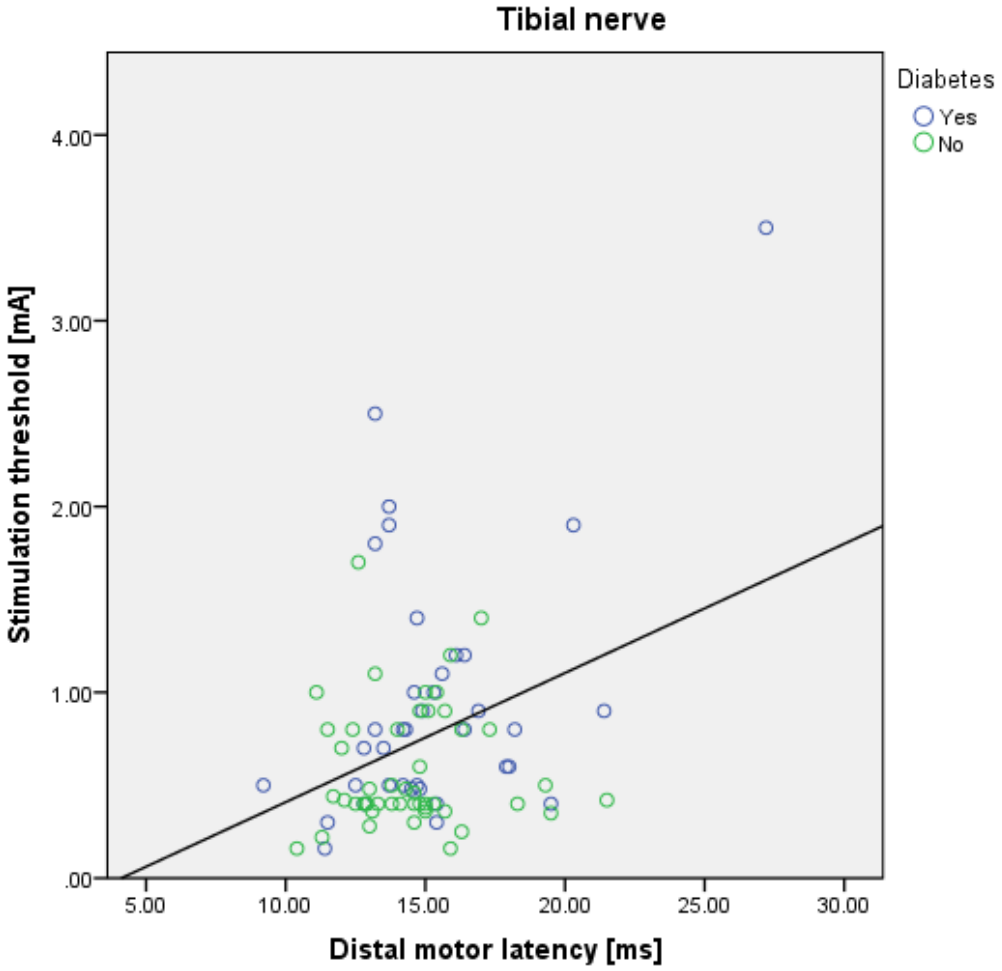

Figure 25: Correlation of the distal motor latency of the TN and the stimulation threshold for the TN

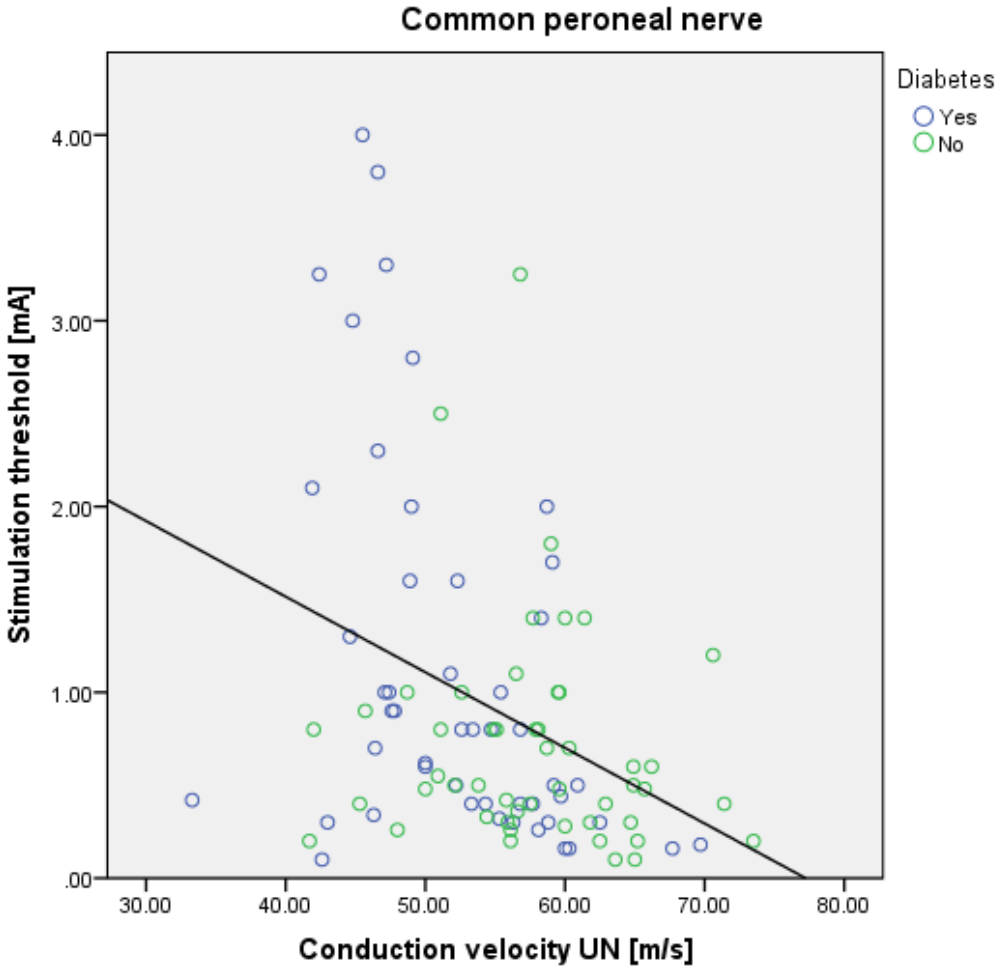

Figure 26: Correlation of the conduction velocity of the UN and the stimulation threshold for the CPN

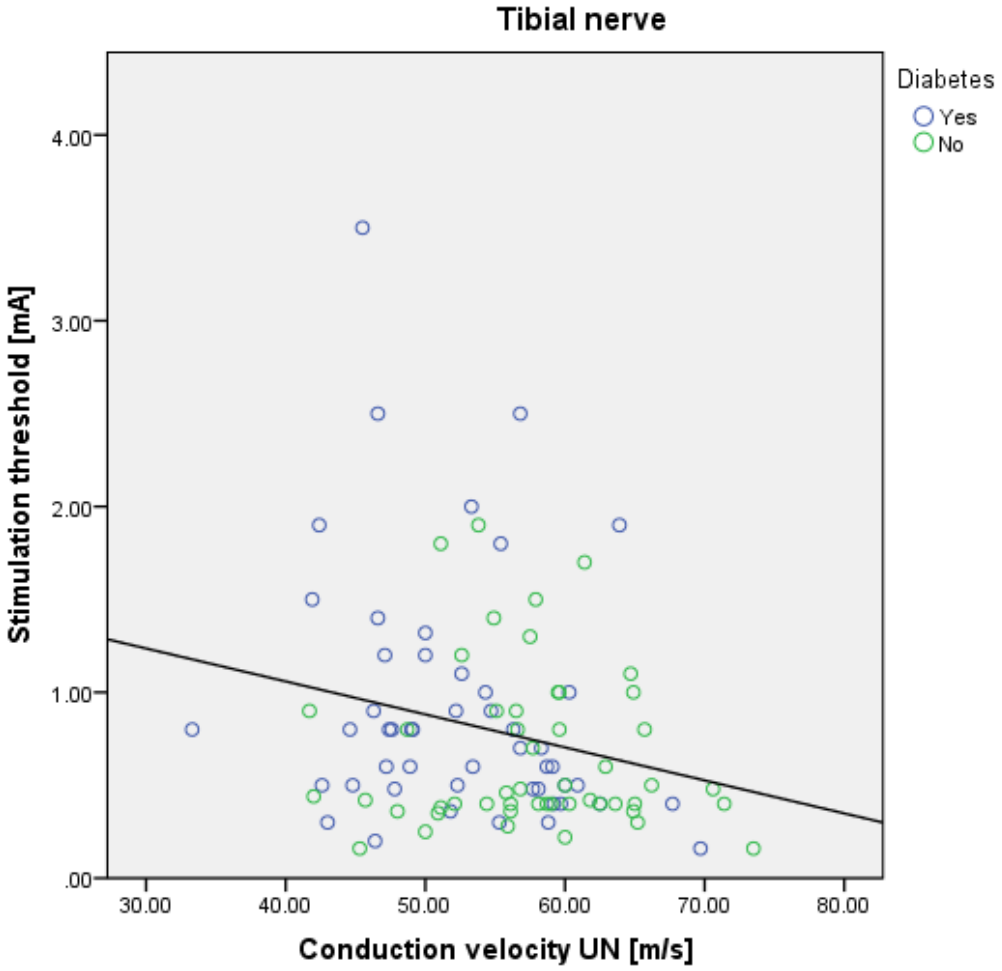

Figure 27: Correlation of the conduction velocity of the UN and the stimulation threshold for the TN

