Lower extremity nerve decompression in painful diabetic polyneuropathy

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Lower extremity nerve decompression in painful diabetic polyneuropathy

Decompressie van zenuwen in het onderbeen bij pijnlijke diabetische polyneuropathie

(met een samenvatting in het Nederlands)

Proefschrift

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in het openbaar te verdedigen op
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door

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geboren op 5 april 1975 te Onderdendam gemeente Bedum

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1

Introduction

Diabetes Mellitus

Diabetes mellitus (DM) is a heterogeneous chronic metabolic disorder, which leads to abnormally elevated blood glucose levels. Several types of diabetes are recognized, including type 1, type 2 and gestational diabetes. Five to 10 % of the diabetes population is diagnosed with type 1 diabetes mellitus (t1DM), which is characterized by an absolute lack of insulin due to auto-immune destruction of the insulin-producing beta cells of the islets of Langerhans, located in the pancreas.[1] It is most common in young patients but it may have its onset in adults. In type 2 diabetes mellitus (t2DM), an unclear etiological factor leads to a combination of a gradual defect in insulin production of the beta cell, a diminished response of target tissue (insulin resistance) and a raised production of glucose in the liver.[2] Type 2 diabetes gradually develops and may be diagnosed after years of relative hyperglycaemia and can, in 60 % of cases, be attributed to weight gain and physical inactivity. With an estimated 1 billion overweight or obese people worldwide, the problem is extensive and still increasing, with a current staggering number of 350 million people worldwide with diabetes.[3,4]

In 2011 the prevalence of diabetes in the group 65 years or older, in the U.S., was 26.9%.[5] The RIVM (Rijksinstituut voor Volksgezondheid en Milieu) data suggest that at least 600.000 people in the Netherlands have diabetes mellitus, 90% of them have t2DM. The prevalence is thought to increase to 737.000 patients in 2025.[6]

Both t1DM and t2DM are characterized by hyperglycaemia, which has to be managed and treated to prevent death and long-term complications. Patients with t1DM need pharmacological support with insulin injections. Depending on the medical status and condition of patients with t2DM, treatment will usually be initiated by lifestyle interventions, targeting obesity and physical inactivity, as these are common causes for insulin resistance. If not contraindicated and tolerated, oral hypoglycaemic agents such as metformin are the pharmacological agent of choice. Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many people.[7]

Complications of Diabetes Mellitus

Long-term complications of diabetes are injurious effects of hyperglycaemia and can be separated into macrovascular complications (peripheral artery disease, coronary artery disease or stroke) and microvascular complications (diabetic nephropathy, neuropathy and retinopathy).[8]

Neuropathy

Diabetic peripheral neuropathy (DPN) is one of the most common complications in diabetes mellitus. Developing over months or years, diabetic neuropathy is typically characterised by sensory symptoms following a symmetrical 'stocking-and-glove' distributing pattern, starting at the toes and extending proximally.

The patient might complain of a burning, electric and stabbing sensation, with or without numbness. Involvement of the motor nerves in motor neuropathy can lead to muscle atrophy and alteration of muscle balance in the foot. Different muscle balance can lead to flexion deformities such as claw toes and prominent metatarsal heads, and thus to increased biomechanical pressure on the metatarsal heads and dorsal aspect of the toes.[9] Autonomic neuropathy can cause dry skin by diminished transpiration and arteriovenous shunting in the foot. Other forms of autonomic diabetic neuropathy lead to other autonomic dysfunction such as gastroparesis and other autonomic dysfunctions of abdominal organs, postural hypotension and erectile dysfunction. Peripheral sensory neuropathy is one of the strongest risk factors for both foot ulcers and amputations in patients with diabetes mellitus, with 15 % of all patients developing an ulcer during the course of their disease.[10–13]

About 7.5% of t2DM patients already have clinical signs of peripheral symmetric neuropathy at diagnosis of diabetes. Historical data have suggested that up to fifty percent of patients develop some form of neuropathy during the course of their disease.[14,15] Diabetic neuropathy is most commonly a bilateral, distal, large-fibre, symmetric polyneuropathy. This neuropathy is thought to be progressive and irreversible.[15,16] Until recent, intense glucose control has been seen as the only remedy to preserve sensory nerve function.[17,18]

Peripheral neuropathies in diabetes are diverse; along with distal symmetric polyneuropathy mononeuropathy, mononeuritis multiplex and entrapment neuropathy are frequently seen. The carpal tunnel syndrome is the most common entrapment neuropathy with a prevalence of 30 percent; its treatment may be surgical. Furthermore focal and multifocal neuropathies are confined to the distribution of single or multiple peripheral nerves and their involvement is referred to as mononeuropathy or mononeuritis multiplex.[19]

Etiology

The primary factors in the pathogenesis of diabetic peripheral neuropathy (DPN) are direct damage to the nerve as a consequence of metabolic changes as well as micro vascular damage causing neurodegenerative changes.

Hyperglycaemia

There are three different pathways leading to cell damage induced by excess intracellular glucose.[13] First, excess in glycolysis can lead to an electron transport overload leading to mitochondrial complex dysfunction and apoptosis by generation of reactive free oxygen species.[20] Second, inflammatory injury is associated with an increased flux through the hexosamine pathway.[21] Third, elevated activity of the polyol pathway induces osmosis and causes nerve edema and eventually nerve degeneration.[22]

Another metabolic cause for neuropathy is given by the production of advanced glycation end products (AGE's), which is seen as a consequence of hyperglycaemia. AGE's initiate an inflammatory process, leading to oxidative stress resulting in nerve damage.[23]

Dyslipidaemia

There is a high incidence of dyslipidaemia, especially in patients with t2DM, which is linked to diabetic neuropathy. Free fatty acids promote inflammatory reactions by cytokine release from adipocytes and macrophages and cause direct injury to Schwann cells.[24–26]

Impaired insulin signalling

Insuline deficiency t1DM and insulin resistance combined with insulin deficiency t2DM induce reduction of neurotrophic signalling which is thought to contribute to the pathogenesis of diabetic neuropathy.

Low levels of C-peptide, which is split from pro-insulin in the pancreas, lead to reduction of sodium-potassium ATPase activity, endothelial nitric oxide synthase (eNOS) activity and endoneural blood flow in patients with diabetes.[27] Ekberg et al proved that administration of C-peptide to patients with type 1 diabetes slows down the progression of neuropathy.[28,29]

Early intensive insulin treatment in patients with t1DM can reduce the incidence of neuropathy. On the other hand, in t2DM, often diagnosed after years of obesity and marginal metabolic control, targeting normoglycaemia is unlikely to reduce the incidence of neuropathy.

Microangiopathy

AGE's bind to collagen and make fibrous structures, e.g. vascular walls and ligamental structures, thicker and stiffer.[30,31] Thickening of the vascular wall in capillaries has been found in type 1 and 2 diabetic patients.[32] The capillary changes have their origin in basal laminar thickening and in endothelial proliferation. Further evidence of an

etiological role of microangiopathy in DPN has been found by Powell et al. who found intra-axonal glycogen accumulation in some axons as well as demyelinisation and axonal degeneration.[32] Furthermore, Ibrahim et al. showed impaired blood flow and reduced nerve oxygenation in the sural nerve in patients with diabetic neuropathy.[33]

Anatomical cause

The microvascular damage combined with elevated endoneural pressure by osmosis as well as the thicker ligaments near the nerves, cause narrowed anatomic spaces and a relative ischaemic environment for nerves. This may lead to damage and impaired regeneration.

The possibility that the symptoms of a systemic metabolic disease such as diabetes may be due to subclinical peripheral entrapments was suggested in the double-crush hypothesis of Upton and McComas in 1973 and was confirmed in 1991 by an experimental animal model.[34,35]

Treatment

The management of diabetes and its long-term complications generates substantial medical costs.[36,37] Therefore, it is of utter importance to minimize morbidity caused by complications in diabetes. Intensive regulation of blood glucose levels is critical to prevent and treat painful neuropathy and other macro and microvascular complications in diabetes. Patients with painful diabetic neuropathy can benefit from medication such as amitriptyline, carbamazepine, duloxetine, pregabalin and gabapentin. These have proven to be effective in diminishing pain and form the first line treatment of choice.[38–41] The neuropathy itself, however, is not treated and since this complication of diabetes is progressive, medication can only give temporarily improvement of symptoms. Medication by itself will not be sufficient to prevent the development of ulceration, and subsequent infection or amputation. For non-painful neuropathy, no therapy exists to reverse symptoms. Even aldose reductase inhibitors, once thought to be the silver bullet as inhibitors of toxic metabolites, have not been proven effective.[42]

Reversing the development of symptomatic neuropathy can be approached from an understanding of the pathophysiology of nerve compression and the realization that many of the symptoms of diabetic neuropathy are similar to those of chronic nerve compression.[43]

Based on this observation, it was demonstrated in 1988 that nerves in diabetic rats are more susceptible to chronic compression syndromes. At narrow anatomic sites, swollen nerves surrounded by thick glycosylated fibrous tissue are prone to

compression.[44] Different studies confirm that carpal tunnel syndrome has a much higher incidence among diabetic patients.[45] Dellon was the first to extrapolate this theory to the lower extremities and started to treat patients with DPN with peripheral nerve decompression, intending improvement of sensibility and decrease of pain sensations.[46,47] Restoration of sensibility in the feet would then be effective in preventing ulceration and amputation.[48,49] To date, multiple non-randomized studies have been executed, all implicating promising results of pain relief in up to 90% and improvement of sensibility in up to 85%.[46,50–57] Chaudhry and Melenhorst both reviewed this topic and concluded that all performed studies lack a prospective, randomized design that is not susceptible to bias. The authors concluded that the level of evidence remains questionable and that the effect of lower extremity nerve decompression surgery for DPN remains unproven.[58,59]

Aim of this study

The objective of this study is to assess the value of surgical decompression of the nerves of the lower extremities in patients with diabetic symmetrical polyneuropathy.
Primary objective:

- To study the influence of decompression on pain. (Chapter 3)

Secondary objectives:

- To study the influence of decompression on tactile sensation. (Chapter 3)
- To study if the posterior tibial nerve can anatomically recover after decompression of the tarsal tunnel. (Chapter 5)
- To study the reduction of edema in the tarsal tunnel and the thickness of the ligament covering the tarsal tunnel. (Chapter 5)
- To study the effect of decompression on nerve conduction. (Chapter 6)
- To study the effect of decompression on postural stability. (Chapter 7)
- To study the effect of decompression on functional status of patients with painful neuropathy. (Chapter 8)

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2

Study design

STUDY DESIGN

In September 2010 a randomized clinical trial, the Lower Extremity Nerve entrapment Study (LENS), was initiated in the Netherlands, comparing peripheral nerve decompression of the lower extremities with standard conservative medical treatment, in patients with painful diabetic polyneuropathy. This randomized controlled study was performed at the University Medical Center Utrecht and was approved by the local Medical Research Ethics Committee (METC). The study was conducted according to the principles of the Declaration of Helsinki (version 22-10-2008) in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO), and was registered at the Dutch Trial Registry number (NTR) 2344.
The research proposal comprised serial examinations that were done before and after surgical decompression of the lower leg. Serial examinations were done with the same time interval in the non-surgery leg of the study (within-patient comparison). The last tests were done one year after surgery. The total duration of the study was four years.

Study population

Population (base)

Patients with painful diabetic neuropathy, assessed with the Diabetic Neuropathy Symptom score (DNS) and Diabetic Neuropathy Examination (DNE), age between 18 and 90 were included.[1,2] In- and exclusion criteria are shown in Table 1.

In order to interpret and compare results of the operated subjects, control groups were obtained for evaluation of the following:

- Stability: two control groups were obtained for evaluation of stability in the normal and diabetic population. One control group consisted of patients with the same study inclusion criteria, but without diabetic neuropathy. The second control group consisted of subjects without diabetes. Control groups were recruited from the outpatient clinics of internal medicine, plastic surgery and urology.
- Mean cross sectional area of the tibial nerve: one control group was obtained for evaluation of the mean cross sectional area of the tibial nerve at the medial ankle in the normal and diabetic population. The control group consisted of subjects without diabetes and was recruited from the outpatient clinics of internal medicine, plastic surgery and urology.

For the extra control groups, i.e. stability and mean cross sectional area measurements, extra exclusion criteria applied:

- Stability: Patients with physical problems leading to instability were excluded for participating in the control group, as well as those with symptoms of peripheral neuropathy, including numbness, burning, tingling or pain in the feet or lower legs or - if performed - a neurothesiometer measurement of >20 V.
- Mean cross sectional area: Patients with a history of diabetes or symptoms of peripheral neuropathy were excluded from participation in the control group

Sample size calculation

We planned a study of a continuous response variable, where the result of surgery on one extremity of a subject was compared to the other extremity that did not undergo surgery. In a previous study, the response in VAS score was normally distributed with standard deviation 2.[3] The difference in pre-and postoperative VAS score were estimated to be 1.5. This change was a conservative estimate compared to somewhat larger differences found in a few available non- controlled studies by Karagoz and Rader. If the true difference in VAS score between the means in the experimental and control limb was 1.5, we needed to study 38 subjects to be able to reject the null hypothesis that the population means of the experimental and control limb were equal with probability (power) of 0,9. For purpose of calculation, the legs were considered matched pairs. The type I error probability associated with this test of this null hypothesis was 0,05. The assumed correlation coefficient was 0. We anticipated a 10 % loss to follow-up, making the total calculated needed sample size 42.

Table 1 In- and exclusion critera LENS

Inclusion criteria
▪ VAS-score >2
▪ Positive Tinel sign of posterior tibial, and common peroneal nerve
▪ Ankle-brachial-index between 0,8-1,15 with a toe-brachial-index of ≥ 0,7
▪ Palpable pulsations at the posterior tibial artery and the dorsalis pedis artery
Exclusion criteria
▪ BMI >35
▪ General condition unsuitable for surgery
▪ History of ankle fractures or amputations proximal to the Lisfranc joints
▪ Ulcer on the foot
▪ Other causes for neuropathy (i.e. HIV, chemotherapy)

The sample sizes of the extra control groups were 42 and 38 for the stability control group and the mean cross sectional area control group, respectively.

Treatment / intervention

Surgery

All decompressions of the lower extremity nerves were carried out in a supine position with general anesthesia, using a tourniquet, by the same surgeon. At the ankle site, the flexor retinaculum was incised over the total length of the retinaculum exposing the underlying structures e.g. tibial artery and veins and the tibial nerve. Distally, the nerve was followed till its division into the calcaneal, lateral and medial branches, releasing the deep fascia of the abductor hallucis muscle and the septum between medial and lateral plantar nerves (Illustration 1). A second incision was made over de dorsum of the foot where the deep peroneal nerve runs under the tendon of the extensor hallucis brevis muscle. Decompression was achieved by removing 1 centimeter of tendon of the extensor hallucis brevis muscle (Illustration 2). A third incision was made 10 -14 centimeters above the lateral malleolus. Identification and division of the crural fascia exposed the superficial peroneal nerve. The last incision was made dorsolateral of the fibular neck. After identification of the common peroneal nerve, the fascia of the peroneal longus muscle was divided (Illustration 3). Wounds were closed in layers with monocryl 4.0. The patients had a supportive dressing post-operatively for two weeks. Patients were instructed to mobilize unburdened for 2,5 weeks.

Conservative treatment

The contralateral limb was used as control, which means 'within patient' comparison' was used. Patients enrolled in this study were allowed to use medication if they suffered from painful neuropathy following the Dutch Polyneuropathy Guideline, which is standard usual care.[4] The last tests were done one year after surgery.

Methods

Study parameters/endpoints

The objective of this study was to assess the value of surgical decompression of the nerves of the lower extremities in patients with painful diabetic polyneuropathy.

Primary objective:

To study the influence of decompression on pain. Primary endpoint was VAS<2 or a greater change in VAS in the surgery leg compared with the control leg after 6 months.

Secondary study parameters/endpoints:

- To study the influence of decompression on tactile sensation.
- To study if the posterior tibial nerve can anatomically recover after decompression of the tarsal tunnel.
- To study the reduction of edema in the tarsal tunnel and the thickness of the ligament covering the tarsal tunnel.
- To study the effect of decompression on nerve conduction.
- To study the effect of decompression on postural stability.
- To study the effect of decompression on functional status of patients with painful neuropathy.

Randomisation, blinding and treatment allocation

All tests were scored by two independent observers blinded for clinical findings and other test results. After completion the first tests, randomisation was done by the computer, using a web based randomisation system.

Study procedures

Patients' regular visits to their diabetes specialist for evaluation of their health status and diabetes mellitus were combined with our study.

- Evaluation of pain with the Visual Analogue Scale.
  The VAS was used for each leg separately.
  The VAS is a straight line, the ends of which are the extreme limits of the sensation being assessed. The line is 10 cm in length using a 10-point scale ranging from 1 to 10, with 1 being barely perceptible and 10 being intolerably painful.

- Evaluation of the tactile sensibility with the Semmes-Weinstein monofilament.
  With 10 g 5.07 Semmes Weinstein monofilament, 10 plantar sites on the forefoot were tested.[5,6] The patient had to say Yes or No when asked if he/she believes the Semmes Weinstein monofilament was being applied. Inability to perceive the monofilament application is associated with clinically large-fiber polyneuropathy.[7]

- Evaluation of the tactile sensibility with two-point discriminator (TPD).
  With TPD the minimum distance between two stimulus points on the skin perceived as distinct points was measured. The foot was divided into ten standard significant areas, as indicated in Peryasami et al.[7]

- Evaluation of the quality of life with the SF-36 and EQ-5D.
  The Short Form-36 (SF)-36 is a short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index.
  EuroQol-5D (EQ-5D) is a generic instrument for measuring health status.[8,9] It defines health along five dimensions: mobility, self-care, daily activities (such as work, study, housework, and leisure activities), pain or discomfort and anxiety or depression. Each dimension has three levels: no problem, moderate problem or severe problem. In the second part of the EQ-5D, the health status is recorded on a vertical visual analog scale (VAS), ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The patients were asked to mark the point on the scale that they felt best reflected their current health state. A summary score was calculated from the five EuroQol dimensions (the utility score), ranging from 1 for perfect health to -0.5 for death.[10]

- Evaluation of the importance of changes in clinical state one year after surgical decompression of the nerves of the lower extremity in patients with DPN, measured as Minimal Clinically Important Difference (MCID).
  Change in clinical state is defined through an anchor question (decrease in well being, no change, minor- or major improvement in well being), being compared to the measured changes in both pain through the change in reported VAS and quality of life through changes in SF-36 and EQ5D.