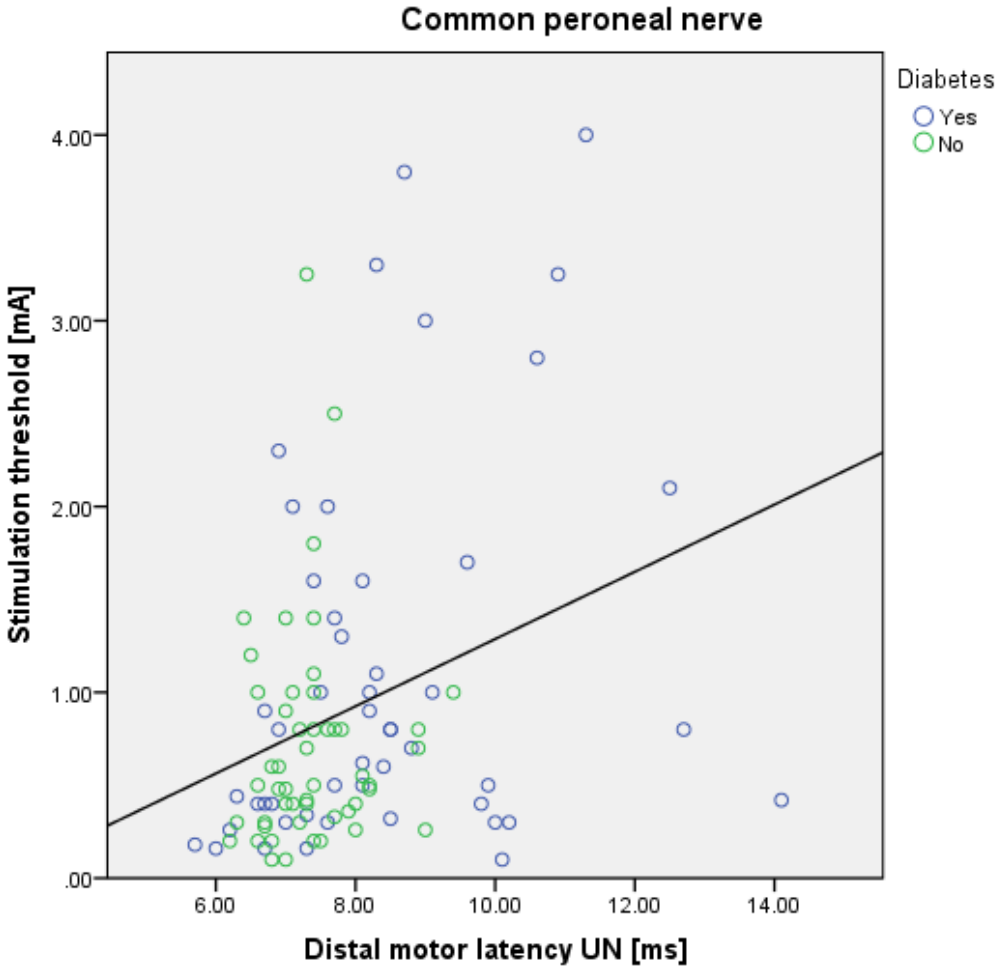

Figure 28: Correlation of the distal motor latency of the UN and the stimulation threshold for the CPN

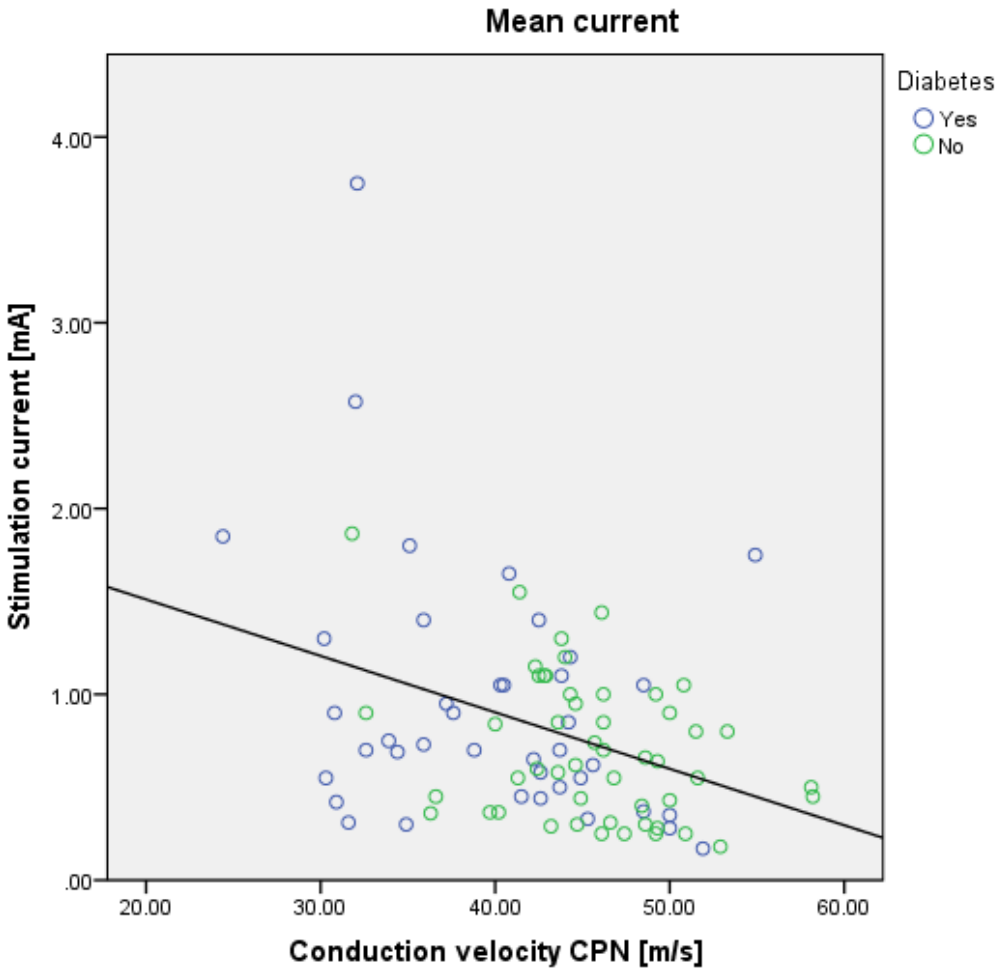

Figure 29: Correlation of the conduction velocity of the common peroneal nerve to the mean stimulation current

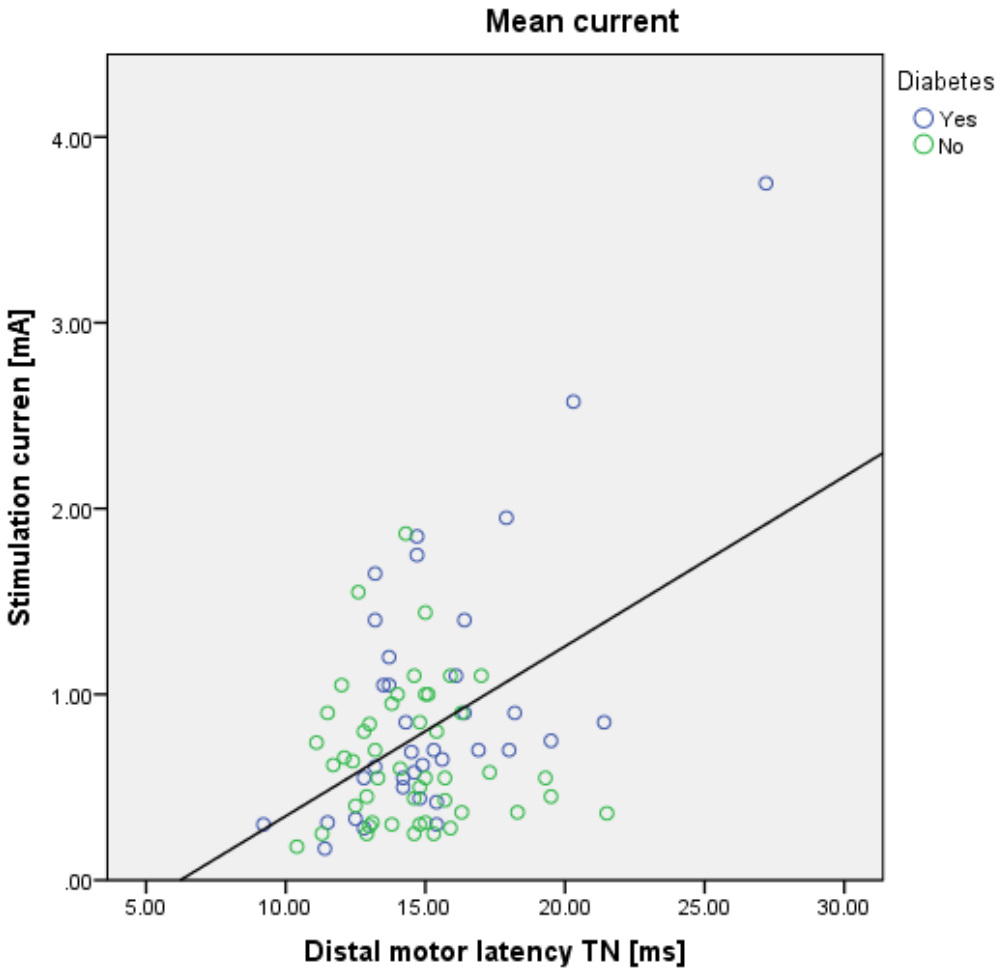

Figure 30: Correlation of the distal motor latency of the tibial nerve to the mean stimulation current

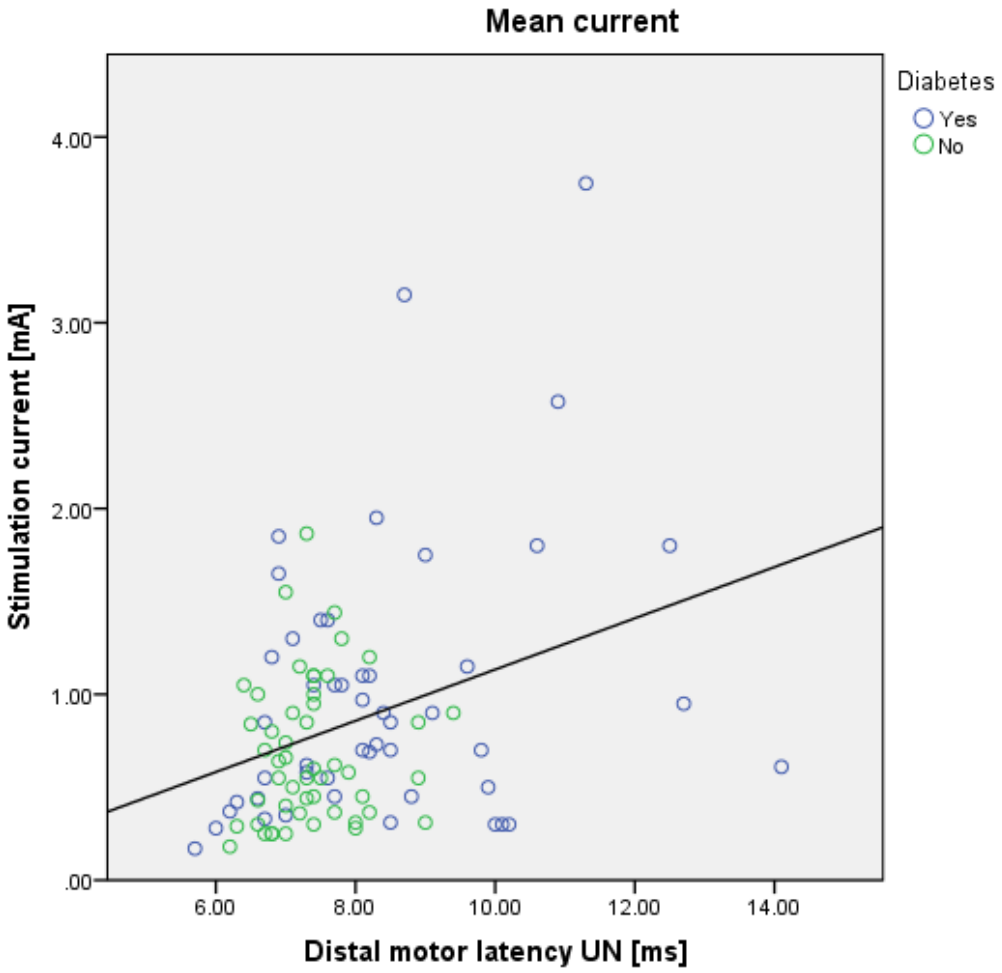

Figure 31: Correlation of the distal motor latency of the ulnar nerve to the mean stimulation current

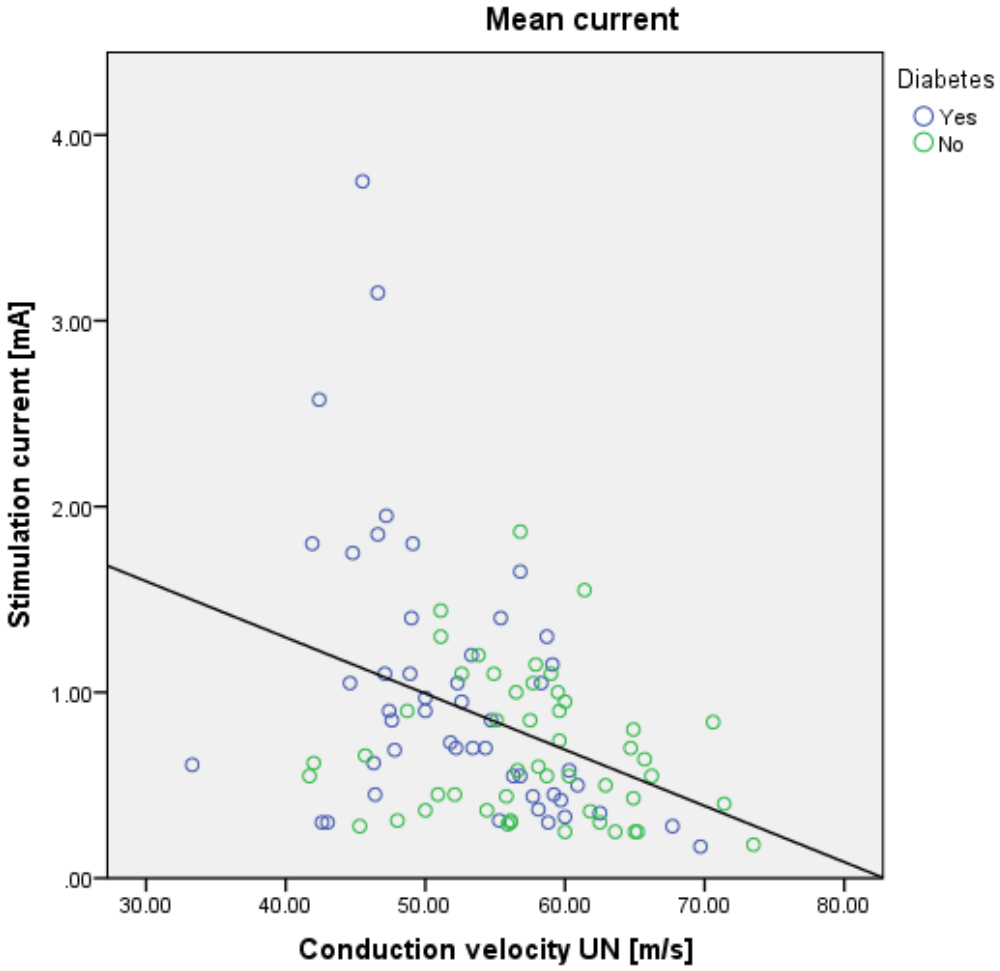

Figure 32: Correlation of the conduction velocity of the ulnar nerve to the mean stimulation current

3.8 Laboratory tests

No form of neuropathy that was not attributable to DM was detected with the use of preoperative laboratory tests, therefore no patient had to be excluded from the study for that reason.

Preoperative laboratory results are shown in Table 17. No test result showed a significant correlation to the mean stimulation current, however lower levels of folic acid were weakly correlated to higher stimulation thresholds of the CPN and higher levels of HbA1c correlated with higher stimulation thresholds for the TN (Table 18).

	DM	Non-DM	p
C-Peptid [ng/ml]	1.08 (0.79 – 2.39)	1.06 (0.93 – 1.39)	0.59
Insulin [mU/l]	5.5 (2.3 – 9.3)	3.8 (2.2 – 6.7)	0.25
fT3 [pmol/l]	3.6 (3.1 – 4.0)	4.3 (3.8 – 4.8)	**<0.001**
fT4 [pmol/l]	14.0 (12.9 – 16.0)	14.9 (13.8 – 16.8)	0.04
TSH [µU/ml]	1.83 (1.31 – 3.25)	1.80 (0.82 – 2.61)	0.28
Vitamin B12 [pg/ml]	361 (296 – 628)	344 (275 – 455)	0.11
Folic acid [ng/ml]	6.3 (3.9 – 10.4)	6.6 (4.9 – 9.3)	0.67
CDT [%]	1.8 (1.5 – 2.2)	1.7 (1.6 – 1.9)	0.96
HbA1c [mmol/mol]	53 (45 – 59)	37 (34 – 39)	**<0.001**

Table 17: Preoperative laboratory results for diabetic and non-diabetic patients. Data are presented as Median (IQR).

	Current CPN		Current TN		Mean current	
	p	r	p	r	p	r
C-Peptid	0.06	-	0.38	-	0.06	-
Insulin	0.50	-	0.81	-	0.71	-
fT3	0.53	-	0.22	-	0.27	-
fT4	0.09	-	0.31	-	0.23	-
TSH	0.94	-	0.22	-	0.39	-
Vitamin B12	0.73	-	.012	-	0.70	-
Folic acid	**0.01**	-0.27	0.85	-	0.05	-
CDT	0.69	-	0.29	-	0.54	-
HbA1c	0.28	-	**0.04**	0.25	0.20	-

Table 18: Correlation between preoperative laboratory tests and stimulation currents

3.9 Urinalysis

A comparison of preoperative urine protein levels can be found in Table 19. The amount of Proteinuria did not correlate with stimulation thresholds (Table 20).

	DM	Non-DM	p
Urine protein [g/dl]	6.0 (5.7 – 6.9)	6.3 (6.0 – 6.7)	0.30

Table 19: Urine protein concentration. Data are presented as Median (IQR).

	Current CPN		Current TN		Mean current	
	p	r	p	r	p	r
Urine protein	0.46	-	0.82	-	0.38	-

Table 20: Correlation between urine protein concentration and stimulation currents

3.10 Immediate complications

No patient reported abnormal sensations, paresthesia or pain during the measurements. The injection of 1ml glucose 5% for verification of the needle position did not lead to an increase in injection pressure above 15psi in any patient.

3.11 Neurologic complications

An overview of possible study related neurologic complications is shown in Table 21. Missing in-hospital data can be explained by early discharge of patients. If the patient could not be reached after three phone calls, no further attempts were made. The three patients who reported possible neurologic sequelae were invited for evaluation by an anesthetist. In two patients the complaints were not study related and one patient was referred to a neurologist for further investigation. Thorough neurologic examination revealed no direct correlation of the patient's complaints to the study procedure.

Therefore no study related neurologic complication was observed after 6 months.

	Possible study related abnormal motor or sensory function	Missing data
Postoperative day 1	3 (2.8)	5 (4.7)
Prior to discharge	0 (0.0)	11 (10.3)
6-month telephone interview	3 (3.9)	29 (38.1)

Table 21: Possible study related neurologic complications

3.12 Post hoc power analysis

The planned sample size of 70 patients in the diabetes and non-diabetes group could not be reached. Only 55 and 52 patients could be recruited in the diabetic and non-diabetic group, respectively. Thus the power was only 65% to detect an effect size of 0.3mA. However post hoc power was calculated with the observed stimulation currents and was found to be 80% to find effect sizes of 0.6 standard deviations. The standard deviations of the measurements were 0.53 mA for the TN and 0.89 mA for the CPN resulting in detectable effect sizes of 0.32mA and 0.53mA, respectively.

4 Discussion

This study investigated the effects of diabetic history and in particular diabetic neuropathy on the stimulation threshold for peripheral nerve stimulation for popliteal SN block. Different clinical tests were evaluated for their ability to predict patients who might require higher stimulation thresholds. Even though no altered stimulation thresholds for diabetic patients compared to non-diabetic patients were observed, there were many interesting findings in regards to the consequences of diabetes mellitus for regional anesthesia and additional insight into the needle-current-nerve relationship of presumed uninjured nerves was gained. Not only did a substantial number of healthy subjects fail to exhibit motor response at 0.3-0.5 mA, the currently accepted safe threshold, but subjects with manifestations of diabetic neuropathy required substantially elevated currents to produce motor responses.