- Evaluation of the change in diameter of the posterior tibial nerve with ultrasound.
  The maximum and minimum diameter in millimeters of the posterior tibial nerve were measured in the tarsal tunnel and cranial of the tarsal tunnel preoperatively and six months postoperatively. The examination of the posterior tibial nerve was done in both legs on the same day. The thickness in millimetres of the retinaculum was measured as well. In order to compare the study population with the normal population, data of a control group with subjects without diabetes were obtained. The control group underwent the same ultrasound evaluation with an additional measurement of the maximum and minimum diameter in millimeters of the posterior tibial nerve 3 cm proximal to the medial malleolus.

- Evaluation of stability using the Matscan Measurement System (Tekscan , Inc., Boston, MA).
  Sway of the center of pressure was measured pre and postoperatively, while

patients walked and stood still with open and closed eyes. The peak pressure and pressure-time integral were evaluated as well. To compare the studied population with the normal population, evaluation of two population based control groups was performed. Control patients underwent exactly the same stability test as the operated group.

- Evaluation of nerve conduction with EMG.
  Nerve conduction of the posterior tibial nerve and peroneal nerve was tested. The EMG was done after inclusion and 12 months later.

- Evaluation of adverse events of surgery,
  Adverse events of surgery were noted, especially infection, hemorrhage and delayed wound healing, at each visit and in case of emergency.

- Evaluation of adverse events of medical treatment.
  Adverse events of medical treatment were noted at each visit and in case of emergency.

Statistical analysis

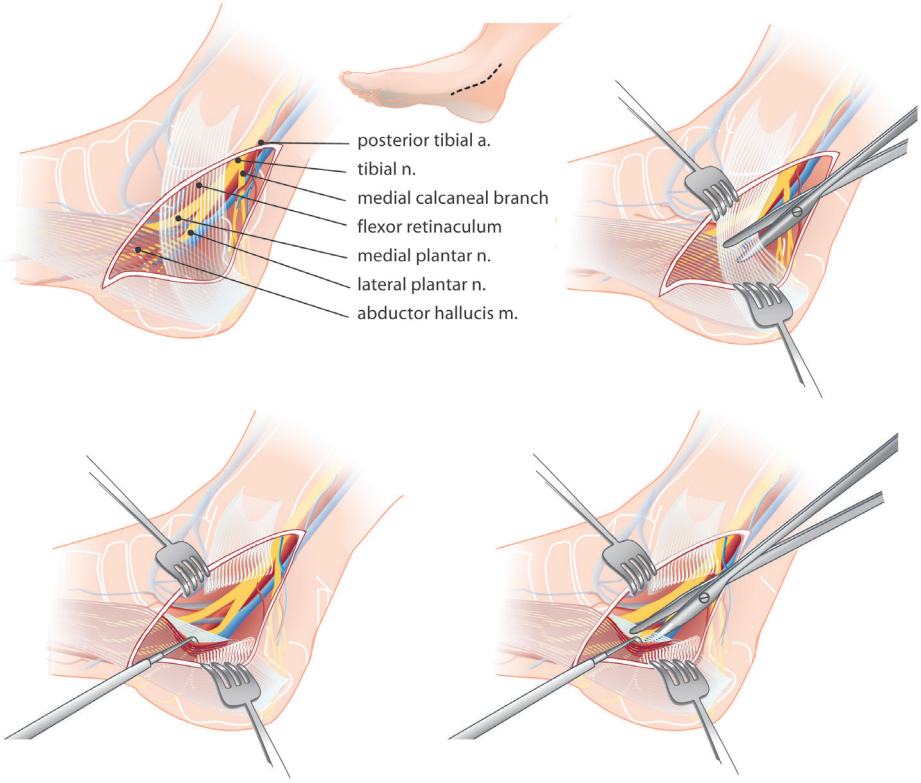
Descriptive statistics

Descriptive continuous variables were expressed as mean and range for normally distributed variables and as median and range for non-parametrically distributed variables. Statistical differences were calculated using Student's t-tests for normally distributed variables, or Mann Whitney U for non-parametrically distributed variables. Categorical variables were presented as number of cases and percentage. Statistical differences were calculated using chi squared tests (Fisher's exact test or, if expected values are large enough, with Pearson's chi-square test). Odds ratios and 95% confidence intervals were calculated for exposure variables using an alpha of 0.05.

Univariate analysis

Univariate analysis were performed for comparison of the legs of patients, treated with or without surgery. As with the descriptive variables, significance was assessed with the Student's t-test or Mann Whitney U tests and chi square tests for continuous and categorical variables, respectively. For comparison between the two legs of the same patients (a within patient comparison), paired versions of the t-test and McNemar's test for categorical outcomes were performed. The preoperative and the postoperative results on a stability test of the study population were compared to the

stability test results of two control groups, using ANOVA and pairwise comparisons of groups with Bonferroni correction. The results of the ultrasound measurements of the study population were compared to the control group using ANOVA as well and the effect of possible confouders was evaluated with MANOVA. Significance was assessed two-sided for all variables. Outcomes with $p<0.05$ were considered significant. Outcomes are calculated with both intention to treat, as well as on treatment analysis.



Illustratrion 1: Decompression of the tibial nerve

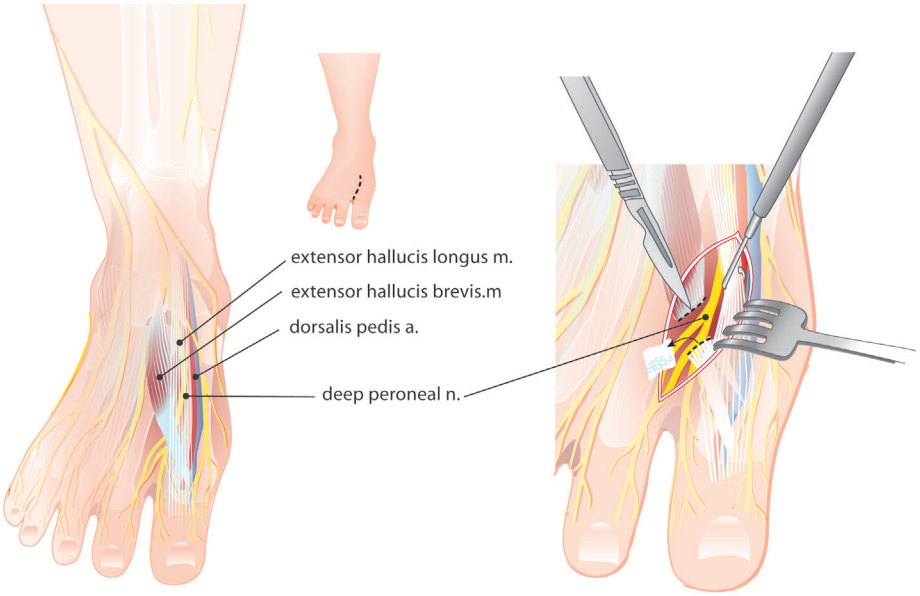


Illustration 2: Decompression of the deep peroneal nerve

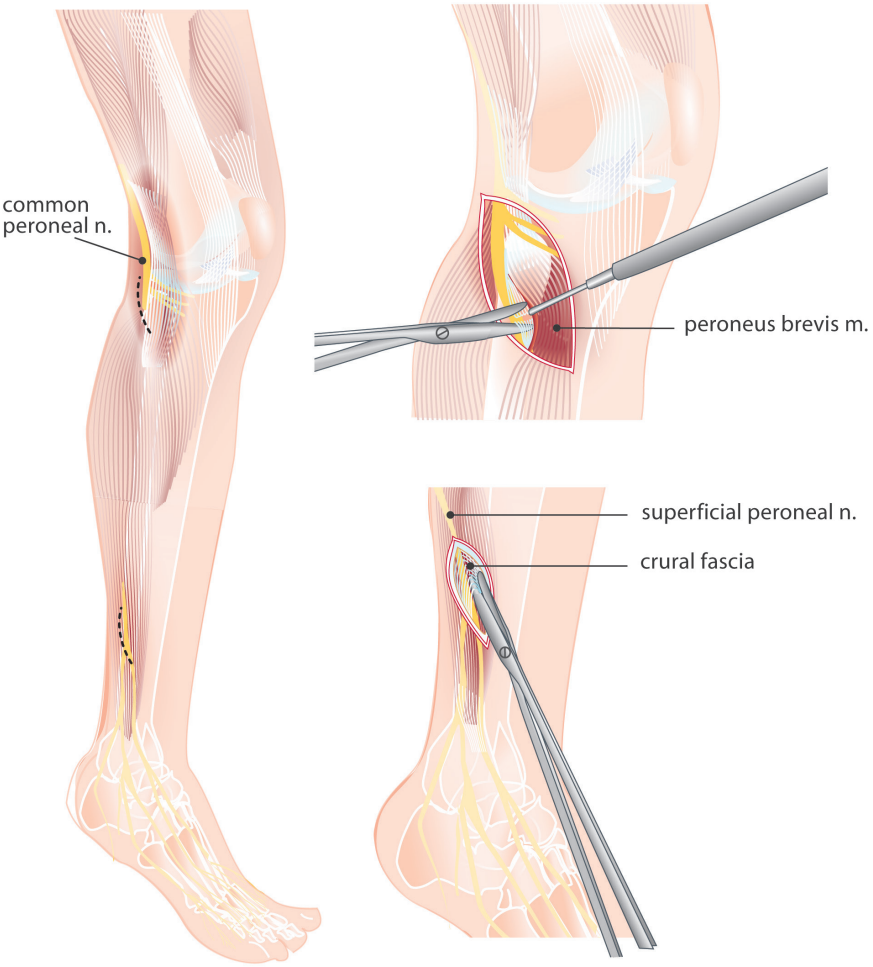


Illustration 3: Decompression of the common peroneal nerve and superficial peroneal nerve

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3

Value of surgical decompression of compressed nerves in the lower extremity in patients with painful diabetic neuropathy

A randomized controlled trial

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ABSTRACT

Background: To assess the value of lower extremity nerve decompression surgery for painful diabetic polyneuropathy (DPN) on pain and sensibility.

Methods: Single center randomized controlled trial of one intervention with one year follow-up. 42 patients with painful diabetic neuropathy were included. After randomization, the lower extremity nerves were decompressed at four sites in one limb. The contralateral limb was used as control (within-patient comparison). All patients were assessed pre-operatively and at 3, 6 and 12 months postoperatively by an independent physician. Primary outcome was the Visual Analogue Scale (VAS) score twelve months after surgery. Secondary outcomes were Semmes Weinstein Monofilament Testing and two-point discrimination outcomes at 3, 6 and 12 months.

Results: VAS scores improved significantly from a mean of 6.1 (95% CI 5.5 – 6.7) preoperatively to 3.5 (95% CI 2.5 – 4.4) at twelve months postoperatively ($p < 0.001$). VAS was also significantly lower compared to the control leg VAS 5.3 (95% CI 4.4 – 6.2) ($P < 0.001$) at twelve months. Overall, 73,7% of the subjects improved in VAS, of which 35,7% decreased more than 5 points on VAS. Sensory function did not significantly improve.

Conclusions: Surgical decompression of the nerves of the lower extremity can be added as therapeutic option for patients with painful diabetic neuropathy, having signs of chronic nerve compression by means of a positive Tinel or other diagnostic criteria, where pain medication fails to reduce pain to an acceptable standard.

INTRODUCTION

Diabetic polyneuropathy (DPN) is the most common complication of diabetes mellitus and is thought to affect up to 50 % of the patients.[1] In 2030, the number of patients with diabetes worldwide is estimated to reach 366 million.[2] Furthermore approximately half of these patients shall develop a form of DPN.[2] The chronic form of distal, symmetric diabetic polyneuropathy is the most common type of diabetic neuropathy.[1,3] It is characterized by a combined loss of nerve sensor- and motor-function in a symmetric stocking-glove distribution, most commonly seen in the lower extremities and is traditionally thought to be an irreversible process.[1,4] A proportion of patients with DPN develop symptoms of pain, which are usually treated by tight glucose control and by medication such as tricyclic antidepressants or *gamma*-aminobutyric acid analogues. The exact etiology for nerve damage is incompletely understood. Hyperglycemia leads to an excess of intramitochondrial radical oxygen species, inflammatory reactions and edema formation in peripheral nerves.[5,6] Dyslipidemia, frequently seen in type 2 diabetes, induces inflammatory reactions and cytokine release from adipocytes and macrophages.[7] These processes, together with disturbed blood flow due to micro-angiopathy, ultimately result in denervation. In 1973, Upton and McComas suggested axons are more prone to compression distally when a (subclinical) proximal compression is present along the same axon.[8] This theory was later confirmed in animal models.[9,10] Elaborating on this hypothesis, diabetic neuropathy can be seen as a result of a double crush; the altered metabolic state makes the nerve prone to compression at narrow anatomical spaces.[4]

Decompressing these anatomical passages may influence the progression of DPN and relieve patients of their pain. In 1992, Dellon was the first to treat DPN patients with peripheral nerve decompression in the lower extremity, reporting 85% improvement of the sensorimotor symptoms.[4] In the following two decades, multiple studies have been reported, all with promising results.[4,11–27] Unfortunately, all of the performed studies lack a prospective randomized controlled design. Review articles therefore concluded that the level of evidence is questionable and, so far, the effect of lower extremity nerve decompression surgery for DPN and superimposed nerve compressions remains unproven.[3,28,29]

The objective of this randomized controlled trial was to assess the value of lower extremity nerve decompression surgery for painful DPN on pain and sensibility.

MATERIALS AND METHODS

This randomized controlled trial was performed between 2010-2013 at the University Medical Center Utrecht as part of the Lower Extremity Nerve entrapment Study (LENS), approved by the Committee of Medical Research Ethics (METC). The study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO), Dutch Trial Registry number (NTR) 2344.

Patients, with diabetes mellitus type 1 or type 2, age 18 – 90 years, were included. All patients suffered from painful bilateral diabetic polyneuropathy, diagnosed with the Diabetic Neuropathy Score and Diabetic Neuropathy Examination.[30,31] Inclusion criteria were a positive Tinel sign, at least at one of the following locations: the posterior tibial, superficial or common peroneal nerve; Ankle-Brachial Index between 0.8 - 1.15 with a toe-brachial index ≥ 0,7 and palpable pulsations in the posterior tibial artery and dorsal pedal artery. Exclusion criteria were a Body Mass Index > 35 kg/m2, a general condition unsuitable for surgery, a history of ankle fractures or amputations proximal to the Lisfranc joint, ulcer on the foot, sufficient effect of pain medication (VAS 0 -1), other causes for neuropathy (e.g. HIV, chemotherapy) or indications for and history of nerve compression at additional sites (e.g. hernia or nerve root compression). Demographic information was recorded for all patients.

Each patient underwent a decompression procedure of the lower extremity nerves according to Dellon in one limb, i.e. of the tibial nerve at the ankle site, the common peroneal, deep peroneal and superficial peroneal nerve.[4] Using a web based randomization system, a computer chose the leg receiving the intervention. Surgery was carried out within 8 weeks of randomization. The contralateral limb was used as a control and served as a within-patient comparison. Patients enrolled in this study could use their medication if they suffered from painful neuropathy following the Dutch Polyneuropathy Guideline or guidelines of the European Federation of Neurological Societies (EFNS). The glucose levels were optimized by the patients' diabetes specialist.

All decompressions of the lower extremity nerves were carried out in a supine position with general anesthesia, using a tourniquet, by the same surgeon (J.F.M.M.M.). At the ankle site, the flexor retinaculum was incised over the total length of the retinaculum exposing the underlying tibial artery, veins and the tibial nerve. Distally, the nerve was followed till its division into the calcaneal, lateral and medial branches, releasing the deep fascia of the abductor hallucis muscle and the septum between medial and lateral plantar nerves. A second incision was made over the dorsum of the foot where the deep peroneal nerve runs under the tendon of the extensor halluces brevis

muscle. Decompression was achieved by removing one centimeter of tendon from the extensor hallucis brevis. A third incision was made 10 - 14 centimeters above the lateral malleolus. Identification and division of the fascia cruris exposed the superficial peroneal nerve. The final incision was made dorsolateral of the fibular neck. After identification of the common peroneal nerve, the fascia of the long peroneal muscle was divided. Wounds were closed in layers with monocryl 4.0 and a compression bandage was applied. Postoperatively patients were instructed to actively flex and extend the ankle during 2.5 weeks, in which patients mobilized unburdened.

For the primary outcome, evaluation of pain was assessed with the Visual Analogue Scale (VAS) for both legs separately. The VAS is a straight line of 10 centimeters in length using a 10-point scale ranging from 0 to 10, with 0 being no perceptible pain and 10 being intolerable pain. The patients were asked to draw a point on the line corresponding with the intensity of their pain on that moment. The value derived after measuring the distance from the left end of the line to the point drawn by the patient scored the VAS. Patients filled out the VAS pre-operatively and at 3, 6 and 12 months postoperatively.

An independent physician evaluated tactile sensibility with a 5.07 (10g) Semmes Weinstein Monofilament (WPB Podopedot Weijer, The Netherlands) and two-point discrimination. Inability to perceive a 10 g monofilament is associated with large-fiber polyneuropathy and with a higher risk of foot ulcers, re-ulceration, and amputation.[32–34] A maximum of nine points could be scored, one point for each positive response at nine designated points.[35] Two-point discrimination was evaluated with the Dellon® Disk-Criminator at the same nine plantar sites of the foot. For each patient, the minimal perceivable distance between two stimuli was recorded. If a patient could not perceive two points at the widest distance, it was recorded as No Discrimination. If a patient could not discriminate nor feel being touched, it was recorded as No Perception.