4.1 Stimulation thresholds

4.1.1 Needle position

As described in the introduction, the anatomy of the sciatic nerve in the popliteal region has been a matter of discussion and controversy in the literature.(31,33–38) For this study, the nomenclature suggested in a recent anatomical publication(40) was used. It is important to note that we did not consider needle placement in the subparaneural space to be subepineural and therefore also not intraneural. When comparing our findings with other published work this has to be considered as the definition of the term “intraneural” is inconsistent between different authors.

This classification of intra- vs. extraneural is somewhat controversial and might be unique to the popliteal region of the sciatic nerve and not transferable to other regions or peripheral nerves, because here the SN consists of more than 50% non-neuronal tissue,(50) which forms a barrier to local anesthetic penetration and nerve stimulation.

Our post-hoc evaluation of ultrasound imaging revealed distinct spread patterns of the injected glucose 5% between the pre-defined needle positions “Extraepineural-subparaneural” and “Extraparaneural”. When the needle was placed in the subparaneural space, there was no spread inside the nerve itself, suggesting that

the integrity of the epineurium was preserved, further supporting our definition of extraneural needle placement.

This subparaneural space has been suggested as the ideal injection point for local anesthetics in a popliteal SN block.(34,40) Recent clinical studies prove that subparaneural injections lead to higher success rates, faster onset of sensory and motor block and improved efficacy without evidence of an increase in neurologic complications.(10,38,39,51,52)

Even though we aimed for subparaneural needle placement this could only be achieved in 75% of patients for the TN and 53% of patients for the CPN. This can be explained by the fact that this anatomical space is very small and becomes discernible only after injection of a small amount of fluid. In the lateral approach, it is however significantly easier to place the needle in this compartment if the area between the TN and CPN is targeted. Here the paraneural space extends between the two branches of the SN, whereas on the lateral side of the CPN the paraneural sheath is often not discernible from the epineurium of the CPN (see Figure 1, Figure 7, Figure 9 and Figure 10). This explains the higher proportion of subparaneural needle placements at the TN.

We did not observe different stimulation thresholds between “Extraepineural-subparaneural” and “Extraparaneural” needle placements. So even though the exact positioning of the needle and administration of local anesthetic has important clinical consequences, it is impossible to guide the needle to this compartments solely relying on electric stimulation. This could be part of the explanation why the overall performance of Ultrasound is better compared to PNS in popliteal SN block as seen in several studies, which includes faster onset of complete block, higher success rates and lower use of local anesthetics.(11,29,52–55)

4.1.2 Motor response thresholds

Stimulation currents in our study showed a high degree of variability for both the TN and the CPN, even in healthy patients. 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,(13,53) and these findings are in accordance with very small variation in stimulation thresholds in healthy volunteers.(56) On the other hand, recent clinical evidence suggests that even when using 0.5mA as the upper limit of accepted nerve stimulation threshold, intraneural injection of the popliteal sciatic nerve frequently occurs,(9,38) suggesting that this threshold may be inappropriate for some patients during popliteal nerve block. Similar observations were made for the supraclavicular block where 59% of patients required stimulation currents >0.5mA to elicit a motor response when the needle was in direct contact with the nerve.(7)

It has also been shown that PNS for supraclavicular block with 0.9mA leads to similar block success rates when compared to 0.5mA.(57) The additional benefit of reducing the stimulation current is therefore questionable.

4.1.3 Diabetes mellitus and nerve stimulation threshold

The stimulation threshold is related to membrane properties of the peripheral nerve,(15,58) but there is no evidence of altered stimulation thresholds in diabetic patients without neuropathy. It has been shown that DM is associated with higher success rates for nerve-stimulator guided supraclavicular brachial plexus block.(59) The authors of this study hypothesize that their clinical findings may be explained by higher sensitivity of diabetic nerve fibres to local anesthetics, a higher proportion of unrecognized intraneural injections and preexisting diabetic neuropathy with decreased sensation. Taking block duration as an experimental surrogate outcome, Kroin et al.(60) showed that neither acute hyperglycemia nor long-standing diabetes without neuropathy influenced nerve block duration, whereas prolonged diabetic state associated with neuropathy led to increased block duration, reflecting substantial physiological transformation associated with diabetic peripheral neuropathy. Similar results were observed by Sertoz et al.(61) who showed that only the group with the highest values of glycosylated hemoglobin experienced longer block duration and Cuvillon et al.(62) who demonstrated longer block duration in diabetic patients with minor nerve injury compared to healthy, non-diabetic patients.

Averaging the stimulation currents observed in our study at the CPN and TN, there was no increase of the threshold in diabetic patients. Considered separately, diabetic patients required higher currents than non-diabetic patients in at the TN but

not at the CPN. The reason for different results at the two branches of the SN remain unclear, particularly in the light of electroneurographic studies that show an earlier and stronger involvement of the CPN in diabetic neuropathy.(63)

The fact that the planed number of included patients could not be reached led to a power to detect a difference of 0.3mA of only 65% However, post hoc power analysis, which was calculated using the actually observed stimulation currents, revealed 80% power to detect differences in stimulation thresholds between diabetic and non-diabetic patients of 0.32mA for the TN and 0.53mA for the CPN. Our diabetic group consisted of patients with different duration of diabetic disease and therefore also different levels of diabetic neuropathy. We hypothesize that we included too many “healthy” diabetics without neuropathy to be able to show a difference between diabetics and the control group.

These findings together with the before-mentioned observations from other authors indicate that neuropathy, rather than the diagnosis of diabetes mellitus per se, is the critical predictor of altered nerve responses to regional anesthesia.

In considering risk however, it may not be sufficient to evaluate group averages alone, since 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 five patients (four diabetic, one non-diabetic) who required stimulating currents exceeding 0.5 mA, even reaching a stimulation threshold of 2.5 mA in one diabetic patient. Additionally, 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 ≥2 mA (12 diabetic of which 1 patient had intraneural needle placement at the TN and required ≥2 mA with close needle-nerve contact for the CPN and 2 non diabetic) and 6 of those patients even required stimulation currents>3 mA (5 diabetic and 1 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 anesthesia without the additional aid of ultrasound.

Together with a generally high variability of stimulation thresholds both in diabetic and non-diabetic patients, these findings challenge the concept that stimulation

thresholds of 0.3-0.5 mA reliably preclude possibly harmful intraneural needle placement during popliteal nerve block. These results may therefore, in part, explain the phenomenon of popliteal intraneural injection despite the use of conventionally adequate nerve stimulator settings.(9,38)

4.1.4 Diabetic neuropathy and nerve stimulation threshold

In contrast to the diagnosis of DM, the presence of diabetic neuropathy, when assessed by electroneurography, is associated with increased nerve stimulation thresholds. This observation has first been described in a case report.(12) In dogs with long-standing diabetes, using conventional stimulation thresholds during sciatic nerve block was associated with a high risk of intraneural injection.(14) A study that systematically looked at stimulation thresholds in patients 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 to healthy controls, with a large interindividual variability in the diabetic group.(7) Diabetic patients in that study had a longer median duration of disease than in our study (12 vs. 9 years) and three out of seven diabetic patients had prediagnosed diabetic neuropathy. In patients with diabetic gangrene, stimulation thresholds were increased seven-fold compared to non-diabetic controls, again with substantial interindividual variability among diabetic patients, but not within the health control group.(13) Patients requiring surgery for this condition are most likely to have advanced diabetic neuropathy and therefore long term effects of DM might be most pronounced in this group. The findings of the present study similarly indicate that the nerve stimulation threshold in diabetic neuropathy is increased, and a large interindividual variability was also observed. In accordance with our hypothesis there is a direct correlation of the duration of DM to the stimulation threshold for the CPN, the nerve that is typically more affected by diabetic neuropathy than the TN.(63)

This means that the diagnosis of diabetes mellitus alone does not change the way a nerve reacts to stimulation, but that diabetic neuropathy is associated with a profound change in nerve physiology. These changes have clinically relevant implications such as increased block duration(61,62,64) and altered nerve excitability.(15,58)

4.2 Clinical tests

The increase of median stimulation threshold of 0.73mA (from 0.57mA to 1.30mA) for the CPN for patients with absent pressure perception is clinically highly relevant and this increase was even more pronounced in patients with diminished pain sensation (1.10mA, from 0.50mA to 1.60mA). These signs of evident neuropathy could easily be observed in a preoperative clinic or even immediately prior to performing the regional anesthetic, which could therefore help identify patients who require elevated stimulation thresholds as the CPN is usually the part of the SN that is encountered first in the lateral approach. The correlation of reduced or absent Achilles tendon reflex to higher stimulation currents, however, was weak and is probably clinically not relevant.

The items of the questionnaire designed to evaluate patients with diabetic neuropathy(65) were unable to predict any alterations in stimulation current and therefore did not prove to be helpful when assessing patients for regional anesthesia. Additionally, the patient's answers were subjective opinions and therefore may have not always been accurate. The reason why patients who reported claudication required lower stimulation currents for the TN remains unclear. Every patient in our study had some sort of medical problem with his or her lower limb, hence the lower limb surgery. We therefore hypothesize that particular reporting of claudication could have been inaccurate.

4.3 Electroneurography

Objective signs of neuropathy in the ENG showed clear correlations to the stimulation parameters for both branches of the SN.

While a deceleration of the CV for the CPN was correlated to higher stimulation thresholds it was an increase of the DML for the TN. Interestingly, however, the strongest correlation and highest significance were observed for measurements at the ulnar nerve, which was used as a reference. A deceleration of the UN's CV was correlated to increased stimulation thresholds for the TN, the CPN and the mean

current. Additionally its DML showed a significant correlation to the stimulation threshold for the CPN and the mean current.

Diabetic patients had a higher BMI and excessive soft tissue can make ENG on the lower extremities sometimes difficult and prone to error(44). The ulnar nerve on the other hand lies very superficial and is easily accessible even in obese patients and we therefore hypothesize that the measurements on the upper limb were more accurate especially in morbidly obese patients. All significant correlations of ENG results to stimulation currents however were moderate to weak. Together with the complexity of the procedure, this reduces its value in the preoperative clinic and limits its use to scientific purposes.

To our knowledge, this was the first study to evaluate patients undergoing regional anesthesia using electroneurography. This objective method could prove to be useful for further studies, as clinical tests such as the monofilament test, demonstrate low discriminatory power for identifying patients with neuropathies on the feet.(66)

Due to the abundance of available electroneurographic tests, it would be beneficial for future research in this field to have a defined set of tests which are standardized, to enable comparison between studies. Additionally, researchers not familiar with this seemingly simple method need to be aware of the potential pitfalls.(44)

4.4 Impedance

In this study, stimulation current, measured at direct needle-nerve contact, showed a significant inverse relationship to the impedance of the tissue only for the CPN. This inverse relationship has already been described for the median nerve, however the authors found a significant correlation only at needle-nerve distances ≥2.5mm and not for direct needle-nerve contact.(6) Electrical impedance measurements have been proposed as means to detect intraneural needle placement.(67) However, observed electrical impedances were extremely heterogeneous across different body regions with the popliteal fossa showing significantly higher impedances than any other anatomical site and the reported sensitivity and specificity were only 57% and 82% respectively. The reported cut-off value for intraneural needle placement of a 4.3% increase in electrical impedance is only of

theoretical nature and not practicable for clinical practice. The authors found no significantly different electrical impedances in diabetic patients, which can be confirmed by our results.

The role of impedance measurements especially in US guided regional anesthesia therefore remains unclear.

4.5 Laboratory results

As described in the introduction, laboratory testing in our study was mainly done to detect non-diabetic neuropathies.

No laboratory test result, including urinalysis, predicted a change in mean stimulation threshold. Only when CPN and TN were analyzed separately, levels of glycosylated hemoglobin were positively correlated to stimulation currents of the TN. This correlation however was only weak. As previously described, Sertoz et al.(61) reported prolonged block duration only in the group with the highest levels of glycosylated hemoglobin, suggesting only this group shows physiological changes in nerve conduction properties. Even though levels of glycosylated hemoglobin correlate with microvascular complications of diabetes mellitus, this correlation is not absolutely reliable and HbA_{1c} levels do not accurately reflect the degree of diabetic complications such as neuropathy.(68)

In accordance with the other findings of our study, it can be concluded that high levels of HbA_{1c} do not predict higher stimulation thresholds for sciatic nerve block, as they are not able to detect patients with diabetic neuropathy.

4.6 Complications

As permanent needle-placement related nerve injury is extremely rare(24), this study, together with most studies in this field, was not powered to determine whether patients with preexisting diabetic neuropathy were at higher risk of nerve injury. Animal data suggests that the risk of local anesthetic induced nerve injury is increased in diabetes(21,22), however evidence from human data is lacking. This lack of literature and inconsistency in recommendations for patients with preexisting

neuropathies, presenting for regional anesthesia explains the heterogeneity of clinical approaches to this subgroup of patients found in a survey among European anesthetists.(69)

In our study, the lack of any persistent neurological deficit at six months despite some clearly intraneural needle placements underlines the fact, that penetration of the epineurium alone must not inevitably cause permanent nerve injury. This observation has also been made by other authors(10,70,71), some of them even intentionally targeting the subepineural space for injection of local anesthetics.(7)

The injection-pressure-monitoring tool did not prove to be useful in our study setting, as no injection exhibited injection pressures above 15psi. This device might not be suitable for small volumes(72), as used in our studies. Even in intraneural injections, injection pressures can remain under 20psi(9), however the device can still be beneficial in avoiding the detrimental effects of high intraneural pressure.(26)

4.7 Limitations

As most clinical trials, this study has several limitations. First of all, resolution of US imaging is a limiting factor and identification of the exact position of the needle tip can be challenging at times, even in the hands of an experienced anesthetist.(24) We tried to overcome this limitation with post-hoc analysis of photo and especially video documentation by two blinded investigators. 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 measurement, as sometimes a transient increase in motor response to PNS can be observed.(73) Therefore nerve order was randomized, we additionally limited the injection volume to 1ml and allowed enough time between the two measurements.

Additionally, preoperative ENG was not always possible on the same side as the measurement due to various reasons (cast, previous amputation). However, as diabetic neuropathy is symmetrical(63,74) this should not alter our results in any way.

The fact that the calculated sample size of 70 patients per group could not be reached limited the power of the study. Post hoc power analysis, which considered the actual variability observed, however revealed 80% power to detect effect sizes of 0.6 standard deviations which translates to clinically relevant threshold differences of 0.32 mA for the TN and 0.53 mA for the CPN.

4.8 Clinical consequences

This study shows that the nerve stimulation threshold is increased in diabetic neuropathy. However, the evaluation of a diabetic neuropathic state is difficult in daily clinical practice. The clinical tests used in the present study (absent pressure perception and pain sensation) were associated with higher stimulation thresholds of the CPN (1.3 mA and 1.6 mA, respectively). These signs of evident neuropathy can be evaluated in a preoperative assessment clinic or even immediately prior to performing the regional anesthetic, which could help to identify patients who require elevated stimulation thresholds. Objective signs of neuropathy in the ENG, especially measurements at the ulnar nerve, were correlated with increased stimulation thresholds for sciatic block, which may result from involvement of the ulnar nerve only at later stages of diabetic neuropathy.(75)

When performing a popliteal SN block, the sole use of PNS is not able to accurately and reliably determine close needle-nerve relationship and exclude intraneural needle placement and even less so to distinguish subparaneural and extraparaneural needle position. Stimulation currents of 0.3-0.5mA do not safely exclude intraneural needle placement and higher thresholds might be needed, especially for patients with diabetic neuropathy but also for healthy subjects. However, given the substantial variability observed, the optimal threshold for any individual, healthy or diabetic, may be impossible to predict a priori. The use of ultrasound for regional anesthesia allows for more accurate needle placement, nevertheless due to its limitations it also cannot guarantee extraneural needle placement.

Even though we found an inverse correlation between impedance and stimulation threshold for the CPN this finding does not help in determining the adequate

stimulation current for the individual patient. Therefore impedance measurements have a very limited role in clinical regional anesthesia.

Even though electroneurography correlated with stimulation thresholds, the test results were also not able to predict the required stimulation threshold for the single patient and because this procedure is cost-, time- and personnel-intensive its role in regional anesthesia remains limited to scientific purposes.

4.9 Conclusion

In conclusion the findings of this study show that diabetic neuropathy has effects on PNS for regional anesthesia.

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. Simple clinical tests might identify patients that require higher stimulation currents for PNS, but given the substantial variability observed, the optimal threshold for any individual diabetic or non-diabetic patient may be impossible to predict a priori.

The variability of stimulation currents found, demonstrates that in a modern approach to regional anesthesia with a combined use of PNS and US the generally accepted target stimulation threshold of 0.3-0.5mA might no longer be adequate and the sole reliance on PNS is obsolete. Even in healthy patients necessary stimulation currents exceeding 0.5mA despite close needle-nerve contact are frequent.

The additional evidence this study adds to the field of patient safety in regional anesthesia justifies a more optimistic approach and therefore proactive use of regional anesthesia in patients with preexisting neuropathies.

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Appendix

Appendix 1: Informed Consent

PatientInneninformation[1] und Einwilligungserklärung zur Teilnahme an der klinischen Studie

Der Einfluss diabetischer Neuropathie auf Stimulationsparamater der peripheren Nervenstimulation im Rahmen einer Regionalanästhesie[2]

Sehr geehrte Teilnehmerin, sehr geehrter Teilnehmer!

Wir laden Sie ein an der oben genannten klinischen Studie teilzunehmen. Die Aufklärung darüber erfolgt in einem ausführlichen ärztlichen Gespräch.

Ihre Teilnahme an dieser klinischen Studie erfolgt freiwillig. Sie können jederzeit ohne Angabe von Gründen aus der Studie ausscheiden. Die Ablehnung der Teilnahme oder ein vorzeitiges Ausscheiden aus dieser Studie hat keine nachteiligen Folgen für Ihre medizinische Betreuung.

Klinische Studien sind notwendig, um verlässliche neue medizinische Forschungsergebnisse zu gewinnen, die wie z.B. in diesem Fall die Sicherheit der Patientenversorgung verbessern sollen. Unverzichtbare Voraussetzung für die Durchführung einer klinischen Studie ist jedoch, dass Sie Ihr Einverständnis zur Teilnahme an dieser klinischen Studie schriftlich erklären. Bitte lesen Sie den folgenden Text als Ergänzung zum Informationsgespräch mit Ihrem Arzt sorgfältig durch und zögern Sie nicht Fragen zu stellen.

Bitte unterschreiben Sie die Einwilligungserklärung nur

- -wenn Sie Art und Ablauf der klinischen Studie vollständig verstanden haben,
- -wenn Sie bereit sind, der Teilnahme zuzustimmen und
- -wenn Sie sich über Ihre Rechte als Teilnehmer an dieser klinischen Studie im Klaren sind.

Zu dieser klinischen Studie sowie zur Patienteninformation und Einwilligungserklärung wurde von der zuständigen Ethikkommission eine befürwortende Stellungnahme abgegeben.

1. Was ist der Zweck der klinischen Studie?

Der Zweck dieser klinischen Studie ist es, das Risiko möglicher Komplikationen von regionalanästhesiologischen Verfahren (gezieltes Betäuben von Nerven, in Ihrem Fall des Ischias-Nervs) besonders in einer speziellen Patientengruppe (zuckerkranke PatientInnen

[1] Wegen der besseren Lesbarkeit wird im weiteren Text zum Teil auf die gleichzeitige Verwendung weiblicher und männlicher Personenbegriffe verzichtet. Gemeint und angesprochen sind – sofern zutreffend – immer beide Geschlechter.

[2] Betäubung eines Nervens, der eine ganze Körperregion versorgt. Dadurch wird eine Schmerzausschaltung in diesem Gebiet erzielt.

mit vorbestehenden Schäden der Nerven), aber auch bei nervengesunden PatientInnen weiter zu verringern.