Sample size calculation was based on a continuous response variable with respect to the primary outcome. The difference in pre- and postoperative VAS score was estimated to be 1.5, based on the non-placebo controlled trials by Karagoz and Rader.[18,36] To reject the null-hypothesis that the true difference in VAS would be 1.5, the population means of the intervention and control limbs are equal with probability of 0.9 and the type I error probability of 0.05, 38 subjects were needed. Anticipated on a 10 % loss to follow-up, the total calculated sample size was 42.

Data analysis was performed with statistical software (IBM SPSS Statistics, Version 21.0. Armonk, NY: IBM corp.). The intervention and control limbs were considered to be matched-pairs and analyzed as dependent variables. Missing values were recorded as such and not included in calculation of statistical differences. The VAS

score was analyzed as a continuous variable and was considered to have a normal distribution. Statistical differences were calculated using ANOVA repeated measures with Bonferroni correction and 2-tailed Student's t-tests. VAS-score was expressed in means with 95% confidence intervals (CI). Categorical variables will be presented as number of cases and percentages. McNemars test was used for statistical analysis of the binominal variables. Differences were considered significant when alpha < 0.05.

RESULTS

Participants

Forty-two patients were included in this study. One patient died during the follow-up period due to unrelated circumstances. One patient was lost to follow-up. Two patients were not evaluated at 3 months and were excluded from statistical analysis. The baseline characteristics of the remaining 38 patients are described in Table 1. There were three complications, one patient had to be operated for a hematoma due to use of anticoagulants. Two patients had an infected wound at the ankle site, both patients were treated with antibiotics and one of them was admitted to the hospital.

Visual Analogue Scale

At baseline, there was no significant difference between the mean VAS-scores in the control and intervention leg (both means were 6.1, p >0.1). At 3 months post-operatively, a significant decrease in VAS-score was noted in both the intervention and control leg (Figure 1A). The mean VAS-score at 12 months was 3.5 (95% CI 2.5 – 4.4) for the intervention group and 5.3 (95% CI 4.4 – 6.2) for the control group, p < 0.001. At 12 months, the mean VAS score improvement from baseline was 2,6 (95% CI 1.6 – 3.7, p < 0.001) for the intervention group and 0.8 (95% CI .0 – 1.7, p > 0.05) for the control group. The mean difference between the control and intervention groups at different moments is represented in Figure 1B. There was a significant overall difference between intervention and control leg over the 12 months follow-up period (p = 0.004, ANOVA repeated measures). At 12 months the difference between control and intervention leg had increased to 1.8 (p = 0.002).

Overall, 73.7% of the subjects improved in VAS, of which 35.7% decreased more than 5 points on VAS, 26.3% of the subjects had no effect or worsened on VAS.

The outcomes did not seem to be influenced by surgical skills, since there was no statistical proof for a surgical learning curve during our study. For example, the VAS outcomes of the first 10 and 20 operated patients compared with latter operated patients were not significantly different (p = 0.305 and p = 0.465 respectively).

Table 1 Baseline characteristics of the participants included for surgical decompression of the nerves in the lower extremity

Variable	Participants (*n*= 38)
Gender	
Male (%)	22 (57.9)
Female (%)	16 (42.1)
Age, mean years ± SD	62.7 ± 10.2
BMI, mean kg/m^2± SD	29.0 ± 4.2
Diabetes Type	
Type 1 (%)	8 (21.1)
Type 2 (%)	30 (78.9)
Duration DM, mean years ± SD	17.6 ± 12.2
Side surgical decompression	
Left (%)	20 (52.6)
Right (%)	18 (47.4)

SD = standard deviation, BMI = body mass index, DM = diabetes mellitus

Semmes Weinstein Monofilament

At baseline, the total score of the Semmes Weinstein Monofilament Testing (SWMT) was not significantly different; the mean score of the intervention group was 4.0 vs. 3.6 in the control group (p = 0.242). At 3 months post-operatively, the SWMT score was 5.4 (95% CI 4.3 – 6.6) in the intervention group, a significant increase compared with the control and baseline scores (4.0 [p = 0.002] and 4.0 [p = 0.001], respectively). At 12 months of follow-up, however, the total SWMT score in the intervention group lowered to 4.6 (95% CI 3.3 – 5.6), not significantly different from the control group (4.1, 95% CI 3.1 – 5.1) and baseline measurements (4.0, 95% CI 3.0 – 4.9). Nevertheless, the effect of the intervention on SWMT is still significant during the entire 12 months follow-up period compared with the control group; mean SWMT-score intervention over twelve months was 4.7 (95% CI 3.7 – 5.7) compared with 3.9 in the control group (95% CI 3.0 – 4.8) (p = 0.011) (Figure 2).

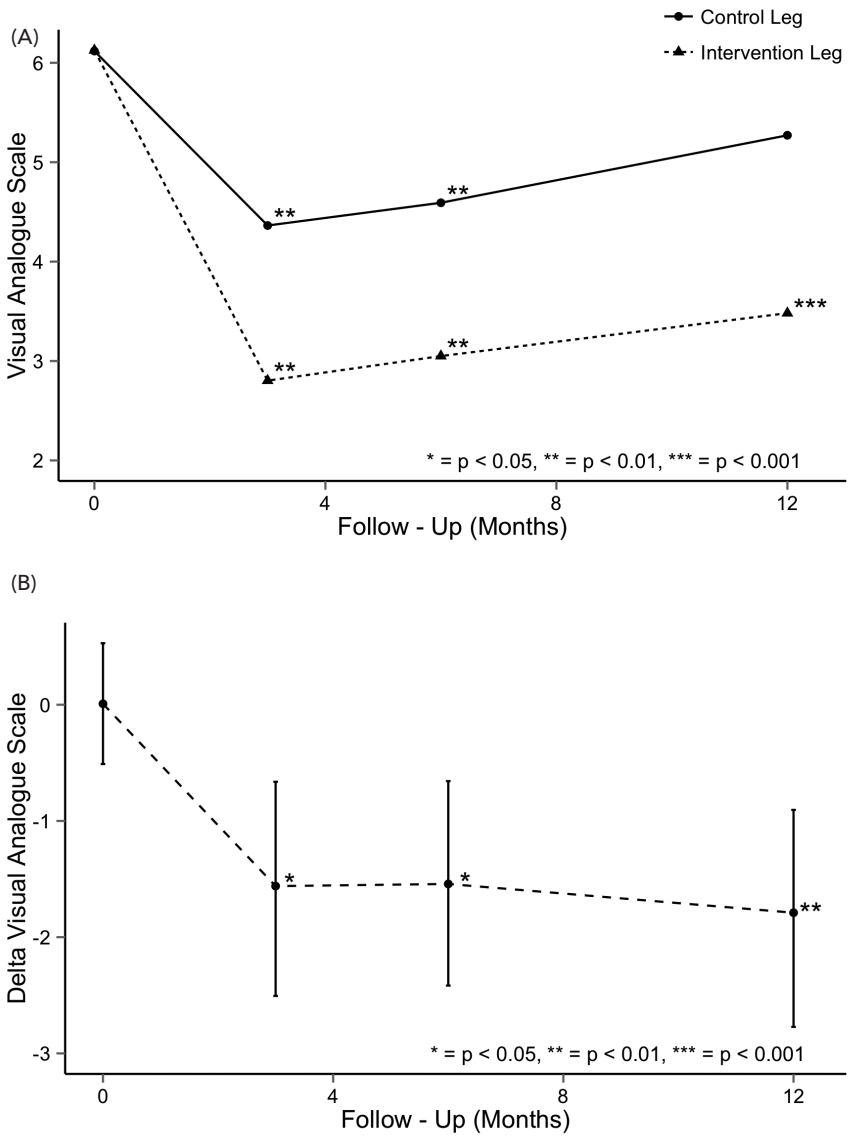

Figure 1 (A) Mean Visual Analogue Scale (VAS) score in the intervention and control leg at different moments of follow-up. Significance levels for the control group in comparison with the pre-operative VAS. Significance levels of the intervention group compared to the corresponding control group. (B) Difference in VAS score between the intervention and the control leg at different moments of follow-up and their corresponding significance levels.

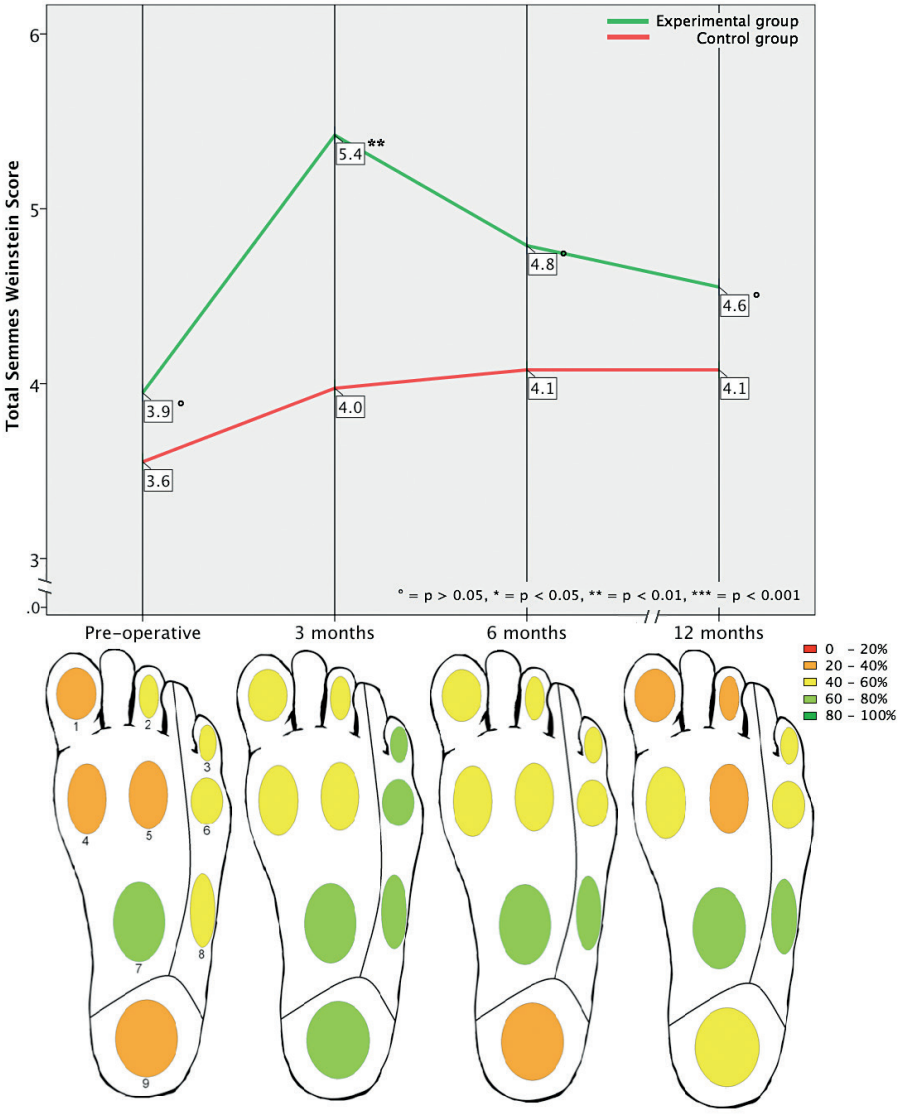

Figure 2 Representation of the different measure points on the foot sole tested with the Semmes Weinstein Monofilament in the experimental leg and the accompanying total SWMT score over time compared with the control leg. The color represents the percentage of subjects with a positive SWMT result on that specific point.

Two-point discrimination

At baseline, intervention and control leg outcomes of two-point discrimination were not significantly different (p 0.750). After 12 months, the comparison between the intervention and control leg revealed no significant improvement in the ability to distinguish between two points (Figure 3). After intervention, the group without touch perception significantly reduced in size (32.7% to 19.9%, p 0.025). This effect is also significant when intervention legs were compared with control legs (19.9% vs. 24.0%, p = 0.042). In both the intervention and the control leg, the group in which patients were capable of two-point discrimination had significantly worsened at 12 months of follow up (4.1% vs. 17.0% respectively, p = 0.006). The non-discriminating group increased significantly in both the intervention and control leg (p<0.001, Figure 3).

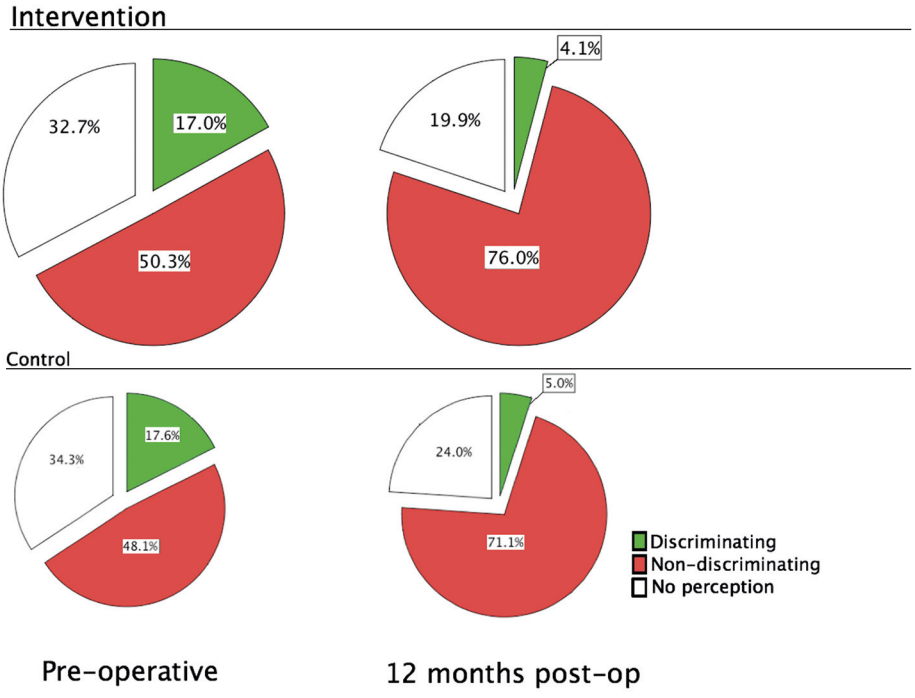

Figure 3 Proportion of subjects able to discriminate between two-points at pre-operative and 12 months follow-up. After intervention, the group without touch perception significantly reduced in size ($p < 0.05$). This effect is also significant when intervention legs were compared with control legs ($p < 0.05$).

DISCUSSION

This study is the first randomized controlled trial for decompression of nerves in the lower extremity in patients with painful DPN. Our results suggest that there is a beneficial effect of decompression surgery for DPN with regard to pain, measured with the VAS score. Since Dellon described the first surgical decompression for DPN in 1992, numerous studies regarding this subject have been carried out showing possible benefits of this intervention.[4] In their Cochrane review, Chaudhry et al. concluded that until 2006 no randomized controlled studies were performed.[3] The available studies were not comparable due to their design. Clear evidence for the existence of double-crush in DPN was therefore lacking, as well as proof of the beneficial effect of nerve decompression in the lower extremity for DPN.[3,28,29] Nevertheless, positive effects on pain, sensibility, balance and nerve conduction velocity were described as results of the decompression in numerous non-randomized studies.[4,11–19,21–27]

We found a reduction in VAS score of 2.6 compared with the baseline and an absolute difference of 1.8 between the intervention and control leg; less positive than earlier outcomes found in non-controlled studies, in which the intervention was not limited to single extremity surgery.[15,18,19,23,24,26,36]

One year after intervention, the SWMT and two-point discrimination were not significantly improved. Although the ANOVA, repeated measures showed that the difference over the 12 months period is significantly different from the control group, this is probably due the peak at 3 months and no definitive conclusions should be made. These results are directly perpendicular to the effects on sensibility mentioned in other studies.[14–16,18,21,25–27,37]

Substantial improvement in two-point discrimination was described in other studies.[21,25–27,37]

An explanation could be the difference in severity of the diabetic neuropathy in the subjects. Approximately 17% of our subjects were able to discriminate between 2 points pre-operatively, whereas in the other studies most subjects had two-point discrimination pre-operative.[21,25–27,37] It is well known that two-point discrimination is lost before the one-point perception.[38] This indicates that in our subjects without two-point discrimination, the results from the SWMT were biased. Selecting patients with intact two-point discrimination might lead to better results in sensibility. Nevertheless 12 months after surgery there were less patients without tactile perception with the 2-point discriminator in the intervention group. The significant reduction in patients capable of discriminating between two points in both the intervention and the control leg, might be caused by progression of the disease.

Interestingly, the VAS-score in the control leg also decreased significantly during the

follow-up period. Pain perception in the operated and non-operated leg possibly influenced each other; a phenomenon which is seen in posttraumatic neuropathic pain.[39–42] The absolute difference in VAS between the intervention and control leg remained significant during the follow up period.
In our study, the mean VAS score slowly increased after an initial post surgical decrease. Formation of scar tissue in the operated area might be an explanation for the decreasing effect over time. Pulling forces and rigid texture of scar tissue could have caused secondary compression of the nerves. On the other hand, decompression of the tarsal tunnel possibly leads to a temporary pressure reduction of the nerve, resulting in restoration of the extrinsic epineural circulation. Nonetheless, intraneural and epineural edema caused by the hyperglycaemic environment is still present and is not reduced by decompression of the tarsal tunnel, shown by evaluation of ultrasound findings in our patients, which pleads for the existence of a double-crush in DPN.[43] In summary, decompression contributes to the pressure reduction but does not solve the underlying problem. Optimization and stabilization of glucose levels therefore remains of paramount importance.

One of the limitations of our study was the blinding of the patients and researchers, which may have led to bias. The ideal study design would have been a double-blinded procedure with a sham surgery group, which is in our opinion an ethically controversial procedure. Only patients with painful neuropathy were included for the study, this selection criterion makes it impossible to generalize our outcomes to all the patients with non-painful diabetic neuropathy symptoms.

In conclusion, decompression of the nerves of the lower extremity in patients with painful DPN significantly decreases pain symptoms. Sensibility improved significantly in the first 3 months, but not at 12 months of follow-up. The postoperative effects on pain and the temporary effect on sensibility plead for an etiological effect of compression on the lower extremity nerves in painful DPN. Decompression of the nerves of the lower extremity should be added as a surgical treatment modality in patients with painful neuropathy where medication fails to achieve decrease of pain symptoms and having signs of chronic nerve compression by means of a positive Tinel or other diagnostic criteria.

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Does surgical treatment of painful diabetic polyneuropathy lead to a change in use of pain medication?

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Submitted

ABSTRACT

Objective: Our main objective was to determine whether surgical decompression of nerves in the lower extremity, in patients suffering from painful diabetic polyneuropathy (painful DPN), would reduce the amount of pain medication taken by patients. Secondary goals were to evaluate the physicians' adherence to the recommendations of the Dutch Guideline for polyneuropathy ('Richtlijn Polyneuropathie', 2005), it's accuracy in respect to the European Federation of Neurological Societies (EFNS) Guideline and the therapy adherence of patients.

Methods: Prescription data for pain medication was collected through patients' pharmacies and evaluated for 42 patients included in the Lower Extremity Nerve entrapment Study, with a VAS>2. Patients underwent a unilateral nerve decompression of the lower extremity between 2011-2013. Pre-operative prescriptions were compared with prescriptions at 3, 6 and 12 months post-operative.

Results: The six months post-operative results show that significantly less medication was used compared to before surgery and 3 months afterwards. The twelve months post-operative results were no longer significant. Of the prescriptions 44% did not meet the recommendations of the Dutch guideline for polyneuropathy; for pregabalin this was 29.

Conclusions: Only at six months after surgical decompression of the nerves in the lower extremity in patients with painful DPN, patients used significantly less pain medication. The Dutch guideline contains incomplete data in respect to the EFNS guidelines, and recommendations are only marginally adhered to. Therefore this guideline should either be revised or physicians should focus on the EFNS guidelines. Therapy adherence, in patients with painful DPN, regarding pain medication is suboptimal.

INTRODUCTION

As one of the most common long-term complications of diabetes mellitus type 1 and type 2 diabetic polyneuropathy (DPN) affects respectively 13-17% and 5,5-35% of patients.[1] The best known type of diabetic polyneuropathy, distal symmetric polyneuropathy, is characterized by loss of sensory function, paraesthesia and pain in the affected limbs. This neuropathy is considered to be progressive and irreversible.[2]

In diabetic patients, neuropathic pain is a frequently occurring symptom with a prevalence of 15-35%.[3–5] It has a considerable impact on the quality of life as it undermines sleep, has a negative effect on emotional wellbeing and is associated with fear and depression.[6]
Prescribing and using a subsequent amount of pain medication brings a remarkable increase in the quality of life of these patients.[7] Pain medication prescribed in painful DPN is a temporary and symptomatic treatment and in consequence has no influence on the progression of loss of sensory function.

The Dutch Guideline for polyneuropathy, released in 2005, offers recommendations on choosing a specific medicine and dose (table 1).[1] Recommendations based upon more recent developments can be found in the "European Federation of Neurological Societies (EFNS) Guidelines on the pharmacological treatment of neuropathic pain" (2010).[8]

By means of osmosis hyperglycemia may lead to the formation of oedema in peripheral nerves. As a result compression of these nerves in narrow anatomical spaces such as the carpal or tarsal tunnel may occur. According to the 'double crush' hypothesis, damage of nerves as a result of metabolic changes leaves nerves more susceptible to compression.[9,10] Since 1992 this hypothesis was the basis for several studies investigating the effect of surgical decompression on sensibility and pain in patients with painful DPN.[9,11–14] Although these studies describe positive effects on pain, sensibility and balance, non were randomized controlled trails and therefore there is no substantial evidence supporting this treatment.[15]

The Lower Extremity Nerve Entrapment Study, a randomized controlled study, preformed in the University Medical Centre Utrecht, Dutch Trial registry number NTR 2344, investigated the effect of surgical decompression of the lower extremity nerves in patients suffering from painful DPN. Pain, sensibility, stability, quality of life, EMG results and echo graphic changes of the tibial nerve were studied.[16,17] As part

of this study the effect of surgical decompression on the use of pain medication was evaluated in retrospect. Secondary goals were to assess the adherence to the Dutch Guideline for polyneuropathy by physicians and to determine it's accuracy in respect to the EFNS Guidelines.

Table 1 Recommended order of treatment for painful DPN by "Richtlijn Polyneuropathie"

	Order of medication		Dosage	
			Minimum	Maximum
Dutch Guideline	1	Atriptyline §	25mg 1x/d	125mg 1x/d
	2	Carbamazepine §	200mg 1x/d	200mg 4x/d
	3	Phenytoin	150mg 2x/d	150mg 2x/d
	4	Valporic acid	200mg 3x/d	400mg 3x/d
	5	Tramadol ER	50mg 2x/d	200mg 2x/d
	6	Paroxetine §	10mg 1x/d	50mg 1x/d
	7	Gabapentin	300mg 1x/d	1200mg 3x/d
	8	Oxycodone CR	5mg 2x/d	60mg 2x/d
	9	Lamotrigine	25mg 1x/d	200mg 2x/d
	10	Capsaicin cream	apply 4x/d	apply 4x/d
	11	TENS *	30min 1x/d	30 min 1x/d
	12	Clonazepam	4mg 1x/d	4mg 2x/d
	13	Carbidopa/Levodopa	125mg 3x/d	125mg 3x/d
EFNS Guideline		Pregabalin	75mg 2x/d	300mg 2x/d
		Duloxetine	60mg /d	120mg /d
		Venlafaxine	150mg/d	225mg/d

Order of treatment in the Dutch Guideline was based upon; number needed to treat, number needed to harm, patient friendliness and price. § In elderly patients (>65 years) amitriptyline should be started at 10mg 1x/d, carbamazepine at 100mg 2x/d and paroxetine has a maximum dosage of 40mg once a day. * Not analysed in this study.

METHODS

Intervention

After receiving information through their physicians, 42 patients suffering from painful DPN (VAS>2) were included in the LENS. In- and exclusion criteria are shown in table

2. All 42 patients signed an informed consent. Within eight weeks of randomization patients underwent a unilateral decompression of the lower extremity nerves; the tibial nerve and three of its branches (the medial plantar nerve, lateral plantar nerve and lateral calcaneal nerve), the common fibular nerve, deep fibular nerve and the superficial fibular nerve. The contralateral leg was used as a control. The patients' diabetes specialist optimized the glucose levels.

Table 2 In- and exclusion critera LENS

Inclusion criteria
▪ VAS-score >2
▪ Positive Tinel sign of posterior tibial, and common peroneal nerve
▪ Ankle-brachial-index between 0,8-1,15 with a toe-brachial-index of ≥ 0,7
▪ Palpable pulsations at the posterior tibial artery and the dorsalis pedis artery
Exclusion criteria
▪ BMI >35
▪ General condition unsuitable for surgery
▪ History of ankle fractures or amputations proximal to the Lisfranc joints
▪ Ulcer on the foot
▪ Other causes for neuropathy (i.e. HIV, chemotherapy)

Prescriptions and use of pain medication

The prescriptions for neuropathic pain medication were obtained from the patients' pharmacy, for the period between 01-01-2005 and 01-08-2013. Prescriptions for dosage increase up to maintenance dose, as well as prescriptions lacking an exact dosage were not analyzed. At three, six and twelve months post-operative the difference in use of pain medication was assessed. Pre-operatively the use of pain medication was set as equal to 0, for each patient. At the three follow up moments the use of less, equal amounts or more pain medication was rated as respectively -100, 0 and 100.

The duration of use was calculated, from the start of the first prescription up until the ending of the final repeat prescription. Repeat prescriptions running until after 01-08-2013 were not included in the analysis. Prescriptions were compared to the daily dose, administration dose and administration frequency as recommended by the Dutch Guideline for polyneuropathy (table 1).[1] In case of pregabalin, duloxetine and

venlafaxine the recommendations from the EFNS Guideline were used as a reference (table 1).[8] Using an ANOVA repeated measures (with Bonferroni correction) statistical differences were calculated; a difference with an alpha <0,05 was considered to be significant.

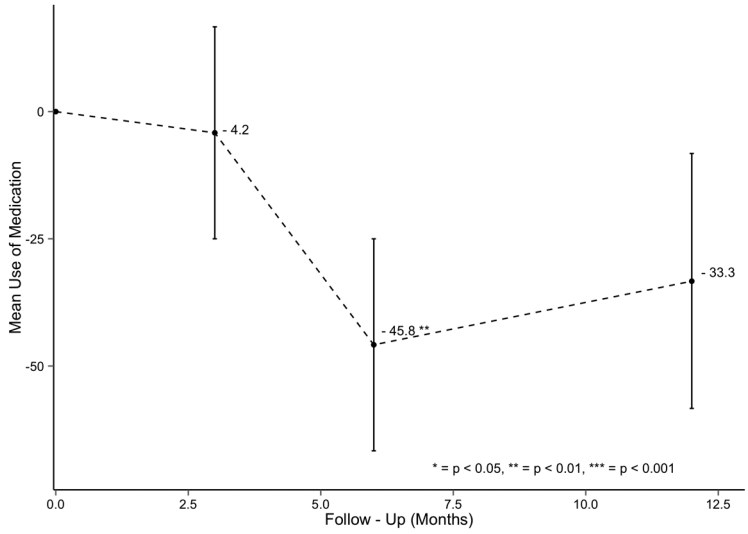
Therapy adherence

Therapy adherence was evaluated by use of the Medication Possession Ratio (MPR). The MPR is calculated by dividing the sum of the amount of days per repeat prescription by the total amount of days between the first and last repeat prescription (x100%). The MPR was calculated per patient (and per prescription) up until 12 months post-operative. Single prescriptions and patients using a medicine roll were excluded from the analyses. An MPR ≥80% is considered to be therapy adherent.[18] All statistical calculations were performed using SPSS Statistics 21 (IBM, Amsterdam).

RESULTS

Intervention

Of the 42 included patients, one patient was lost to follow up and one patient died due to a cause not related to the study. Two patients suffered from wound infection,



Graph 1 Use of medication at follow up; 3 months (p=1,000; 95%CI=-0,366-0,282), 6 months (p=0,001; 95%CI=-0.673--0,243), 12 months (p=0,104; 95%CI=-0,602--0,064).

which required antibiotic treatment, one of them was admitted to hospital to receive iv antibiotics. One patient had to be re-operated for a hematoma due to the use of anticoagulants.

Prescriptions and use of pain medication

Twenty-four patients used pain medication during the one year follow-up of this study. Six months post-operative there was a significant decrease in the use of pain medication compared to post-operative and three months post-operative, as shown in graph 1. The difference at three and twelve months post-operative was not significant.

From 01-01-2005 up until 01-08-2013, 25 patients used medication as described in the Dutch Guideline for polyneuropathy. In this period there was a total of 84 prescriptions of which 50 for medication mentioned in the Dutch Guideline. Phenytoin, lamotrigine and carbidopa/levodopa were not prescribed.

Amitriptyline was the most frequently used medicine, as it was used by 11 patients at some moment in time. Twenty-two of the prescriptions (44%) were not in correspondence with the guideline. Pregabalin was used by 22 patients where duloxetine was used by six and venlafaxine by four patients during this period. Remarkably nor pregabalin, duloxetine or venlafaxine are mentioned in the Dutch Guideline for polyneuropathy, but they are part of the 2010 EFNS Guidelines.[1,8] Yet in 10 cases (29% pregabalin was nog prescribed according the the recommendations, and 33% of the prescriptions for duloxetine and venlafaxine did not meet the

Table 3 Prescriptions compared to recommendations

Guidelines		Amount of prescriptions n (%)
Dutch Guideline for polyneuropathy	In accordance with recommendations	22 (44)
	Not in accordance with recommendations	28 (56)
EFNS Guideline	In accordance with recommendations	10 (29)
Pregabalin	Not in accordance with recommendations	24 (71)
EFNS Guideline	In accordance with recommendations	7 (33)
Duloxetine, venlafaxine	Not in accordance with recommendations	14 (67)

recommendations.[8] Table 3 shows the adherence to different guidelines.[1,8] Of the 25 patients using pain medication, seven patients (26%) received a dose below the minimum daily dose. In case of venlafaxine the maximum daily dose was exceeded in two of the four patients.
Sixty-nine prescriptions with a stop date before 01-08-2013 were analysed. The medication as mentioned in the Dutch Guideline for polyneuropathy was used for an average of 12 weeks. Pregabalin was used for an average of 68 weeks. Only carbamazepine, valporic acid and gabapentin were on average used for more than 3 months. Amytriptilin and Ocycodon CR were in respectively 42% and 43% of cases, used for duration under two weeks.

Therapy adherence

After exclusion of patients using a medicine roll and single prescriptions the MPR was calculated for 16 patients. The mean MPR showed therapy non-adherence at 79%, seven patients had an MPR<80%.

DISCUSSION

Although a previous study showed a significant VAS decrease throughout the follow-
60 up of the LENS only at six months after surgery did patients use significantly less pain medication compared to pre-operative as well as 3 months post-operative use.[17] At three and at 12 months after surgery the use of pain medication was not significantly reduced. A possible explanation for these late results could be that physicians waited three months for the results of the decompression and only then decided to lower medication.

At twelve months post-operative the use of pain medication increased again which correlates with a relative increase in VAS score.[17] Increasing pain medication is probably an easier step for patients, and physicians, than lowering pain medication. This could explain the relatively quick rise in the use of pain medication after the initial, late, reduction.

To reduce pain in diabetic polyneuropathy medication is the treatment of choice. Therefore it is of great importance to adequately prescribe and use pain medication. Although this study was preformed in a small research population, in 44% of the prescriptions, the recommendations of the Dutch Guideline for polyneuropathy were not adhered to. This was also the case in 29% of the prescriptions for pregabalin

and in 33% for duloxetine and venlafaxine. Of all patients 26% received a dose under the minimal daily dose. Furthermore, the therapy adherence for our study population was determined with a Medication Possession Rate (MPR) of 79%, which is suboptimal, since an MPR ≥80% is considered to be therapy adherent.[18] Even though, as mentioned earlier, painful diabetic polyneuropathy leads to a decrease in quality of life and adequate pain medication can increase the quality of life.[7]
The Dutch Guideline for polyneuropathy was released in 2005 and does not contain some of the more recent developments such as the use of pregabalin, duloxetine and venlafaxine. Recommendations for these medicines can be found in the EFNS Guidelines.[8,19] These more recent guidelines are composed in different ways en therefore differ greatly in their recommendations.[5] For Dutch physicians and patients revision of the Dutch Guideline for polyneuropathy would be appropriate. For this the EFNS Guidelines could be used as a reference.

One of this studies exclusion criteria, 'sufficient effect of pain medication (VAS 0-1)', could have contributed to a selection bias. This means that the results of this study cannot be extrapolated to all patients with painful diabetic neuropathy.

CONCLUSION

At six months post-operatively decompression of the nerves in the lower extremity in patients suffering from painful diabetic polyneuropathy leads to a decrease in the use of pain medication. Recommendations from the Dutch Guideline for polyneuropathy are incomplete and in need of revision based upon the EFNS Guideline. Prescriptions do often not meet the recommendations. Therapy adherence, in patients with painful DPN, regarding pain medication is suboptimal.

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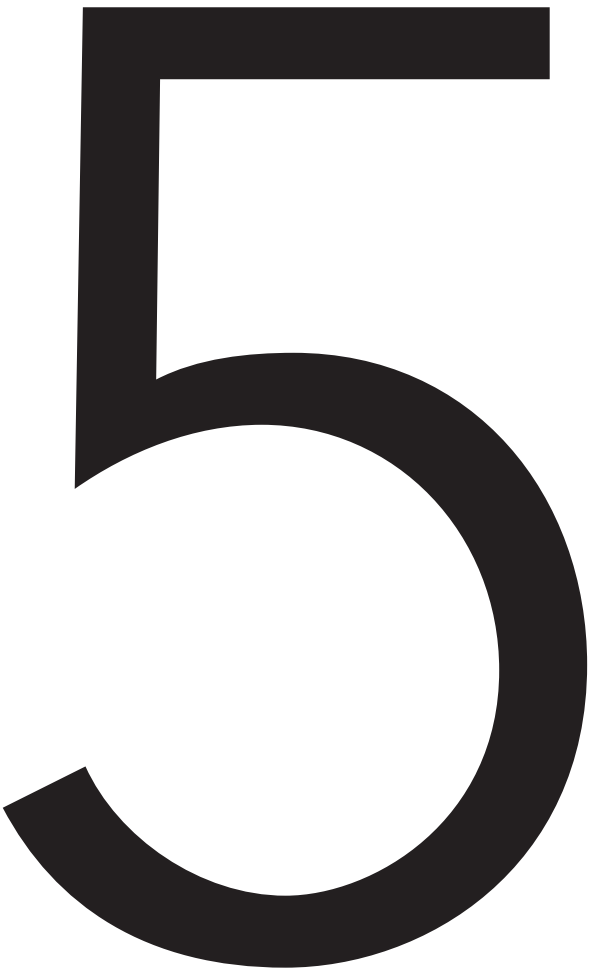

Ultrasound findings after surgical decompression of the tarsal tunnel in patients with painful diabetic polyneuropathy

A prospective, randomized, study

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Results were presented at a scientific meeting: Annual Dutch Diabetes Research Meeting, November 2013, Oosterbeek, the Netherlands

ABSTRACT

Objective: It has been hypothesized that the development of diabetic polyneuropathy (DPN) is due to swelling of the nerve, as well as thickening and stiffening of the surrounding ligaments, causing chronic compression of nerves. The authors aimed to examine the effect of surgical decompression of the tibial nerve on the mean cross sectional area (CSA).

Research Design and Methods: We performed a randomized controlled trial of 42 subjects with painful DPN diagnosed using the Diabetic Neuropathy Score (DNS). A computer randomised for the surgery arm of the study. A control group consisting 38 healthy subjects was included. An experienced sonographer measured the CSA and Thickness/Width (T/W) ratio of the tibial nerve, as well as the thickness of the flexor retinaculum.

Results: CSA is significantly larger in patients with painful DPN (8.4 mm^2± 3.9) than in controls (6.4 mm^2± 1.3) p=0.007. The T/W ratio in patients with painful DPN is 0,64 and in controls 0,59, p=0,03. Patients with DPN have a significantly thicker retinaculum (1.1 mm) than controls (0.84 mm), p<0.005. Mean follow-up was 28.2 weeks (range 23-45). Difference between baseline and follow-up in the operated leg was 1.49 mm^2 and in the control leg 1.82mm^2, p=0.674.