Im Rahmen regionalanästhesiologischer Techniken kommt standardmäßig ein sogenannter Nervenstimulator zum Einsatz. Nachdem eine dünne Nadel durch die Haut gestochen wurde, kann durch elektrische Stimulation (Erregung) des gesuchten Nervs und die dadurch ausgelösten Bewegungen der von ihm versorgten Muskeln die Entfernung der Nadel zum Nerv abgeschätzt werden. Dies ist wichtig, damit man das Lokalanästhetikum (vorübergehend nervenbetäubendes Medikament) nahe genug an den Nerv spritzen kann, um eine ausreichende Wirkung zu erzielen. Andererseits aber muss man das Einspritzen des Medikaments direkt in den Nerv verhindern, da dies zu Schäden führen kann. Der international anerkannte Schwellenwert zur Vermeidung eines Nervenschadens für die elektrische Stimulation beträgt 0,3-0,5mA (Milliampere). Dieser Wert wurde jedoch bei zuckerkranken PatientInnen noch nicht ausgetestet und auch bei Nervengesunden noch nicht ausreichend bestätigt. Zusätzlich legen tierexperimentelle Studien die Vermutung nahe, dass dieser Wert für die spezielle Patientengruppe der Zuckerkranken zu niedrig sein könnte. Durch die Einführung des Ultraschalls ist es nun möglich, die Annäherung der Nadel an den Nerv auch auf einem Bildschirm zu kontrollieren und somit die optimale Nadelposition zu finden. Dies gibt uns somit die Möglichkeit zu messen, welche Stromstärken für die elektrische Stimulation notwendig sind um eine motorische Antwort (Bewegung der jeweiligen Muskeln) zu erreichen.

Mit den Ergebnissen dieser Studie erhoffen wir uns den Zusammenhang zwischen Stromstärke und Abstand zum Nerven bei der Regionalanästhesie besser verstehen zu können. Darauf basierend planen wir dementsprechende Empfehlungen zu verfassen, die regionalanästhesiologische Verfahren bei Zuckerkranken, aber eventuell auch bei nervengesunden PatientInnen noch sicherer machen sollen.

2. Wie läuft die klinische Studie ab?

Diese klinische Studie wird am LKH Univ.-Klinikum Graz durchgeführt und es werden insgesamt ungefähr 140 Personen daran teilnehmen.

Ihre Teilnahme an dieser klinischen Studie erfolgt im Rahmen Ihres stationären Krankenhausaufenthalts.

<u>Folgende Maßnahmen werden ausschließlich aus Studiengründen durchgeführt:</u>

Ihr Narkosearzt hat für Ihre Operation eine distale Ischiadicusblockade (auch Poplitealblock genannt) mit Ihnen vereinbart und Sie anhand des dafür vorgesehenen Aufklärungsbogens eingehend darüber aufgeklärt. Es wird also der Ischias-Nerv auf der Höhe der Kniekehle entweder mit dem Nervenstimulator oder mit dem Ultraschallgerät aufgesucht und das lokal Betäubungsmittel (Lokalanästhetikum) dort eingespritzt.

Im Rahmen dieser Studie wird ein(e) erfahrene(r) AnästhesistIn (Narkoseärztin/arzt) die Regionalanästhesie (Blockade des Ischias-Nervs) bei Ihnen durchführen. Dabei wird er die Nadel mit Hilfe eines Ultraschallgeräts an den Nerv heranführen. In unmittelbarer Nähe

des Nervs wird nun an 2 Messpunkten die minimal notwendige Stromstärke gemessen, die nötig ist um eine Zuckung der jeweiligen Muskeln auszulösen. Nach Beendigung der Messungen wird das Lokalanästhetikum wie für die Operation erforderlich in der Nähe des Nervs eingespritzt. Durch diese Messungen kommt es zu keiner zusätzlichen Punktion (Einstich) an ihrem Bein. Während des Einspritzens wird der dazu notwendige Druck gemessen. Dies stellt eine zusätzliche Sicherheitsmaßnahme dar um das möglicherweise schädliche Verabreichen des Medikaments direkt in den Nerv zu verhindern. Während der gesamten Prozedur wird das Ultraschallbild aufgezeichnet, damit dieses zu einem späteren Zeitpunkt von 2 unterschiedlichen AnästhesistInnen beurteilt werden kann. Anschließend wird gewartet bis die Blockade Ihres Ischias-Nervs voll ausgeprägt ist (das heißt keine Schmerzempfindung und keine Bewegung mehr möglich), woraufhin Sie für die Operation freigegeben werden. Ihre Operation wird durch die Teilnahme an der Studie nicht verzögert.

Vor Ihrer geplanten Operation und der dazu notwendigen Nervenblockade wird untersucht, ob Ihre Nerven bereits geschädigt sind oder nicht. Zu diesem Zweck benötigen wir von Ihnen eine zusätzliche Blut- (19ml) und Harnprobe um mehrere Laborwerte messen zu können, die auf einen vorbestehenden Nervenschaden hinweisen können. Außerdem werden Sie klinisch untersucht und ein Test Ihrer Nervenleitgeschwindigkeit wird durchgeführt, welcher für Sie unangenehm sein kann, aber in der Regel nicht schmerzhaft ist. Zusätzlich werden Ihnen spezielle Fragen zu Ihrer Krankengeschichte gestellt. Sollten an Ihrem Bein bereits Hautverletzungen durch einen vorbestehenden Nervenschaden bestehen, so wird diese Stelle mittels Foto dokumentiert.

Am ersten Tag nach Ihrer Operation und noch einmal bevor Sie das Krankenhaus wieder verlassen, werden Sie von einer/einem StudienmitarbeiterIn zu Ihrem Befinden befragt und untersucht. Zusätzlich bieten wir Ihnen an vor Ihrer Krankenhausentlassung noch einmal Ihre Nervenleitgeschwindigkeit zu messen, um eventuell aufgetretene Komplikationen zu erfassen.

6 Monate nach Ihrer Operation werden wir Sie einmal per Telefon kontaktieren um ebenfalls eventuelle Komplikationen zu erfassen. Damit ist Ihre Teilnahme an dieser Studie beendet.

Zusätzlich zu dieser Studie möchten wir auch 2 Röhrchen Blut (20ml) sowie eventuell bei der Operation entferntes Gewebe in der Biobank der Medizinischen Universität Graz für spätere Untersuchungen aufbewahren. Genauere Informationen hierzu finden Sie einem eigenen Aufklärungsbogen, den Ihr Anästhesist mit Ihnen besprechen wird. Sollten Sie die Aufbewahrung nicht wünschen, können Sie diese natürlich ablehnen und trotzdem ohne Einschränkungen an der Studie teilnehmen.

3. Worin liegt der Nutzen einer Teilnahme an der klinischen Studie?

Es ist möglich, dass Sie durch Ihre Teilnahme an dieser klinischen Studie keinen direkten Nutzen für Ihre Gesundheit ziehen. Jedoch ist es uns aufgrund der Studie möglich alle bis heute bekannten Sicherheitsmaßnahmen zu ergreifen, die eine genauere Überwachung während des Eingriffs ermöglichen.

Ebenso ist es möglich, dass durch die genaue Untersuchung Ihrer Nerven vor der geplanten Operation ein bereits vorliegende Nervenschaden in einem frühen, noch beschwerdefreien Stadium zu entdecken und eine entsprechende Therapie frühzeitig eingeleitet oder gegebenenfalls verbessert werden.

Die Ergebnisse dieser Studie sind jedoch sehr wichtig für spätere PatientInnen, da Sie uns helfen werden die Beziehung zwischen Nerven und den notwendigen Schwellenwerten zur elektrischen Stimulation besser verstehen zu können. Damit kann hoffentlich das Risiko für Komplikationen bei regionalanästhesiologischen Verfahren vor allem bei zuckerkranken PatientInnen minimiert werden.

4. Gibt es Risiken, Beschwerden und Begleiterscheinungen?

Alle in dieser Studie angewandten Verfahren sind bereits klinisch etabliert.

Die Messung der Nervenleitgeschwindigkeit kann für Sie unangenehm sein, ist jedoch ungefährlich.

Die zusätzliche Blutabnahme erfolgt unmittelbar vor Ihrer Operation über den dafür gelegten Venenzugang, das heißt, es ist kein weiterer Stich notwendig.

5. Zusätzliche Einnahme von Arzneimitteln?

Sie müssen im Rahmen dieser Studie keine zusätzlichen Arzneimittel einnehmen.

6. Hat die Teilnahme an der klinischen Studie sonstige Auswirkungen auf die Lebensführung und welche Verpflichtungen ergeben sich daraus?

Ihre Teilnahme an dieser Studie hat keine sonstigen Auswirkungen auf Ihre Lebensführung und es ergeben sich keinerlei Verpflichtungen für Sie.

7. Was ist zu tun beim Auftreten von Symptomen, Begleiterscheinungen und/oder Verletzungen?

Sollten im Verlauf der klinischen Studie irgendwelche Symptome, Begleiterscheinungen oder Verletzungen auftreten, müssen Sie diese Ihrem Arzt mitteilen, bei schwerwiegenden Begleiterscheinungen umgehend, ggf. telefonisch (Telefonnummern, etc. siehe unten).

8. Wann wird die klinische Studie vorzeitig beendet?

Sie können jederzeit auch ohne Angabe von Gründen, Ihre Teilnahmebereitschaft widerrufen und aus der klinischen Studie ausscheiden ohne dass Ihnen dadurch irgendwelche Nachteile für Ihre weitere medizinische Betreuung entstehen.

Ihr Studienarzt wird Sie über alle neuen Erkenntnisse, die in Bezug auf diese klinische Studie bekannt werden, und für Sie wesentlich werden könnten, umgehend informieren. Auf dieser Basis können Sie dann Ihre Entscheidung zur **weiteren** Teilnahme an dieser klinischen Studie neu überdenken.

Es ist aber auch möglich, dass Ihr Studienarzt entscheidet, Ihre Teilnahme an der klinischen Studie vorzeitig zu beenden, ohne vorher Ihr Einverständnis einzuholen. Die Gründe hierfür können sein:

a) -Sie können den Erfordernissen der klinischen Studie nicht entsprechen;

b) -Ihr Studienarzt hat den Eindruck, dass eine weitere Teilnahme an der klinischen Studie nicht in Ihrem Interesse ist;

9. In welcher Weise werden die im Rahmen dieser klinischen Studie gesammelten Daten verwendet?

Sofern gesetzlich nicht etwas anderes vorgesehen ist, haben nur die StudienärztInnen und deren MitarbeiterInnen Zugang zu den vertraulichen Daten, in denen Sie namentlich genannt werden. Diese Personen unterliegen der Schweigepflicht.