Conclusions: Decompression of the tibial nerve does not result in significant difference between baseline and follow-up in CSA using ultrasound between the operated and the control leg. US measurements show a significant increased CSA, a significant thicker retinaculum and a significant increased T/W ratio in patients with painful DPN compared to healthy controls.

INTRODUCTION

Polyneuropathy is a common complication in diabetes mellitus. The prevalence of neuropathy in patients with diabetes is about 30%. During the course of the disease up to 50% of the patients will eventually develop neuropathy.[1] Its clinical features are characterized by numbness, tingling or burning sensations and typically extends in a distinct stocking and glove pattern. Prevention plays a key role since poor glucose control is a major risk factor in the development of diabetic polyneuropathy.[1,2]
There is no clear definition for the onset of painful diabetic neuropathy. Different hypotheses have been formulated.

Hyperglycemia in diabetes can lead to osmotic swelling of the nerves, related to increased glucose conversion into sorbitol by the enzyme aldose reductase.[2,3] High sorbitol concentrations might also directly cause axonal degeneration and demyelination.[2] Furthermore, stiffening and thickening of ligamental structures and the plantar fascia make underlying structures more prone to biomechanical compression.[4–6] A thicker and stiffer retinaculum might restrict movements and lead to alterations of the nerve in the tarsal tunnel. Both swelling of the nerve and changes in the tarsal tunnel, might lead to nerve damage through compression.
Furthermore vascular changes may diminish endoneural bloodflow and oxygen distribution. Decreased blood supply in the (compressed) nerve might lead to ischemic damage as well as impaired nerve regeneration.

Several studies suggest that surgical decompression of nerves at narrow anatomic sites, e.g. the tarsal tunnel, is beneficial and has a positive effect on pain, sensitivity, balance, long-term risk of ulcers and amputations and quality of life.[3,7–10] Since the effect of decompression of the tibial nerve in patients with DPN has not been proved with a randomized clinical trial its contribution as treatment for patients with painful DPN is still controversial. Lee et al. observed that nerves in patients with diabetic neuropathy are swollen and their cross sectional area (CSA) is significantly greater than in patients with diabetes but without neuropathy.[11] Watanabe et al found that the CSA of both the tibial and median nerve in patients with diabetes is significantly increased compared to healthy controls.[12]

In this study we compare the mean CSA and any changes in shape of the tibial nerve before and after decompression of the tarsal tunnel using ultrasound in order to test the hypothesis that the tarsal tunnel leads to compression of the tibial nerve in patients with DPN.

RESEARCH DESIGN AND METHODS

Design: This single center randomised controlled trial was performed at the University Medical Center Utrecht between 2011-2013. This study is part of the 'Lower Extremity Nerve entrapment Study' (LENS).

Subjects: 42 patients, with diabetes mellitus type 1 or type 2, age 18- 85 years, were enrolled in the study. All subjects suffered from painful bilateral diabetic polyneuropathy, diagnosed using the Diabetic Neuropathy Score (DNS) and Diabetic Neuropathy examination (DNE), with a pain score >2 on the Visual Analogue Scale.[13–15] All patients had a positive Tinel sign of the tibial nerve at the malleoli and common peroneal nerve and a Ankle-Brachial Index (ABI) between 0.8 and 1.15 with palpable peripheral pulsations in the posterior tibial artery and dorsal pedal artery, the toe-brachial blood pressure ≥ 0.7.[16]

To compare the results with the normal population a control group consisting 38 healthy subjects, aged 18-90 years with no anamnestic medical history of a poor vascular state was enrolled. Subjects with previous ankle fractures were excluded as well as subjects with a Body Mass Index (BMI) >35 kg/m^2 or with other causes for neuropathy (e.g. HIV infection, chemotherapy). Demographic information of age, height, weight, BMI, sex was recorded for all subjects and for patients type of diabetes and duration of diabetes as well.

Randomisation: Randomisation was done by the computer, using a web based randomisation system. Subjects were matched for VAS, age and sex.

Protocol: The protocol of the LENS was approved by the Commitee of Medical Research Ethics of the University Medical Centre of Utrecht. The study was conducted according to the principles of the Declaration of Helsinki (version 22-10-2008) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO).

Surgery: All patients underwent decompression of the nerves of the lower limbs by the same surgeon (J.F.M.M.M). Decompression of the lower limb nerves included: the tibial nerve and its calcaneal, medial and lateral plantar branches at the ankle, the deep peroneal nerve over the dorsum of the foot, the common peroneal nerve near the head of the fibula and the superficial peroneal nerve at the calf.

Ultrasound: One single radiologist (I.K.) performed an ultrasound in both legs of the tibial nerve at the medial ankle, with the patient in supine position and the hip in exorotation, using a Philips iU22 with a 15-7 MHZ transducer. The short axis and long axis of the tibial nerve were measured at two specific locations: the medial plantar branch of thetibial nerve under the flexor retinaculum and the tibial nerve cranial to flexor retinaculum; 3 cm proximal to the malleolar calcaneal line. Measurements were performed by drawing an ellipse around the nerve, after which the program

calculated the minor and major axis and the CSA. (Figure 1) The thickness of the flexor retinaculum itself was measured as well. All measurements were performed twice. All subjects underwent ultrasonography at baseline and patients at six months follow-up as well. At baseline the radiologist randomly examined healthy controls and patients with DPN. At follow-up the radiologist was not blinded for the groups. CSA was calculated by major axis × minor axis × π × ¼. The Thickness/ Width ratio was determined by dividing the shortest axis by the longest axis.

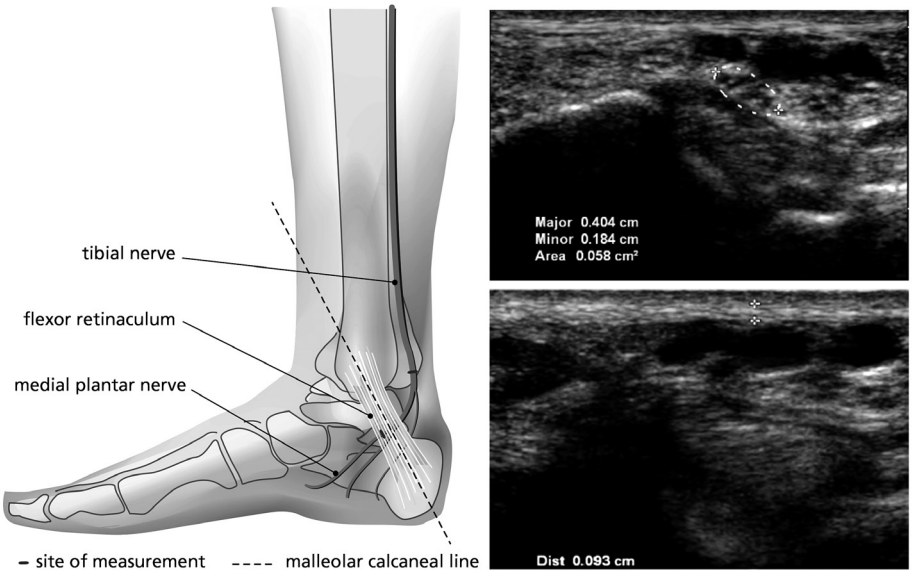

Figure 1 Location ultrasound measurements
Left panel: Ultrasound probe placement.
Right panel: Above is the tibial nerve shown in the ellipse with corresponding measurements. Below between the plus signs the flexor retinaculum is shown with corresponding measurement.

Statistical analysis: Analyses were performed in IBM SPSS statistics version 20.0. All measured values were compared between the patients with DPN and the controls. The mean and standard deviations for the CSA, T/W ratio and thickness of the retinaculum were assessed. To determine whether there were significant differences between the patients and controls an independent samples t-test was applied for continuous variables and the chi-squared test for categorical variables. For comparison of values within patients a paired t-test was applied. To identify potential confounding effects multivariate analysis was performed using MANOVA. To test the reliability of the ultrasound measurements intraclass correlation coefficients (ICC) were calculated using a two-way mixed model and consistency measures. Statistical significance was assessed as $p<0.05$. The current study was performed as a sub study from a randomized controlled trial. The sample size of the study was therefore not tailored to the current research question. Using 38 controls and 42 patients, we have 80% power to detect differences between the groups of 0.65 standard deviations (=Cohen's D) per variable, which is a medium size difference.

RESULTS

Patient characteristics

Thirty-eight control subjects and forty-two patients with painful DPN were enrolled in this study. The painful DPN patient's characteristics are summarized in Table 1. Patients with painful DPN were significantly taller, heavier and had a higher BMI and were more likely to be male.

Nerve appearance

Nerve size was significantly different between painful DPN group and controls (Table 2). Baseline data from 1 patient were missing and from 9 subjects, data were not obtained due to difficulties identifying the nerve.

The nerve size was significantly larger in the painful DPN group than in the control group in the tarsal tunnel, but different between the groups cranial to the tarsal tunnel. The thickness of the flexor retinaculum was significantly larger in subjects with painful DPN compared to controls (Table 2).

No significant differences in CSA in the tarsal tunnel at baseline and at follow-up after tarsal tunnel release were observed between the painful DPN group and the control group (Table 3). Follow-up measurements were obtained 23-45 weeks after surgery (mean 28.2 weeks). Data at baseline from 1 patient were missing. Follow up data of 4 patients were not obtained due to death (not study related), loss to follow up, disturbed architecture and Charcot foot.

Table 1. Patient characteristics

	Painful DPN Group ± SD (n=42)	Control group ± SD (n=38)	P-value
Age (years)	60.36 ± 11.34	61.29 ± 14.62	0.75
Height (cm)	175.74 ± 9.10	170.21 ± 8.05	0.002
Weight (kg)	89.76 ± 17.22	70.84 ± 11.71	<0.001
BMI (kg/m^2)	28.98 ± 4.70	24.40 ± 3.21	<0.001
Male (number (%))	26 (61.90)	11 (28.95)	0.003
Duration DM (years)	18.53 ± 11.96	-	-
Type 1 DM (number)(%))	10 (23.81)	-	-

Legend: Painful DPN = Painful diabetic polyneuropathy, SD = standard deviation, BMI = Body Mass Index, DM = Diabetes Mellitus

Table 2. Results patients with DPN compared to controls

	Location	Painful DPN group	Controls	Δ (95%CI)	P-value
Mean CSA	Tarsal Tunnel (mm^2) ± SD	8.45 ± 3.99	6.43 ± 1.32	2.02 (0.69;3.34)	0.004
	Cranial to Tarsal Tunnel(mm^2) ± SD	8.08 ± 3.48	9.20 ± 1.96	1.11 (-2.44;0.22)	0.10
T/W ratio	Tarsal Tunnel(mm^2) ± SD	0.64 ± 0.12	0.59 ± 0.12	0.06 (0.004;0.11)	0.03
	Cranial to Tarsal Tunnel(mm^2) ± SD	0.69 ± 0.10	0.65 ± 0.12	0.04 (-0.01;0.09)	0.13
Flexor Retinaculum		1.07 ± 0.22	0.84 ± 0.11	0.23 (0.15;0.3)	<0.001

Legend: Painful DPN = Painful diabetic polyneuropathy, Δ = difference, CI = Confidence Interval, CSA = mean cross sectional area, SD = Standard Deviation, T/W ratio = Thickness / Width ratio

The Thickness/Width (T/W) ratio of the nerve in the tarsal tunnel was significantly larger in patients with painful DPN compared with controls. The T/W ratio cranial to the tarsal tunnel was not significantly different between patients with painful DPN and controls (Table 2). Baseline data of 1 patient were missing and of 8 patients data were not obtained due to difficulties with nerve identification. The difference at baseline and at follow-up in the operated leg was not significantly different from the difference in the control leg (Table 3).

Table 3. Results differences at baseline and follow-up

		Difference baseline and follow-up in operated leg	Difference baseline and follow-up control leg	Δ (95%CI)	P-value
CSA	Tarsal Tunnel (mm^2) ± SD	1.49 ± 3.91	1.81 ± 4.10	0.32 (-1.88; 1.23)	0.67
T/W ratio	Tarsal Tunnel (mm^2) ± SD	- 0.004 ± 0.16	0.018 ± 0.14	0.02 (-0.03; 0.08)	0.42

Legend: + indicates a decrease at follow up and - an increase, CI = Confidence Interval,
 CSA = mean cross sectional area, SD = Standard Deviation, T/W ratio = Thickness / Width ratio

Multivariate analysis

Possible confounders that were taken into account were height, weight, BMI and gender. After correction for these factors with MANOVA differences between patients and controls remain significant (p=0.006). When also correcting for age the p value is 0.007.

Intraclass correlation coefficients

Ultrasound measurements of the patients were performed at baseline and follow-up and the controls were measured once. All measurements were performed by one single radiologist. The ICC for all the measurements in the right leg was 0.66. In the group of first 59 recorded measurements the ICC was 0.62 (good), while the ICC in the last 59 measurements was 0.76 (very good), suggesting an improvement of reliability of ultrasound in time.

DISCUSSION

Polyneuropathy is a common complication in diabetes. Because of diabetes mellitus and changes in glucose levels, nerves will swell due to osmosis and ligamental structures will be stiffer and thicker.[1,2,4,6,11] In this study we aimed to demonstrate the changes in these structures and the influence of decompression of the tarsal tunnel on the tibial nerve at the ankle using ultrasound.

First our study demonstrates that the CSA in the tarsal tunnel is significantly larger in patients with painful DPN (8.4 mm^2± 3.9) than in healthy controls (6.4 mm^2± 1.3) p=0.007. Variation in methods in the current literature give a variation in results and make the studies difficult to compare.[11,12,17–22] For example Lee et al. found an increased CSA using ultrasound in patients with DPN (24 mm^2) compared to healthy controls (12 mm^2).[11] Four studies evaluated healthy individuals and describe CSA's between 7.9 mm^2 and 13.7 mm^2. All the CSA's were measured at different locations in the ankle.[17–19,21] Riazi et al. compared persons with diabetes with and without polyneuropathy and found a significant increase in CSA in patients with diabetic polyneuropathy.[19] Watanebe et al. found a significant increase in CSA in persons with diabetes with a low conduction velocity compared to persons with a high conduction velocity and also in persons with diabetes with a low conduction velocity compared to healthy controls.[12] The CSA's found in patients with polyneuropathy varies between 15.0 mm^2 and 23.0 mm^2.[12,22]

Interestingly in our study decompression of the tibial nerve did not lead to a significant difference in CSA between baseline and follow-up between the operated and the control leg. At follow-up a decrease was found in both the operated leg as and the control leg. Since the effect was found in both legs it is unlikely to be due to the decompression. It might be explained by improved accuracy of measurements due to increasing experience of the radiologist. The reliability improved from 'good' in the measurements performed in the first half of the study to 'very good' in the measurements in the second half. The changes in CSA might be too small to be measurable with ultrasound. Also, there were follow up data missing of some subjects, which might have lead to non-significant outcomes.

Only one recent study of Zhang et al. evaluates the CSA in patients with DPN before and after decompressive surgery and compares this with persons with diabetes.[23] A significant swelling and increase of CSA in patients with DPN compared to patients with diabetes mellitus is noted. And a significant improved CSA after decompression is described. Exact numbers are not given and it is unclear what results are used for the comparison. Baseline characteristics of the patients are concise and the baseline

characteristics of the controls are missing. Therefore possible confounders are not taken into account, which may lead to inaccurate and misleading results.

Current study results in literature suggest that the CSA also differs at other locations than the tarsal tunnel. Liu et al. found a significantly increased CSA and T/W ratio in the sural nerve in persons with diabetes with neuropathy compared to persons with diabetes without neuropathy and to healthy controls.[24] The CSA of the median nerve in the carpal tunnel of patients with DPN was greater than without DPN and healthy controls.[25] CSA in patients with idiopatic carpal tunnel syndrome is also greater than in controls.[26] Besides the increased CSA in idiopatic carpal tunnel syndrome the nerve is also significantly more flattened, determined using US and MRI.[27] Based on these results a flattened tibial nerve might be expected although contrary to our findings. This might be explained by the larger amount of soft tissue and structures surrounding the tibial nerve leading to more diffusely spread pressure. In patients with idiopatic carpal tunnel syndrome and without diabetes mellitus release of the flexor retinaculum results in a decrease of CSA.[28–30] One study showed an increase of CSA and T/W ratio.[31] We found no studies evaluating the nerve with ultrasound after carpal tunnel release in patients with diabetes or DPN.
Cranial to the tarsal tunnel, the CSA is larger than in the tarsal tunnel. The measurement cranial to the tarsal tunnel was proximal to the bifurcation of the tibial nerve into the medial and lateral branch. No significant differences between patients with DPN and controls in CSA were found. This might be caused by a relatively large proportion of missing values (12.5%) due to difficulties identifying the nerve at this location using a 15-7 MHZ transducer. The use of a 12 MHZ transducer cranial of the tarsal tunnel might be helpful since the nerve is located deeper at that location than in the tarsal tunnel. Riazi et al. measured the CSA of the tibial nerve at three locations, respectively 1,2 and 3 cm proximal to the medial malleolus and found at 3cm a sensitivity of 0.69 and a specificity 0.77 for determining DPN.[19] Based on these findings we suggest future studies to measure at this location.

Diabetes mellitus and changes in glucose levels have been suggested to lead to peripheral nerve swelling due to osmosis.[2,3] Swelling would then lead to ischemia of the swollen nerve in the stiff tarsal tunnel the so called double crush theory.[32,33] Our increased CSA and T/W ratio outcome supports this theory. Diabetes mellitus also leads to thickening and stiffening of ligamental structures. This is concordant with our findings as well. Based on these two findings we might conclude that the tibial nerve at the ankle in patients with diabetes is more prone to compression due to nerve swelling and the thicker flexor retinaculum. Nevertheless we did not see

direct compression of the nerve using ultrasound. Recent reviews discussing the pathophysiology of painful diabetic neuropathy describe many potential mechanism e.g. changes in channel function, loss of spinal inhibitory control and increased thalamic vascularity. Compression of peripheral nerves is not mentioned.[34,35] A large RCT using electromyography to evaluate the conduction velocity at the ankle site before and after decompressive surgery in patients with painful DPN will be necessary.

There are a few limitations to our study. Peripheral nerves consist of multiple nerve fascicles surrounded with epineurium. The number and size of the fascicles depend on the type of nerve.[36] Fascicles that are oblique and not perpendicular to the ultrasound beam may remain undetected and the epineurium might lead to artefacts.[37] This might lead to a small underestimation of the CSA of the nerve using ultrasound and imaginably for all imaging devices using perpendicular beams e.g. MRI.
Since the patient group contains only patients with painful diabetic neuropathy our findings may not be generalizable to diabetic neuropathy in general.

CONCLUSIONS

This study with a large sample size and standardized sonographic imaging procedure with a good reliabilty, is the first randomized controlled trial which evaluates the effect of decompression of the tibial nerve on the cross sectional area. Although no effect on CSA after surgery was found, this study using ultrasound demonstrates a larger and swollen tibial nerve and thicker flexor retinaculum at the ankle in patients with diabetic polyneuropathy compared to healthy controls.

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Nerve conduction studies after decompression in painful diabetic polyneuropathy

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Submitted

ABSTRACT

Objectives: We investigated the influence of nerve decompression at potential entrapment sites in the lower extremity in painful diabetic polyneuropathy (DPN) on nerve conduction study (NCS) variables.

Methods: Forty-two patients with painful DPN were included in this prospective randomized controlled trial. Preoperative NCS were performed bilaterally. Each patient underwent unilateral surgical decompression of the tibial nerve, common, superficial and deep peroneal nerve. The contra-lateral side was used as control: within-patient comparison. One year post-operatively, the NCS were repeated. Univariate paired sample T-tests and a multivariate MANOVA were done to compare data.

Results: Univariate analysis: of the peroneal nerve, the distal CMAP amplitude measured at the EDB of the intervention legs decreased significantly from 3.1 (SD 2.6) to 2.1 (SD 1.8) mV ($p \leq 0.001$). The distal motor latency measured at the EDB of the intervention legs increased from 4.3 (SD 1.1) to 4.7 (SD 1.2) ms ($p \leq 0.01$). The area drop in the lower leg measured at the EDB of the control legs decreased from 11 (SD 11) to 6 (SD 8) % ($p \leq 0.05$). The distal CMAP amplitude measured at the anterior tibial muscle of the control legs increased from 4.8 (SD 1.5) to 5.2 (SD 1.3) mV ($p \leq 0.05$). For the tibial nerve, the distal CMAP duration decreased significantly from 5.1 (SD1.6) to 4.6 (SD1.8) ($p \leq 0.05$) in the control legs. The multivariate analysis showed no significance overall.

Conclusion: Decompression of nerves of the lower extremity in patients with painful DPN has no beneficial effect on NCS variables twelve months after surgery.

INTRODUCTION

Diabetic polyneuropathy (DPN) is the most common complication of diabetes mellitus and is an ever increasing health and economic issue in the western world.[1] DPN can present itself with symptoms of numbness or pain. Characteristic symptoms of painful DPN are itching and burning sensations in a symmetric stocking-glove distribution. Although the etiology is not fully elucidated, metabolic changes as well as microvascular damage may cause neurodegenerative changes. Treatment focuses on stabilizing glucose levels and, if necessary, medication for pain, which unfortunately does not slow down progression. In 1991, Dellon suggested that the altered metabolic state makes nerves more prone to compression at certain anatomic spaces.[2] Since 1992, several studies reported on the effect of nerve decompression on visual analogue scale (VAS) or on late complications such as ulceration and amputations. Very few researchers investigated the effect of decompression on nerve conduction study (NCS) results.[3–13] The few published reports showed promising results for relief of pain and restoration of sensorimotor function, but the investigations lacked a prospective randomized controlled design.[14]

The Lower Extremity Nerve entrapment Study (LENS) is a randomized controlled study, performed at the University Medical Center Utrecht. Outcomes included pain, sensibility, quality of life, echo graphic changes, and EMG results.[15,16]

The aim of this randomized controlled study is to investigate the effect of nerve decompression surgery on NCS results in patients with painful diabetic polyneuropathy.

Methods

Patients

Forty-two patients with painful diabetic neuropathy, assessed by the Diabetic Neuropathy Symptom Score (DNS) and Diabetic Neuropathy Examination (DNE), were included in the Lower Extremity Nerve entrapment Study (LENS), a randomized controlled study.[17,18] The study with Dutch Trial Registry number (NTR) 2344 was conducted according the principles of the Declaration of Helsinki and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO), and was approved by the local medical ethical committee.

All patients provided written informed consent.

Inclusion criteria were: age between 18 and 90; a positive Tinel sign of the tibial nerve and deep common peroneal nerve; Ankle-Brachial Index (ABI) between 0.8 and 1.15 with palpable peripheral pulsations of the posterior tibial artery and dorsal pedal

artery; a toe-brachial index of ≥0.7 (to minimize the risk for postoperative wound complications); patients had to understand written and spoken instructions.
Exclusion criteria were: Body Mass Index > 35 kg/m2; poor medical condition unsuitable for surgery; ankle fractures in the patient history; amputations proximal to the Lisfranc joint; active foot ulcers; satisfactory effect of pain medication (VAS 0 – 1) and other causes for polyneuropathy than diabetes mellitus.

Procedure

Patients were operated on one leg, using the other leg as a within-patient control. A web based randomization program was used to choose the leg receiving intervention. According to the procedure described by Dellon, the following nerves were decompressed: (i) tibial nerve and its calcaneal, medial plantar and lateral plantar branch at the medial ankle site, (ii) common peroneal nerve at the level of the fibular head, (iii) superficial peroneal nerve at the level of the lower leg, 10-14 cm above the lateral malleolus, (iv) deep peroneal nerve at the level of the first web.[3] All nerve decompressions were carried out by the same surgeon (JFMMM) with the patient in supine position under general anesthesia; a tourniquet was placed around the upper leg. After the operation a compression bandage was applied around the lower leg and patients were instructed to mobilize unburdened for 2.5 weeks. Pre- and 12 months post-operatively, the pain was evaluated with the Visual Analogue Scale (VAS).

NCS protocol

NCS were performed on both the intervention and control leg, using a Viking Select EMG apparatus. Pre-operatively and 12 months post-operatively NCS were performed by three specially trained and skilled technicians using a specially designed protocol. To ensure reproducibility between the first and second NCS, stimulation and recording sites were marked and photographed from a standard angle and distances between stimulation electrodes and between distal stimulation and recording electrodes were noted; furthermore, each patient was investigated by the same technician for both NCS. Prior to NCS, both legs were warmed in water at 37°C during 30 minutes; during NCS the legs were kept warm under an infrared heater set at 37°C.[19]
Motor NCS were performed in the (i) deep peroneal nerve (recording: extensor digitorum brevis muscle (EDB), stimulation: between malleoli, 3cm distal to the fibula head, and 5cm proximal to the fibular head), (ii) deep peroneal nerve (recording: anterior tibial muscle, stimulation: 3 cm distal and 5cm proximal to the fibular head), (iii) tibial nerve (recording: abductor hallucis muscle, stimulation: behind the medial

malleolus and popliteal fossa). Per nerve, we analyzed: amplitude, area, and duration of the negative compound muscle action potential (CMAP) part, distal motor latency (DML), motor nerve conduction velocity (MCV) per segment, and area-drop per segment calculated as: [(distal area - proximal area)100%]/[distal area].
Sensory NCS was performed for the superficial peroneal nerve (recording: one third of the distance from the lateral malleolus towards the medial malleolus, stimulation: 12 cm more proximally on the lateral aspect of the lower leg). We analyzed: amplitude of the sensory nerve action potential (SNAP) and sensory conduction velocity (SCV). SNAPs were averaged until they were clearly distinguishable from baseline.

Statistical Analysis

NCS of both the intervention leg and of the control leg were simultaneously performed before and after surgery. For individual patients, a change between the first and second NCS was considered meaningful if it exceeded intra-observer variability as established in a previous study.[20] Thus, changes had to exceed 1.5 mV for distal CMAPs, 5 μV for SNAPs, 5 m/s for MCV or SCV, and 25% for segmental CMAP changes reflecting conduction block or temporal dispersion.
NCS variables of pre- and postoperative intervention and control legs were compared using paired samples T-test.To compare the change in NCS outcomes for the intervention and control legs after the operation, we created Δ-values for both legs. The Δ-values were calculated by subtracting the post-operative values from the pre-operative values within the intervention and control legs respectively. The difference in Δ-values between the intervention legs and the control legs were then calculated in order to obtain paired samples. Using a multivariate analysis (MANOVA), this data was then analyzed to look for significant differences between the intervention legs and the control legs. Differences were considered significant when $p \leq 0.05$.
Data analysis was performed with statistical software (IBM SPSS Statistics, version 21.0 Armonk, NY: IBM corp.).

RESULTS

Of the 42 patients who were initially included, one was lost to follow-up and another patient died due to an unrelated cause before the end of the study. The remaining 40 patients were investigated in this study. Of these 40 patients, 2 had an infection of the wound at the ankle site; both of them were treated with antibiotics, one of them was re-admitted to the hospital. A third patient had to be re-operated for a hematoma due to the use of anticoagulants.

The mean DNE and DNS scores were 8 and 4 respectively. At baseline, the VAS was 6.1 (95% Confidence Interval (CI) 5.5 – 6.7) for both the intervention and control legs, and the mean HbA1c was 57.3mmol/mol. Baseline characteristics are summarized in table 1.

One year after operation, VAS had significantly decreased in both the intervention and control legs to 3.5 (95% CI 2.5 – 4.4) and 5.3 (95% CI 4.4 – 6.2 ($p<0.001$)) respectively.[16] The mean HbA1c was 59.5mmol/mol (95% CI 54.6 – 64.6).

NCS outcomes between the intervention and control legs are summarized in (Table 2).

At baseline, the intervention legs did not differ from the control legs.

For the univariate analysis, paired sample T-tests were performed for each individual parameter.

For the peroneal nerve: distal CMAP amplitude measured at the EDB of the intervention legs decreased significantly. The distal motor latency measured at the EDB of the intervention legs increased significantly. The area drop in the lower leg measured at the EDB of the control legs decreased significantly. The distal CMAP amplitude measured at the anterior tibial muscle of the control legs increased significantly.

When comparing intervention and control legs, the post-operative distal CMAP amplitude was significantly higher in the control legs.

For the tibial nerve, the distal CMAP duration decreased significantly in the control legs.

To analyze the overall effect of the decompression, a multivariate analysis of variance (MANOVA) was performed on all variables; no significant difference in NCS outcome was noted between intervention and control legs ($p=0.120$).

Univariate analysis results were therefore redundant.

Table 1. Baseline characteristics, n (either % or SD)

Variable	Participants, N = 40
Male (%)	26 (65 %)
Female (%)	14 (35 %)
Age, mean years (±SD)	61.2 (± 10.96)
BMI, mean kg/m²(±SD)	29.3 (± 4.27)
Diabetes mellitus	
Type 1	10 (25 %)
Type 2	30 (75 %)
Duration DM, mean years (±SD)	19.5 (± 12.2)
HbA1c,mean mmol/mol (±SD)	57.3(± 13.8)
Surgical decompression	
Right leg (%)	18 (45 %)
Left leg (%)	22 (55 %)

Table 2.

		Intervention legs			Control legs		
		Pre-operative (±SD)	Post-operative (±SD)	p-value†	Pre-operative (±SD)	Post-operative (±SD)	p-value†
Peroneal nerve	**m. extensor digitorum brevis**						
	Distal CMAP amplitude (mV)	3.1 (2.6)	2.1 (1.8)	***	3.4 (2.7)	2.9 (2.4)	*ns*
	Distal CMAP duration (ms)	4.9 (1.5)	4.9 (1.3)	*ns*	4.5 (1.6)	4.6 (1.7)	*ns*
	Distal motor latency (ms)	4.3 (1.1)	4.7 (1.2)	**	4.1 (1.4)	4.4 (1.3)	*ns*
	Motor conduction velocity: lower leg (m/s)	38 (9)	37 (8)	*ns*	37 (12)	37 (10)	*ns*
	Motor conduction velocity: fibular head (m/s)	41 (10)	41 (10)	*ns*	42 (18)	43 (15)	*ns*
	Area drop: lower leg (%)	12 (14)	9 (15)	*ns*	11 (11)	6 (8)	*
	Area drop: fibular head (%)	4 (7)	6 (12)	*ns*	5 (11)	7 (12)	*ns*
	m. tibialis anterior						
	Distal CMAP amplitude (mV)	5.0 (1.5)	4.9 (1.4)	*ns*	4.8 (1.5)	5.2 (1.3)	*
	Motor conduction velocity (m/s)	54 (13)	54 (14)	*ns*	53 (12)	54 (10)	*ns*
	Superficial peroneal nerve						
	SNAP amplitude (mV)	3.0 (4.9)	2.3 (4.5)	*ns*	3.7 (5.0)	2.6 (3.5)	*ns*
	Sensory conduction velocity(m/s)	23 (21)	19 (21)	*ns*	22 (20)	21 (21)	*ns*
Tibial nerve	Distal CMAP amplitude (mV)	4.7 (4.0)	4.1 (3.9)	*ns*	4.3 (3.7)	4.1 (3.6)	*ns*
	Distal CMAP duration (ms)	4.8 (1.7)	5.0 (1.5)	*ns*	5.1 (1.6)	4.6 (1.8)	*
	Distal motor latency (ms)	4.3 (1.4)	4.5 (1.4)	*ns*	4.3 (1.3)	4.1 (1.6)	*ns*
	Motor conduction velocity(m/s)	36 (13)	37 (10)	*ns*	36 (12)	35 (13)	*ns*
	Area drop (%)	13 (16)	16 (18)	*ns*	13 (12)	12 (12)	*ns*

Legend: p-values: * = p≤0.05; ** = p≤0.01; *** = p≤0.001, *ns* = no significance, p> 0.05;
CMAP = compound muscle action potential; SNAP = sensory nerve action potential. p-value† = measured using paired sample T-test.NB: when comparing intervention and control legs, the post-operative distal CMAP amplitude measured at the EDB was found to be significant (p≤0.01).

DISCUSSION

As part of the LENS study, we investigated the influence on NCS variables of nerve decompression at potential entrapment sites of lower extremity nerves in painful diabetic neuropathy.
Using multivariate tests, our results showed no significant change between intervention legs and control legs.
Other, non-randomized studies showed VAS decrease after decompression of lower extremity nerves in patients with painful DPN, suggesting direct nerve compression an etiological factor for painful DPN. Contrary to results in these previous studies, our results suggested that nerve decompression had no influence on NCS variables.[3,12]
These findings correspond with the results of an ultrasound study of the tibial nerves in which we showed that decompression of the tarsal tunnel did not influence the cross sectional area of the tibial nerve.[15]
Since the study could not be blinded accurately, a sham procedure was initially discussed but was rejected on ethical grounds. However, a strict NCS protocol was used to help keep bias at a minimum.
The results of our study revealed several, albeit small differences in NCS variables when using univariate paired sample T-test analysis. However, when using a multivariate MANOVA analysis, no significance was observed.
Although the postoperative worsening in some NCS variables in our study is likely to be clinically irrelevant, the decline in peroneal nerve CMAP amplitude suggests that the nerve itself might even be adversely affected by the surgical decompression.

The improvement in VAS following decompression seems to be attributable to other factors than to those measurable with NCS or ultrasound.[15] With NCS, large myelinated axons are tested, while the function of small non-myelinated fibers have to be examined physically; for example Quantitative Sensory Testing (QST) might be a useful tool for detection of small fiber threshold alterations for thermal pain and sensation in future studies to surgical decompression.[21] It would also be interesting to investigate (micro)vascular alterations after surgical decompression in this population.
Other studies on the effect of nerve decompression on NCS variables in DPN showed beneficial effects. A prospective cohort study of 560 patients with diabetic polyneuropathy found significant improvement in nerve conduction velocity of the posterior tibial, common peroneal and superficial peroneal nerves.[12] Other variables such as DML, CMAP amplitude, CMAP duration, or SNAP amplitude were not reported. Furthermore, nerves were cooled to 30 °C in a water bath, thereby

decreasing MCV, SCV, and increasing DML.[19] For these reasons our NCS results cannot be compared to that study. Another prospective cohort study included 60 patients with both diabetes mellitus type 1 and type 2.[3] Improvement in unspecified electrodiagnostic tests was found in 68% of patients, and no change in 30% of patients. Only excellent, good, fair and poor results were described but no results for NCS variables. Both upper and lower limb nerves were investigated, but the study was not stratified accordingly.[3] The study described better results after decompression of nerves in the upper extremities than in lower extremity nerves, possibly related to the higher conduction velocity in upper limb nerves.[22,23]
In conclusion, decompression of lower extremity nerves in patients with painful DPN has no effect on NCS variables twelve months after surgery.

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7

Effect of surgical decompression of nerves in the lower extremity on static balance in patients with painful diabetic neuropathy

A randomized controlled trial

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Submitted

ABSTRACT

Objective: To investigate the effect of decompression of nerves in the lower extremity in patients with painful diabetic polyneuropathy on static balance using a sensitive pressure mat system.

Design: Non-blinded randomized controlled trial.

Setting: Single center study performed at the University Medical Center Utrecht between 2010-2013.

Subjects: Patients with painful diabetic polyneuropathy assessed with the Diabetic Neuropathy Symptom score and Diabetic Neuropathy Examination between 18-90 years. Exclusion criteria were: physical problems leading to instability, BMI>35 kg/m2, ankle fractures in history, amputations proximal to Lisfranc joint, active foot ulcer(s), severe occlusive peripheral vascular diseases.

Intervention: Unilateral surgical nerve decompression at four sites in the lower extremity, the contralateral limb was used as control (within-patient comparison), with one year follow-up.

Main measures: Preoperatively and 6 and 12 months postoperatively, weight bearing and five variables of sway of the center of pressure were measured with a pressure mat with eyes open and eyes closed. T-test was used for evaluation of postoperative results.