Die Weitergabe der Daten erfolgt ausschließlich zu statistischen Zwecken und Sie werden ausnahmslos darin nicht namentlich genannt. Auch in etwaigen Veröffentlichungen der Daten dieser klinischen Studie werden Sie nicht namentlich genannt.

10. Entstehen für die Teilnehmer Kosten? Gibt es einen Kostenersatz oder eine Vergütung?

Durch Ihre Teilnahme an dieser klinischen Studie entstehen für Sie keine zusätzlichen Kosten und Sie erhalten keine Vergütung.

11. Möglichkeit zur Diskussion weiterer Fragen

Für weitere Fragen im Zusammenhang mit dieser klinischen Studie stehen Ihnen Ihr Studienarzt und seine MitarbeiterInnen gern zur Verfügung. Auch Fragen, die Ihre Rechte als PatientIn und TeilnehmerIn an dieser klinischen Studie betreffen, werden Ihnen gerne beantwortet.

Kontakt des Studienteams über das Studientelefon +43/316/358-80339

oder

Name der Kontaktperson: ....Priv.Doz. Dr. Marcel Rigaud (Studienleiter)

Ständig erreichbar unter: .....+43/316/385-14909

Name der Kontaktperson: .....Ass. Dr. Stefan Heschl (1. Stellvertreter)

Ständig erreichbar unter: .....+43/316/385-13027

Name der Kontaktperson: .....Priv.Doz. Dr. Geza Gemes (2. Stellvertreter)

Ständig erreichbar unter: .....+43/316/385-14909

12. Sollten andere behandelnde Ärzte von der Teilnahme an der klinischen Studie informiert werden?

Bitte informieren Sie andere behandelnde Ärzte im Zuge dieses Krankenhaus-aufenthalts, dass Sie bereits an einer Studie teilnehmen. Diese Information ist wichtig falls Sie an einer weiteren Studie teilnehmen sollen. Der Hausarzt muss nicht darüber informiert werden.

13. Einwilligungserklärung

Name des Patienten in Druckbuchstaben: .....

Geb.Datum: ..... Code: .....

Ich erkläre mich bereit, an der klinischen Studie **„Der Einfluss diabetischer Neuropathie auf Stimulationsparameter der peripheren Nervenstimulation im Rahmen einer Regionalanästhesie“** teilzunehmen.

Ich bin von Herrn/Frau *Dr.med.*..... ausführlich und verständlich über mögliche Belastungen und Risiken, sowie über Wesen, Bedeutung und Tragweite der klinischen Studie, sich für mich daraus ergebenden Anforderungen aufgeklärt worden. Ich habe darüber hinaus den Text dieser Patientenaufklärung und Einwilligungserklärung, die insgesamt 7 Seiten umfasst gelesen. Aufgetretene Fragen wurden mir vom Studienarzt verständlich und genügend beantwortet. Ich hatte ausreichend Zeit, mich zu entscheiden. Ich habe zur Zeit keine weiteren Fragen mehr.

Ich werde den ärztlichen Anordnungen, die für die Durchführung der klinischen Studie erforderlich sind, Folge leisten, behalte mir jedoch das Recht vor, meine freiwillige Mitwirkung jederzeit zu beenden, ohne dass mir daraus Nachteile für meine weitere medizinische Betreuung entstehen.

Ich bin zugleich damit einverstanden, dass meine im Rahmen dieser klinischen Studie ermittelten Daten aufgezeichnet werden. Um die Richtigkeit der Datenaufzeichnung zu überprüfen, dürfen Beauftragte der zuständigen Behörden oder Institutionen beim Studienarzt Einblick in meine personenbezogenen Krankheitsdaten nehmen.

Beim Umgang mit den Daten werden die Bestimmungen des Datenschutzgesetzes beachtet.

Eine Kopie dieser Patienteninformation und Einwilligungserklärung habe ich erhalten. Das Original verbleibt beim Studienarzt.

.....
(Datum, Zeit und Unterschrift des Patienten)

.....
(Datum, Zeit, Name und Unterschrift des verantwortlichen Arztes)

(Der Patient erhält eine unterschriebene Kopie der Patienteninformation und Einwilligungserklärung, das Original verbleibt im Studienordner des Studienarztes.)

Appendix 2: Case report form (CRF)

CASE REPORT FORM

THE INFLUENCE OF DIABETIC NEUROPATHY ON CURRENT SETTINGS DURING NERVE-STIMULATION FOR PERIPHERAL REGIONAL ANESTHESIA

Brief title:

PERIPHERAL NERVE STIMULATION IN DIABETIC PATIENTS

Study reference number: 24-064 ex 11/12

CLINICAL TRIAL SITE:

Medical University of Graz,
Department of Anesthesiology and Intensive Care Medicine

PRINCIPAL INVESTIGATOR:

Priv.-Doz. Dr. med. univ. Marcel Rigaud

Subject Initials: __ __ __

Subject randomization number (ID): __ __ __

I am confident that the information supplied in this case report form is complete and accurate data. I confirm that the study was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the study.

Investigator's Signature: .....

Date of signature: __ __ - __ __ __ - __ __ __ __
D D M M M Y Y Y Y

SCREENING (Part 1):

__ __ - __ __ __ - __ __ __ __
D D M M M Y Y Y Y

Inclusion Criteria	yes / no*	Exclusion Criteria	yes / no*
Patients of both sexes, age ≥ 18 years	☐ ☐	Pregnancy	☐ ☐
Eligible for popliteal sciatic nerve block	☐ ☐	Unwilling or incapable to sign inform consent	☐ ☐
ASA 1-4	☐ ☐	Preexisting neuropathy not attributed to diabetes	☐ ☐
Negative pregnancy test (if suspected by subject)	☐ ☐	Allergies to local anesthetics	☐ ☐
		Ongoing dual anti-platelet therapy	☐ ☐

* If any inclusion criteria is ticked "no" or any exclusion criteria ticked "yes" then the patient is not eligible for the study

Informed Consent:

Has the subject freely given informed consent? yes: ☐ no: ☐ __ __ - __ __ __ - __ __ __ __ (D D M M M Y Y Y Y)

Please note: Written informed consent must be given before any study specific procedures take place or any current therapy is discontinued for the purposes of participation in this study.

Preoperative Evaluation

Is the original preoperative evaluation sheet attached? yes: ☐ __ __ - __ __ __ - __ __ __ __ (D D M M M Y Y Y Y)

no: ☐ (Please follow before procedure!)

Demographic Data

age: __ __ years heigth: __ __ __cm weight: __ __ __ kg female: ☐ male: ☐

END OF SCREENING CHECKLIST:

	yes / no
• Does the subject satisfy the inclusion and exclusion criteria?	☐ ☐
• Have all screening procedures been completed?	☐ ☐
• Is the subject willing to proceed?	☐ ☐
• Is the subject approved for study?	☐ ☐

Follow up contact number:__ __ __ __ __ __ __ __ __ __ __ __

Signature: _____ __ __ - __ __ __ - __ __ __ __
D D M M M Y Y Y Y

Neurologic evaluation:

__ __ - __ __ __ - __ __ __ __
D D M M M Y Y Y Y

Questionnaire diabetic neuropathy:

	yes / no
• History of diabetes Diagnosed since: __ __ __ __ (yyyy) **or** approx. for: __ __ years	☐ ☐
• Previous ulcer/amputation, previous foot education, social isolation, poor access to healthcare, bare-foot walking?	☐ ☐
• Symptoms, such as tingling or pain in the lower limb, especially at night	☐ ☐
• Claudication, rest pain?	☐ ☐
• Deformities (e.g. claw toes, hammer toes) or bony prominences?	☐ ☐
• Family history of diabetes	☐ ☐
• Family history of ulcera	☐ ☐

Neurologic examination:

Pedal Pulses	**left**		**right**	
	pos	neg	pos	neg
A. dorsalis pedis				
A. tibialis posterior				

Ankle Brachial (Pressure) Index, ABI	**left**	**right**
A. dorsalis pedis	__ . __	__ . __
A. tibialis posterior	__ . __	__ . __

Cotton wool	**left**		**right**	
	pos	neg	pos	neg
Dorsum of the foot				

Tiptherm	**left**		**right**	
	pos	neg	pos	neg
Dorsum of the foot				

Monofilament	**left**		**right**	
	pos	neg	pos	neg
Planta pedis				

Vibration perception	**left**	**right**
Hallux	__ /8	__ /8
Malleolus medialis	__ /8	__ /8

Pin prick	**left**		**right**	
	pos	neg	pos	neg
Dorsum of the foot				

Achilles tendon reflexes	**left**	**right**
0= no reflex; 1= week reflex; 2= normal reflex		

Motor function (dorsal or plantar flexion of toes/foot)	**left**		**right**	
	dorsal	plantar	dorsal	plantar
0: no movement; 1: min.; 2: no gravity; 3: gravity; 4: resistance; 5: normal				

Neurologic evaluation (Part 2):

Electroneurography*:

Motor neurography*	DML (msec)	Conduction Velocity (m/sec)	Amplitude (mV)
N. medianus R □ L □			
N. peroneus R □ L □			
N. tibialis R □ L □			
N. _ _ _ _ _ _ R □ L □			
N. _ _ _ _ _ _ R □ L □			
N. _ _ _ _ _ _ R □ L □			

Sensible neurography*	Conduction Velocity (m/sec)	Amplitude (mV)	
N. medianus R □ L □			
N. suralis R □ L □			
N. _ _ _ _ _ _ R □ L □			
N. _ _ _ _ _ _ R □ L □			

F-Waves*	Average latency (msec)	Persistenz (%)	
N. tibialis R □ L □			
N. peroneus R □ L □			

H-Refex*	Latency (msec)		
Right / Left			

* For assessment of neuropathy, the nerves of one lower extremity are evaluated. Additional measurements will only be performed if any further differentiation is needed. In unclear situations (e.g. where laboratory results are inconclusive) additional independent examinations are scheduled as necessary.

Laboratory analysis: Urin samples taken? yes: □

Signature: _____ __ __ - __ __ __ - __ __ __ __
D D M M M Y Y Y Y

Procedure recordings:

__ __ - __ __ __ - __ __ __ __
D D M M M Y Y Y Y

Laboratory analysis: Blood samples taken? yes: □

__ __ - __ __ __ - __ __ __ __
D D M M M Y Y Y Y

- 3 x Serum: - Endo: TSH / fT3,4, Insulin, C-Peptid
  - LB2: CDT, Vit. B12, Folic acid, electrophoreses
  - Biobank
- 1 x Hematology: - HbA1c (already measured? yes: □ -> see standard lab)
- 1 x Clinical Chemestry: - Biobank

Photo documentation: Please save images at following points of the procedure!

1. Nerve area before needle insertion □
2. Each final needle position before injection □
3. Record a video clip while injecting □
4. nerve area after injection □

(Possible pictures for publication □)

Procedure recordings: (Stimulator settings: 0,1ms / 1Hz) left: □ right: □

Nerve randomization group: (1: Peroneal nerve first; 2: Tibial nerve first) 1 □ 2 □

Local Anesthetic: Ropivacain □ Mepivacain □

Common peroneal nerve: Injection time: __ __:__ __ (hh:mm)

__.__ mA __ __.__ kΩ

Area before: __ __ cm^2 Area after: __ __ cm^2 Needle nerve distance: __.__ mm

Tibial nerve: Injection time: __ __:__ __ (hh:mm)

__.__ mA __ __.__ kΩ

Area before: __ __ cm^2 Area after: __ __ cm^2 Needle nerve distance: __.__ mm

---

Complications:

Pain during injection: □ Paresthesia: □ PSI >15: □ Other: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Block success: (assess every 10 min, up to 60 min)

1. **Sensory block** (pin prick (p), cold (c) ; Grading: 3= normal sensation, 2= discomfort; 1= analgesia; 0= anesthesia)

   Onset: __ __ min Grade (p): __ @onset or 60min Grade (c): __ @onset or 60min (Sole of foot = tibial nerve)
   Onset: __ __ min Grade (p): __ @onset or 60min Grade (c): __ @onset or 60min (dorsal foot = superficial peroneal nerve)
   Onset: __ __ min Grade (p): __ @onset or 60min Grade (c): __ @onset or 60min (between 1. & 2. toes = deep peroneal nerve)

2. **Motor block** (Grading: 3= full strength; 2= weak response; 1= paresis; 0= paralysis)

   Onset: __ __ min Grade: __ @onset or 60min (toe flexion = tibial nerve)
   Onset: __ __ min Grade: __ @onset or 60min (toe extension= peroneal nerve)

3. **Clinical block success** (surgery start: __ __:__ __ (hh:mm))

   Yes □ No □ If "No", which management?:__ __

Signature: _____ __ __ - __ __ __ - __ __ __ __
D D M M M Y Y Y Y

Post procedure visit 1 (POD1):

__ __ - __ __ __ - __ __ __ __
D D M M M Y Y Y Y

Physical examination:

General appearance: _____

Heart: _____

Lungs: _____

Abdomen: _____

Extremities: _____

Vital Signs: Heart Rate: __ __ __ BPM Blood pressure: __ __ __ / __ __ __ mmHg

Neurologic evaluation:

Sensation:

Normal sensation: □ Paresthesia: □ Anesthesia: □

Other complications: _____

Approx. time of complete regression: __ __:__ __ (hh:mm) Duration in hours: __ __ h

Motor function: (Grading: 0: no movement; 1: min.; 2: no gravity; 3: gravity; 4: resistance; 5: normal)

Dorsal flexion of toes/foot: __ Plantar flexion of toes/foot: __

Approx. time of complete regression: __ __:__ __ (hh:mm) Duration in hours: __ __ h

End of visit checklist:

	yes / no
Is there any neurological abnormality, which needs further evaluation?	☐ ☐

If **"yes"**, please contact principal investigator and proceed following the ASRA practice advisory on neurologic complications and fill out "Adverse Events" form.

Signature: _____ __ __ - __ __ __ - __ __ __ __
D D M M M Y Y Y Y

Post procedure visit 2 (POD 3 or discharge): __ __ - __ __ __ - __ __ __ __
D D M M M Y Y Y Y

Physical examination:

General appearance: _____

Heart: _____

Lungs: _____

Abdomen: _____

Extremities: _____

Vital Signs: Heart Rate: __ __ __ BPM Blood pressure: __ __ __ / __ __ __ mmHg

Neurologic evaluation:

Sensation:

Normal sensation: □ Paresthesia: □ Anesthesia: □

Other complications: _____

Motor function: (Grading: 0: no movement; 1: min.; 2: no gravity; 3: gravity; 4: resistance; 5: normal)

Dorsal flexion of toes/foot: __ Plantar flexion of toes/foot: __

Motor neurography*	DML (msec)	Conduction Velocity (m/sec)	Amplitude (mV)
N. medianus R □ L □			
N. peroneus R □ L □			
N. tibialis R □ L □			
N. _____ R □ L □			
N. _____ R □ L □			
N. _____ R □ L □			

Sensible neurography*	Conduction Velocity (m/sec)	Amplitude (mV)	
N. medianus R □ L □			
N. suralis R □ L □			
N. _____ R □ L □			
N. _____ R □ L □			

F-Waves*	Average latency (msec)	Persistenz (%)	
N. tibialis R □ L □			
N. peroneus R □ L □			

H-Reflex	Latency (msec)		
Right / Left			

* see information on page 5

End of visit checklist:

yes / no

Is there any neurological abnormality, which needs further evaluation? ☐ ☐

If **"yes"**, please contact principal investigator and proceed following the ASRA practice advisory on neurologic complications and fill out "Adverse Events" form.

Signature: _____ __ __ - __ __ __ - __ __ __ __
D D M M M Y Y Y Y

Telephone visit (6 months after discharge):

Neurologic evaluation:

Sensation:

Normal sensation: □ Paresthesia: □ Anesthesia: □

Other complications: _

Subjective motor function:

Normal function: □ Abnormal function: □

End of visit checklist:

	yes / no
Is there any neurological abnormality, which needs further evaluation?	☐ ☐

If **"yes",** please contact principal investigator and proceed following the ASRA practice advisory on neurologic complications and fill out "Adverse Events" form.

Signature: _____ __ __ - __ __ __ - __ __ __ __

D D M M M Y Y Y Y

Off study form:

__ __ - __ __ __ - __ __ __ __
D D M M M Y Y Y Y

Reason off Study (Pleas mark only the primary reason. Reason other than "**Completed Study**" require explantion next to the response)

- □ Completed study
- □ AE/SAE (complete AE form, if applicable) _____
- □ Lost to follow up _____
- □ Non-compliant participant _____
- □ Medical contraindication _____
- □ Withdraw consent _____
- □ Death (complete AE form, if applicable) _____
- □ Other _____

Appendix 3: General study algorithm

Studienablauf

Periphere Nervenstimulation bei Diabetikern

Ansprechpartner:
Studientelefon 80339
Stefan Heschl 81057
Marcel Rigaud 80513
Geza Gemes 81101

Univ.-Klinik für Anästhesiologie und Intensivmedizin
Medizinische Universität Graz

Appendix 4: Study algorithm operating theatre

Studienablauf OP

Periphere Nervenstimulation bei Diabetikern

Blut abnehmen

↓

Standardvorbereitung für Ultraschall-gezielten distalen Ischiadicusblock
+B-smart Injektionsdruckmesser

↓

Durchführung des Blocks inklusive Messungen
Fotodokumentation vor und nach Injektion
Videodokumentation während Injektion

↓

Evaluation des Blockadeerfolgs alle 10 Minuten

Genaues Prozedere siehe Rückseite!

Ansprechpartner:
Studientelefon 80339
Stefan Heschl 81057
Marcel Rigaud 80513
Geza Gemes 81101

Univ.-Klinik für Anästhesiologie und Intensivmedizin
Medizinische Universität Graz

CRF Seiten 2-4 ausgefüllt?

Leitung legen, Blut abnehmen (4x Serum, 1x Blutbild, 1x Klinische Chemie + Laborzettel vorbereitet)

Standardvorbereitung für distalen Ischiadicusblock
Überprüfen welche Randomisierungsgruppe (siehe CRF)
Monitoring, O_2-Maske
Dormicum 0,01-0,05mg/kg KG
Ultiva 0,05-0,1µg/kg KG/min
Ultraschallgerät inkl. sterile Abdeckung + steriles Gel + Ultraschallnadel (BBraun)
Nervenstimulator
B-smart Injektionsdruckmesser
30 ml Naropin 0,5%

Studienspezifische Durchführung des Blocks
Hilfsperson (Studienteam bzw. DGKS/P) bedient den Nervenstimulator
Aufsuchen des N.peroneus + N. tibialis knapp distal der Aufzweigungsstelle des N.ischiadicus ,
Fotodokumentation
Punktion

Ultraschall-gezielte Annäherung an den ersten Nerven (siehe Randomisierung) unter ausgeschaltetem Nervenstimulator
Positionierung der Nadel am Nerv ohne Epineurium zu durchstechen (Identitfikation der Nadelspitze!),
Fotodokumentation
Nervenstimulator einschalten (0,1ms, 1Hz, 0,00mA)
Durchführender Arzt darf Werte weder sehen noch hören!
Stromstärke steigern bis motorische Antwort erkennbar
Langsamen Reduktion der Stromstärke bis motorische Antwort verschwindet
Niedrigsten Wert mit motorischer Antwort dokumentieren lassen, Nervenstimulator ausschalten
1ml Glucose 5% einspritzen , **Videodokumentation** während **+ Fotodokumentation** nach Injektion
Injektionsdruck überwachen, dokumentieren falls über 15 PSI
Eventuelle Komplikationen (Injektionsschmerz, Parästhesien, systemische Nebenwirkungen,…) dokumentieren

Gleiches Prozedere an 2. Nerv

Injektion von 15ml Naropin 0,5% an finaler Nadelposition
Neuerliche Annäherung an 1. Nerv, Injektion der restlichen 15ml Naropin 0,5%

Ultiva beenden
Patient/in weiter überwachen (Aufwachraum, OP-Vorraum)
Evaluation der motorischen und sensorischen Blockade alle 10 Minuten

Vollständige sensorisch + motorische Blockade
Zeitpunkt notieren

Keine vollständige motorische + sensorische Blockade nach 60 Minuten
Grad notieren

Freigabe zur Operation
Ende des studienspezifischen Prozederes

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