Results: 39 Patients met inclusion criteria and were enrolled for stability testing. Postoperatively no significant differences for sway variables and weight-bearing were seen compared to preoperative measurements.

Conclusions: There is no evidence that surgical decompression of nerves of the lower extremity influences stability within one year after surgery in patients with painful diabetic polyneuropathy.

INTRODUCTION

Diabetic polyneuropathy is a bilateral, distal, symmetrical neuropathy and one of the most common complications of diabetes mellitus. Clinical signs and symptoms of diabetic polyneuropathy affect up to 50% of patients with diabetes.[1,2] Initially it is characterized by loss of sensory function with itching or burning sensations, numbness and pain. Furthermore, motor nerve involvement can lead to muscle atrophy and alteration of muscle balance in the foot, resulting in unreliable static stability and increased risk for falling.[3–6] Medication is helpful in treatment of pain in a limited number of patients with diabetic neuropathy, but does not prevent progression.

Multiple non-randomized studies on the effect of decompression of nerves in patients with diabetic polyneuropathy have been reported, since Dellon treated the first patients in 1992.[7–10] Despite the lack of evidence, they all show promising results on pain, sensibility and nerve conduction studies.[11–13] Furthermore, positive influence of decompression on sway in patients with peripheral neuropathy was suggested in an exploratory case study in 2006.[14]

The Lower Extremity Nerve entrapment Study is a randomized controlled study performed at the University Medical Center Utrecht. Outcomes included pain, sensibility, quality of life, echografic changes and nerve conduction study results.[15,16] The aim of this randomized controlled study was to investigate the effects of lower extremity nerve decompression on postural stability in painful diabetic polyneuropathy.

METHODS

Design

Between 2010 and 2013 this randomized controlled study was performed at the University Medical Center Utrecht, as part of the Lower Extremity Nerve entrapment Study (LENS) and was approved by the Medical Research Ethics Committee (METC). The study was conducted according to the principles of the Declaration of Helsinki (version 22-10-2008) in accordance with the Medical Research Involving Human Subjects Act (WMO), Dutch Trial Registry number NTR 2344.

Participants

Patients with painful diabetic polyneuropathy diagnosed with the Diabetic Neuropathy Symptom score (DNS) and Diabetic Neuropathy Examination (DNE) [17–19],

age 18-90, with diabetes mellitus type 1 or type 2, were recruited in the outpatient clinic of the internist specialized in diabetes mellitus. Patients were selected for surgery when they met all the in- and exclusion criteria. All patients gave informed consent to participate in the study.
In- and exclusion criteria are summarized in Table 1.

Table 1. In- and exclusion criteria Lower Extremity Nerve entrapment Study

Inclusion criteria
▪ Pain score measured with Visual Analogue Scale (VAS) >2*
▪ Positive Tinel sign of posterior tibial, and common peroneal nerve
▪ Ankle-brachial-index between 0,8-1,15 with a toe-brachial-index of ≥ 0,7
▪ Palpable pulsations at the posterior tibial artery and the dorsalis pedis artery
Exclusion criteria
▪ BMI >35 kg/m2
▪ General condition unsuitable for surgery
▪ History of ankle fractures or amputations proximal to the Lisfranc joints
▪ Ulcer on the foot
▪ Other causes for neuropathy (i.e. HIV, chemotherapy)

*The VAS score is a straight line of 10 centimeters in length using a 10-point scale ranging for 0-10 with 0 being no perceptible pain and 10 being intolerable pain.

Intervention

Patients underwent a unilateral surgical procedure, previously described by Dellon, i.e. of the tibial nerve and its three branches at the ankle site, the common peroneal nerve near the fibular head, the superficial peroneal nerve at the lateral lower leg and the deep peroneal nerve in the first web.[8] A web based computer system was used for a balanced randomization on age, sex and pain score. Within eight weeks of randomization, one single surgeon (JFMMM) performed the surgical decompression under general anesthesia with a tourniquet around the upper leg. The contralateral leg was used as control: within-patient comparison.

Outcome measures

The primary outcome for this study is patients' static stability, which was tested preoperatively, at 6 and 12 months of follow up with eyes open and eyes closed.

The Matscan Measurement System[a] was used for all balance tests. Barefoot plantar pressures were measured during 30 seconds. 900 individual sway frames were recorded and merged into a movie.
To precisely measure the static balance, the center of pressure was determined.[14] Sway was reflected by five variables i) the total length of the path travelled by the center of pressure (Distance), ii) the maximum anterior-to-posterior center of pressure movement (AP length), iii) the maximum left to right (or medial to lateral) center of pressure movement (LR length). iv) An elliptical area in which the center of pressure trajectory moved during the measurement was defined 'Area' and v) 'Variability' was defined as the standard deviation of individual movements of the center of pressure between frames during the recording.
Furthermore 'weight-bearing' was the mean amount of weight (in percentage) a patient put on one leg in 30 seconds compared to contralateral leg.

In total, two static stability measurements were conducted, including standing on bilateral legs, with eyes open and with eyes closed. All subjects were given the same instructions and all tests were performed under the same conditions by one single examiner masked for operation side. The Sway Analysis Module software version 6.3 (Tekscan Inc., Boston, MA, USA) was used for extracting and processing data.

Statistical analysis

Data analysis was performed with statistical software (IBM corp. SPSS Statistics, Version 21.0. Armonk, NY, USA). For the descriptive variables, significance of differences was assessed with the Student's unpaired t-test. Chi square tests were used for categorical variables.
A within subject comparison was done for comparison between preoperative and postoperative measurements with eyes closed or open. Therefore, paired versions of the t-test were performed. Significance was assessed two-sided for all variables. Outcomes with $p<0.05$ were considered significant. For determining the significance of the difference between two percentages the z-score was calculated with the following formulas:

$$\mathbf{Z} = \frac{P1-P2}{s_{P1-P2}} \qquad s_{P1-P2} = \sqrt{\frac{P1 \times Q1}{n1} + \frac{P2 \times Q2}{n2}}$$

Z-score >1.96 was considered significant.

Sample size calculation

Sample size calculation was based on the primary outcome for the Lower extremity nerve entrapment study, which was the visual analogue score for pain (VAS), a continuous response variable. The difference in pre- and postoperative pain score was estimated to be 1.5, based on the few available non-placebo controlled trials by Karagoz and Rader.[8, 13] The legs were considered matched pairs. Therefore, the study population needed to be 38 subjects to reject the null hypothesis that the population means of the experimental and control limb were equal with probability of 0,9. The Type I error probability associated with this test of this null hypothesis was 0,05. The assumed correlation coefficient was 0. Anticipated on 10 % of lost to follow-up, the total calculated sample size was 42.

RESULTS

Participants

Of the original 42 patients of the Lower Extremity Nerve Entrapment cohort, three patients were excluded because it was not possible for them to stand barefoot

Table 2. Baseline characteristics

Number of patients	39
Age at inclusion (years)	61.3 ± 10.6
Gender, n = male (%)	24 (61.5)
Height (cm)	175.2 ± 9.8
Weight (kg)	88.2 ± 15.0
BMI (kg/m^2)	28.7 ± 4.1
Diabetes mellitus type, n = type 2 (%)	30 (76.9)
History of diabetes (years)	11.2 ± 9.9
Pain score, VAS	6.1

Presenting numbers are mean ± SD, unless specified otherwise

Table 3. Mean sway measurements in patients with painful diabetic polyneuropathy preoperative and postoperative with eyes open and eyes closed

	preoperative	6 months	12 months
Eyes open (N)	39	36	35
Distance	35.13 (21.42)	38.37 (18.19)	37.32 (12.46)
Variability	0.036 (0.044)	0.04 (0.06)	0.03 (0.013)
Area in cm^2	2.81 (3.65)	3.18 (4.5)	2.69 (2.12)
AP length	2.68 (1.61)	2.81 (1.4)	2.74 (0.87)
LR length	2.0 (1.99)	2.23 (2.15)	1.97 (1.25)
Operation side left (N)	21	20	20
WB left leg %	49.8	50.0	50.8
Operation side right (N)	18	16	15
WB right leg %	47.7	45.2	47.9
Eyes closed (N)	39	36	35
Distance	51.37 (35.7)	50.81 (27.55)	54.19 (29.9)
Variability	0.047 (0.04)	0.04 (0.02)	0.05 (0.03)
Area in cm^2	4.14 (6.43)	3.48 (3.28)	4.08 (4.89)
AP length	3.28 (1.54)	3.36 (1.54)	3.58 (1.83)
LR length	2.61 (3.10)	2.08 (1.17)	2.07 (1.39)
Operation side left (N)	21	20	20
WB left leg %	49.4	50.4	50.35
Operation side right (N)	17	16	15
WB right leg %	46.9	45.8	48.2

Presenting numbers are mean in cm (standard deviation), unless specified otherwise. Distance = total length of the path travelled by the center of pressure (COP). Variability = standard deviation of individual movements of the COP between frames during the recording, AP = anterior to posterior COP movement, LR = left to right COP movement. DPN= subjects with diabetic painful peripheral neuropathy, WB= weight bearing

for prolonged periods of time (e.g. Charcot foot). There were three postoperative complications: one patient underwent reoperation for a hematoma due to the use of anticoagulants. Two patients had an infected wound, and were treated with antibiotics. Of these two, one was re-admitted to the hospital for intravenous treatment. Four patients did not complete the total follow up period. One patient died due to a cause unrelated to the study, two patients missed their control visits.

Table 4. Sway measurements: preoperative measurements compared to postoperative measurements

	Pre versus 6 months	Pre versus 12 months
Eyes open (N)	36	35
Distance	2.08 (-10-5.8)	0.85 (-7.7-5.98)
Variability	0.005 (-0.02-0.01)	0.005 (-0.01-0.02)
Area in cm^2	0.28 (-2.3-1.7)	0.23 (-1.2-1.6)
AP length	0.04 (-0.74-0.66)	0.04 (0.3--5.6)
LR length	0.25 (-1.22-0.72)	0.02 (-0.72-0.76)
Eyes closed (N)	36	35
Distance	0.64 (-9.6-10.9)	2.80 (-11.09-5.49)
Variability	0.004 (-0.007-0.016)	0.00 (-0.01-0.01)
Area in cm^2	0.55 (-1.58-2.68)	0.02 (-2.26-2.21)
AP length	0.10 (-0.77-0.56)	0.33 (-0.86-0.21)
LR length	0.44 (-0.57-1.48)	0.48 (-0.52-1.47)

Presenting numbers are mean differences of preoperative measurements minus Postoperative measurements in cm with eyes open and eyes closed in cm (95% confidenceinterval). No significant p value < 0.05 in this table. Distance = total length of the path travelled by the COP, Variability = standard deviation of individual movements of the COP between frames during the recording, AP = anterior to posterior COP movement, LR = left to right COP movement.

One patient missed the last control visit. Baseline characteristics are shown in Table 2.

Sway measurements

All results of the mean sway measurements are summarized in Table 3.
Postoperatively mean sway differences changed slightly, though not significant (Tables 3 and 4). For weight bearing no significant differences were calculated between pre- and postoperative percentages, all z-scores were below 1.96.

Visual perturbations

Visual perturbations (eyes closed) increased sway of the center of pressure for all variables, except left to right length 6 months after surgery. Preoperatively, this increase was more evident and statistically significant in four out of five sway variables. Six months after surgery, only one sway variable, Distance, was significantly longer (Table 5). At one year follow up, mean sway differences were more comparable to preoperative measurements, three out of five sway variables were significantly increased in patients with eyes closed (Distance, Variability and Anterior-Posterior length). For weight-bearing no significant differences were seen between eyes open and eyes closed.

Table 5. Mean differences of sway measurements between eyes closed and eyes open

	preoperative	6 months	12 months
N	39	36	35
Distance	16.24 (7.745-24.725)[a]	12.48 (2.87-22.08) [a]	16.87 (7.83-25.91) [a]
Variability	0.01 (-0.008- 0.02)	0.00 (-0.019-0.020)	0.015 (0.007-0.0240) [a]
Area in cm^2	1.33 (0.2-2.45) [a]	0.30 (-2.26-1.67)	1.39 (-3.15-0.268)
AP length	0.61 (0.13-1.08) [a]	0.55 (-1.23-0.14)	0.84 (0.27-1.42) [a]
LR length	0.61 (0.12-1.01) [a]	0.15 (-0.66-0.96)	0.09 (-0.66-0.47)

Presenting numbers are mean difference of measurements of eyes closed minus eyes open in cm. (95% confidence interval). [a] = significant p value < 0.05. COP = center of pressure Distance = total length of the path travelled by the COP, Variability = standard deviation of individual movements of the COP between frames during the recording, AP = anterior to posterior COP movement, LR = left to right (lateral) COP movement.

DISCUSSION

The aim of this randomized controlled study was to evaluate the effect of surgical decompression of the nerves in the lower extremity on static balance in patients with painful diabetic polyneuropathy. We hypothesized that nerve decompression would influence the nerve function positively, with a decrease in sway as a consequence. However, no improvement of postural stability was observed.
Furthermore, this study confirmed that visual perturbations (eyes closed) increase sway in patients with painful diabetic polyneuropathy.

One single surgeon performed all decompressions, which minimized performance bias. Nevertheless the outcome for this present study may be influenced by a surgical learning curve, though it did not play a role for the significant decreased pain score, measured with VAS, throughout the follow-up of the Lower Extremity Nerve entrapment Study.[15] By all means surgery had not influenced the stability of the patients negatively.

Missing data, may have led to selection bias, because this conceivably has filtered out the most unstable patients and may have resulted in underestimating sway in our study population.

The within-patient comparison design of the study provides evident information on many trial endpoints e.g. pain, nerve conduction studies and sensibility. However, in static balance, the somatosensory system is considered responsible for the majority of postural control.[20] Therefore, during bilateral stance, both feet contribute to the postural stability.

A previous non-randomized study investigated the effect of unilateral decompression of nerves on stability with the Matscan Measurement System[a] in patients with neuropathy of different origins. An, albeit non-significant, trend for improvement of sway after unilateral or bilateral decompression was reported.[14] We cannot confirm these findings. Though the results of this study are not applicable for all patients with diabetic polyneuropathy since only patients with painful diabetic polyneuropathy were included. Besides, it is conceivable to forecast an improvement of stability in patients who will be operated on both legs.

The influence of painful symmetrical diabetic neuropathy in the lower extremities on static balance is clear.[21–23] Patients with diabetic polyneuropathy sway more than patients with diabetes mellitus but without polyneuropathy and closure of eyes

will influence stability negatively.[20] In our population, while eyes closed, the sway increased as well and probably more than in patients without polyneuropathy, because of the subjects' poor somatosensory function. This makes patients even more dependent on the visual system for correction of instability. Unfortunately unilateral decompression of the nerves of the lower extremity in patients with painful diabetic polyneuropathy did not contribute to a more stable stance in this vulnerable population.

In conclusion, the results of this randomized controlled trial indicate that there is no evidence that unilateral decompression of nerves in the lower extremity influences postural stability in patients with painful diabetic polyneuropathy.

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8

The effect of lower extremity nerve decompression on health related quality of life and perception of pain in patients with painful diabetic polyneuropathy

A prospective randomized trial

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Submitted

ABSTRACT

Background: Painful diabetic polyneuropathy (DPN) has a profound impact on health related quality of life (HRQoL). To study the effect of neuropathy on HR-QoL, the 36-Item Short-Form Health Survey (SF-36) and EuroQol 5 dimensions (EQ-5D) questionnaires are frequently used instruments. Surgical decompression of lower extremity nerves in patients with painful DPN is described as possible treatment for this very common complication of diabetes mellitus. The goal of this study was to assess whether surgical decompression of nerves of the lower extremity in patients with DPN would have an effect on HRQoL and to determine minimal clinically important differences (MCID) in pain- and quality of life scores.

Methods: The design was a randomized controlled trial in which 42 patients with painful DPN underwent unilateral decompression of lower extremity nerves on their left or right leg, using the other leg as control, with a 12 months follow-up. Decompression was performed at the tibial, common peroneal, superficial peroneal and deep peroneal nerve. Preoperatively and at 6 and 12 months postoperatively, a visual analog scale (VAS) for pain, SF-36 and EQ-5D questionnaires were filled out. Additionally, an anchor question was administered, asking patients what effect surgery had on their complaints.

Results: At 12 months follow up the VAS was significantly reduced, but decompression of lower extremity nerves did not significantly alter quality of life scores. An MCID for VAS reduction was determined at 2.9, this threshold was reached by 42.5% of the study population.

Conclusions: Decompression of nerves of the lower extremity in patients with painful DPN does not influence the HRQoL, it manages to achieve a clinically meaningful reduction of pain in approximately 42.5% of the patients. It can therefore be considered as a treatment option in patients who do not adequately respond to pain medication.

INTRODUCTION

Diabetic polyneuropathy (DPN) is a common complication of diabetes mellitus, affecting up to 50% of the patients.[1] The symptoms are characterized by loss of sensory and motor nerve function and often by painful sensations in the affected limbs.

Loss of nerve function and occurrence of pain in the leg make that DPN has a profound impact on health related quality of life (HRQoL).[2–4] To study the effect of neuropathy on HR-QoL, the 36-Item Short-Form Health Survey (SF-36) and EuroQol 5 dimensions (EQ-5D) questionnaires are frequently used instruments.[2–10]

The etiology of nerve damage as complication of diabetes mellitus is thought to be progressive and irreversible but is incompletely understood. Changes in the metabolic state lead to swelling of nerves, which makes them more vulnerable.[11–13] In combination with anatomic narrowed passages it may lead to compression of nerves.[14]
Tight glucose control is of utmost importance to minimize the risk for complications in diabetes mellitus including DPN. Medications, such as tricyclic antidepressants or gamma-aminobutyric acid analogues, are the first choice of treatment in painful DPN, unless there are contra-indications. A more definitive treatment is desirable. Although different studies on the effect of decompression of nerves in the lower extremity in DPN reported promising results for pain relief, a pilot study in six patients by Nelson and Little remarkably showed no significant differences in HRQoL measured with the SF-36 after surgical decompression of lower extremity nerves in patients with DPN compared to control groups.[15–23]

A Minimal Clinical Important Difference (MCID) can help to ascertain if a statistically significant response is meaningful to actual patients. It represents the smallest improvement considered worthwhile for a patient.[24] In painful DPN, a MCID for pain score measured with the Visual Analogue Scale (VAS), may specify the effect of treatment.

The aim of this study was to assess the effects of surgical decompression on the HR-QoL in patients with painful DPN, both measured with the SF-36 and EQ-5D instruments, as well as the MCID for the VAS, EQ-5D and SF-36 domains in a randomized controlled trial.

MATERIALS AND METHODS

This randomized controlled study was carried out as part of the Lower Extremity Nerve entrapment Study (LENS), at the University Medical Center Utrecht between 2010 and 2013. This study was conducted according to the principles of the Declaration of Helsinki as revised in 2008 and in accordance with the Dutch Medical Research Involving Human Subjects act (WMO), Dutch Trial Registry number (NTR) 2344.

Included were: patients with diabetes mellitus type 1 or 2, age 18 – 90 years, suffering from painful bilateral DPN, diagnosed with the Diabetic Neuropathy Score (DNS) and Diabetic Neuropathy Examination (DNE)[25,26], a positive Tinel sign of the posterior tibial and common peroneal nerve, an Ankle-Brachial Index between 0.8 - 1.15 with a toe-brachial index ≥ 0,7 and palpable pulsations in the posterior tibial artery and dorsal pedal artery. Exclusion criteria were a Body Mass Index > 35 kg/m2, a general condition unsuitable for surgery, a history of ankle fractures or amputations proximal to the Lisfranc joint, an ulcer on the foot, sufficient effect of pain medication (VAS 0 -1) or other causes for neuropathy (e.g. HIV, chemotherapy). Demographic information was recorded for all patients.

After informed consent was obtained, randomization was performed with a web based computer system, the leg receiving the intervention was determined. Each patient underwent decompression of the lower extremity nerves as previously described by Dellon in one limb, i.e. of the tibial nerve at the ankle site, the common peroneal, deep peroneal and superficial peroneal nerve.[14] Patients enrolled in this study could use their medication if they suffered from painful neuropathy according to the Dutch Polyneuropathy Guideline or to the guidelines of the European Federation of Neurological Societies (EFNS). Every three months the HbA1c was tested; the glucose levels were optimized by the patients' diabetes specialist.

Preoperatively and at 3, 6 and 12 months postoperatively, the pain was evaluated with the VAS. To measure HRQoL, patients filled out the SF-36 and EQ-5D questionnaires and the EQ-VAS scale preoperatively and at 6 and 12 months postoperatively.

The SF-36 has eight specific subdomains: physical functioning (PF), social functioning (SF), role limitations due to physical problems (RP), role limitations due to emotional problems (RE), bodily pain (BP), general health perception (GH), vitality (VT) and general mental health (MH). Scores are linearly converted with 0 being worst imaginable health and 100 being perfect health. Scores in the Physical- and Mental

Composite Scores (PCS, MCS) are calculated from z-values of their respective subdomains. In addition, PCS encompasses physical functioning, role-physical, and bodily pain, whereas MCS includes social functioning, role-emotional, and mental health. Again a higher score is indicative of better health.

All 5 EQ-5D domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) were evaluated based on the ratio of three possible responses to each domain. The EQ-5D index score was calculated from its domains, based on the time trade off tariff determined for the Dutch population.[27] The resulting score displays the way the health state, as one of the 243 specific combinations of scores on the subdomains, is valuated in the population, ranging from 0.0 (worst imaginable health) through 1.0 (best imaginable health). The valuation of every health state has been ascertained by determining the trade off in healthy life years that people in the specific population would be willing to make, to avoid the described health state.

The EQ-VAS is a visual analog scale ranging form 0 (worst imaginable health) through 100 (best imaginable health), where people may visually indicate the current state of their health.

Additionally for both SF-36 and EQ-5D at baseline a comparison was made to known Dutch population values, to evaluate the specific differences in health related quality of life.[5,27]

MCID's were determined using both an anchor based method and a distribution based method. First a Minimal Detectable Change (MDC) was determined by using the distribution-based method, this value is defined as the smallest amount of change in a score that indicates a real change above that expected by measurement error. The MDC's were calculated from the standard error of measurement (SEM). The SEM is an error estimate for single use of a test and is indicative of the reliability of the scale. Calculating the SEM is done by using the SD of the pretreatment score and the intraclass correlation coefficient (ICC) using the formula $SEM = SD \times (1-\sqrt{ICC})$. From the SEM, the MDC is calculated using the formula $MDC = SEM \times z\text{-}value \times \sqrt{2}$. The calculation of the MDC is made using a z-value of 1.96 as this corresponds to the 95% confidence threshold in a normal distributed variable, thus rendering the MDC_{95} value. This value states with 95% confidence that it is a reliably measured change and not due to error.

For the purpose of defining a single MCID per variable, the patients were grouped to either improved (slightly improved, much improved) of unimproved (no difference, worsened). The actual MCID scores were determined by using receiver operating characteristics (ROC) curves, plotting sensitivity (y-axis) against 1-specificity (x-axis) for all possible cut-off points. The most efficient cut-off value in terms of sensitivity and specificity was chosen as MCID. Area under the curve (AUC) was evaluated to establish the ability to differentiate between improved and unimproved, with 0,5 being differentiation purely by chance and 1,0 being perfect prediction. MCID's were only found meaningful if they exceeded the MDC value.[24,28]

Sample size was set based on the expected VAS outcomes for the LENS study and determined the need of 38 subjects. Anticipating a 10% loss to follow-up, the total calculated sample size was 42.

Data analysis was performed with statistical software (IBM SPSS Statistics, Version 21.0. Armonk, NY: IBM corp.). Missing values were recorded as such and not used in the calculation of any statistical differences. The SF-36 and EQ-5D scores were considered to have a normal distribution. Statistical differences were calculated using 2-tailed Student's t-tests and ANOVA repeated measures with Bonferroni correction. All scores were expressed as means with 95% confidence intervals (CI). Differences were considered significant when alpha < 0.05.

RESULTS

Forty-two patients were included in this study. One patient died due to unrelated circumstances during follow-up and one patient was lost to follow-up. Two patients were not evaluated at 3 months and were therefore excluded from statistical analysis. The baseline characteristics of the remaining 38 patients are described in Table 1. One of the remaining patients did not complete the questionnaires at six months postoperative, but completed these at 12 months and was therefore included in the pre-operative and 12 months postoperative analyses. Three complications were noted in the 38 patients. Two patients had an infected surgical wound at the ankle, for which they were treated with antibiotics. One of these patients was admitted to the hospital. One patient had to be operated for a hematoma after the initial surgery due to the use of anticoagulant therapy.

Table 1 Baseline characteristics of the study population

Variable	Participants
N	38
Male (%)	22 (57.9)
Female (%)	16 (42.1)
Age (mean years ± SD)	62.7 ± 10.2
BMI (mean kg/m^2 ± SD)	29.0 ± 4.2
Diabetes mellitus type 1 (%)	8 (21.1)
Diabetes mellitus type 2 (%)	30 (78.9)
Duration of diabetes (mean years ± SD)	17.6 ± 12.2

Legend: N = number of patients, SD = standard deviation, BMI = Body Mass Index

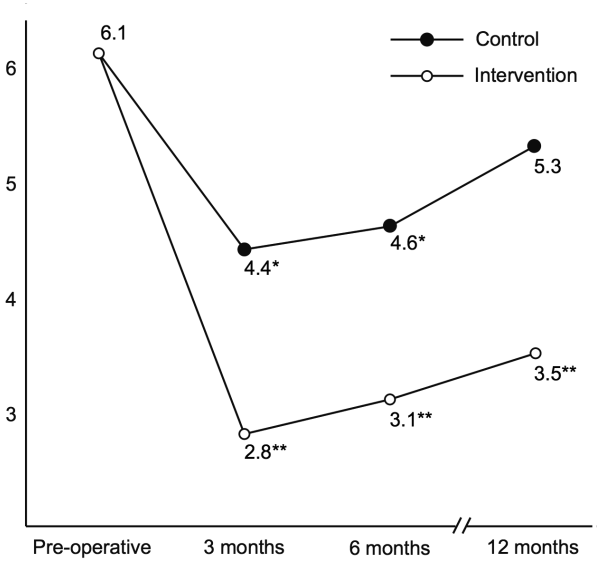

Figure 1 VAS outcome after decompression

Legend: * p<0.05, ** p<0.001

VAS

At baseline the VAS was 6.1 for both the case and control leg. At 12 months postoperatively, the VAS was significantly lower in the operated leg, compared to preoperatively (3.5 vs 6.1, p< 0.001) (Figure 1).[29]

Health related quality of life

Both SF-36 and EQ-5D scores showed no significant improvement at 12 months post-operatively (Table 2). The SF-36 questionnaire showed that the only significant impact on quality of life after surgical decompression was found in the domain Bodily Pain at six months postoperatively (54.5 versus 46.4, p< 0.05). There was no significantly positive effect 12 months after the procedure (50.5 versus 46.4, not significant). On further exploration of the domain, this effect seemed to come from a reduction in the severity of pain (58.1 versus 48.2, p 0.002), rather than pain being less of an obstruction in daily life (67.6 versus 64.3, not significant).

Compared with the Dutch general population, patients with painful DPN scored significantly worse on all domains of the SF-36 and the EQ-5D domains of mobility, usual activities and pain/discomfort (Table 2).

MCID

Based on the responses to the anchor question as shown in Table 3, MCID values were calculated for the VAS, SF-36 domain scores and the EQ-5D index score.

A MCID was determined for the VAS (2.900), its MCID exceeded the corresponding MDC (2.052) with an AUC of 0,730 (0,569-0,892). According to this MCID value, the success-rate of lower extremity nerve decompression for markedly reducing pain (VAS difference 2.900) in our study population is approximately 42.5%.

MCID values could not be obtained for EQ-5D and SF-36 scales, due to determined values not exceeding the minimal detectable change threshold.

Table 2 Quality of life as measured by SF-36 and EQ-5D

Scale	Domain		Dutch Population		Pre-operative	6 months post-operative		12 months post-operative
SF-36	N		1742		38	38		38
	Physical Functioning		83.0	**	56.4	56.1		55.0
	Role Physical		76.4	**	40.6	41.9		35.1
	Role Emotional		82.3	**	64.0	72.1		61.3
	Social Functioning		84.0	**	67.6	68.2		64.5
	Bodily Pain		74.9	**	46.4	54.5	*	50.5
	Pain in last 4 weeks		-		48.2	58.1	*	52.7
	Hindrance due to pain		-		64.3	67.6		66.5
	Mental Health		76.8	*	70.5	71.1		69.3
	Vitality		68.6	**	53.5	58.0		53.0
	General Health		70.7	**	46.2	46.8		42.2
	Physical Composite Score		-		36.5	37.2		36.1
	Mental Composite Score		-		47.3	48.8		46.3
EQ-5D	N	†	134		38	37		38
		1	89.8		23.7	29.7		23.7
	Mobility (%)	2	9.4	**	76.3	70.3		73.7
		3	0.8		0.0	0.0		2.6
		1	93.8		86.8	91.9		81.6
	Self-care (%)	2	5.4		13.2	8.1		18.4
		3	0.8		0.0	0.0		0.0
		1	78.3		39.5	29.7		21.1
	Usual activities (%)	2	20.2	**	52.6	67.6		71.1
		3	1.6		7.9	2.7		7.9
		1	52.3		5.3	16.2		7.9
	Pain/discomfort (%)	2	46.2	**	63.2	67.6	*	73.7
		3	1.5		31.6	16.2		18.4
		1	84.4		73.7	67.6		71.1
	Depression/anxiety (%)	2	13.3		23.7	29.7		26.3
		3	2.3		2.6	2.7		2.6
	EQ-5D index score		-		0.60	0.68		0.62
	EQ-VAS		-		61.2	62.8		60.8

Legend: * p<0.05, ** p<0.001

Table 3 Distribution of anchor question outcomes

What was the effect of surgery on your: a. Operated leg, b. Control leg, c. Daily functioning					
Category	Worsened	Slightly worsened	Unchanged	Slightly improved	Improved
Operated leg (%)	15.8	*	39.5	23.7	21.1
Unoperated leg (%)	28.9	*	57.9	2.6	10.5
Daily functioning (%)	10.5	10.5	36.8	18.4	23.7

Legend: * Category not included in the specified question

DISCUSSION

The Lower Extremity Nerve Entrapment Study (LENS) is the first randomized controlled trial on the effect of surgical decompression of lower extremity nerves in patients with painful diabetic polyneuropathy. Ever since Dellon first described surgical decompression of nerves in DPN in 1992, the possible benefit of this procedure has been the subject of different studies. Positive effects on pain, sensibility, balance and nerve conduction velocity have been described in numerous observations non-randomized trials.[15,19,21,30]

Specific focus on the possible influence of decompression surgery on health related quality of life has thus far been limited, with only Nelson and Little showing no significant findings in SF-36 scores in a six-patient pilot study.[23]

The results of our study suggest that surgery has a clinically meaningful effect on pain in patients with DPN who opt for surgical decompression. However, surgery did not seem to improve quality of life as measured with the SF-36 and EQ-5D questionnaire.

As shown in Table 2, our population of patients with painful DPN experienced significantly worse health related quality of life, as measured in the SF-36 and EQ-5D questionnaires compared with the general Dutch population.[5,27,31] With all SF-36 domains and the EQ-5D domains Mobility, Usual Activities and Pain being significantly worse, our study showed a large impact on both physical, and to a lesser extent mental health, due to painful DPN.

Twelve months after surgery we found, contrary to the improvement of VAS, no statistically significant impact on health related quality of life, as measured through SF-36 and EQ-5D questionnaires. The sole significant impact on the domain Bodily Pain of the SF-36 questionnaire at 6 months after surgery correlates with the VAS-diagram (Figure 1). This effect seemed to come solely from a reduction in the actual pain patients experienced, as hindrance due to pain did not seem to be significantly altered. Even with a significant 12-months VAS improvement we conclude that no lasting improvement in HRQoL, measured with EQ-5D and SF-36, could be made through nerve decompression surgery. Pain defines a small part of HRQoL, furthermore patients were operated on one leg, which may have diminished the effect on HRQoL further. Interestingly, during the follow-up period the VAS-score in the control leg also decreased significantly. Possibly the pain perception in the operated and non-operated leg influenced each other; in posttraumatic neuropathic pain this phenomenon is seen as well.[32–35] The absolute difference in VAS between the intervention and control leg remained significant. This does not refute a possible placebo effect. After one year patients were asked if they wanted to undergo the same surgical procedure on the contralateral leg; to this date only eight patients took that opportunity.

Although unilateral surgery does not improve patient's quality of life in a statistically significant way, the MCID supports that surgery can be meaningful to patients well being through alleviating pain symptoms.

The second objective of this study was to determine MCID for the pain measurement and the HRQoL questionnaires. After determining MCID cut-off points for these measures, only the MCID for the VAS at a reduction of 2.900 was found to exceed its minimal detectable change threshold of 2.502. Stratification of the study population on meeting the MCID threshold yielded an estimated efficacy of the decompression surgery of 42.5% for clinically meaningful pain reduction. MCID is thought to be useful as a benchmark for improvement of individuals. Therefore the outcome of MCID in our study may be of importance in information supply towards patients interested in this procedure. The actual effect of decompression at certain sites is still not elucidated. Examination of the tibial nerve at the ankle site with ultrasound did not reveal any effect after decompression.[11] Until now, the only registered benefit of the operation is found in improvement of the VAS.

To determine the MCID, responders to the anchor question were grouped into improved versus unimproved groups. The last group comprised both worsened and unchanged burden due to DPN, which might be seen as a limitation but tells us most about the prospective of decompression surgery for alleviating pain. Another

limitation is that only patients with painful DPN were included, thus rendering it impossible to generalize our findings to patients with non-painful diabetic neuropathy symptoms. Future studies in determining predictors for which patients gain clinically meaningful pain reduction will be interesting.

In conclusion, surgical decompression of nerves in the lower extremity in patients with painful DPN has no effect on HRQoL as measured through EQ-5D and SF-36 at 12 months follow-up. A clinically meaningful reduction in pain was evident, as demonstrated by the determined MCID for the VAS. This shows that surgical decompression has the potential to alleviate pain in a clinically meaningful way in 42.5% of patients with painful DPN. Decompression of nerves of the lower extremity might therefore be considered in patients with painful DPN who cannot achieve adequate pain reduction using medication.

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Summary, conclusions and future perspectives

The aim of the study was to evaluate the effect of surgical decompression of nerves in the lower extremity in patients with painful diabetic polyneuropathy (DPN).

1. Introduction

In the Netherlands at least 600.000 people have diabetes mellitus, the prevalence is thought to increase to 737.000 patients in 2025. Diabetic symmetrical peripheral neuropathy (DPN) is a well-known complication in patients with diabetes affecting up to 50% of the patients. The symptoms vary from a burning or itching sensation to pain or numbness. Because of diminished protective sensibility, the risk of ulcers and amputations in the lower extremity is increased. Medication is helpful in treatment of pain in a limited number of patients with diabetic neuropathy, but does not prevent progression of neuropathy.

In 1992 Dellon described the first surgical decompression of nerves for DPN. The possible benefit of this procedure has been subject of different studies. In a systematic Cochrane review in 2008, no randomized studies were found to the effectiveness of surgical decompression, but positive effects on pain, sensibility, balance and nerve conduction velocity have been described in non-randomized studies. The lack of randomized and controlled studies, together with an increasing population of patients with diabetes mellitus (DM) and limited results for treatment of pain in DPN led to the start of this study.

2. Study design

Over a period of two years, 42 patients with painful DPN were enrolled in the Lower Extremity Nerve entrapment Study (LENS).

Patients with type 1 or 2 diabetes mellitus, age 18 – 90 years, a positive Tinel sign at least at one of the following locations: the posterior tibial, superficial or common peroneal nerve, ankle-brachial Index between 0.8 - 1.15 with a toe-brachial index ≥ 0,7 and palpable pulsations in the posterior tibial artery and dorsal pedal artery were included. The intervention consisted of surgical decompression of the nerves, previously described by Dellon, in one limb, i.e. of the tibial nerve and its three branches at the ankle site, the common peroneal, deep peroneal and superficial peroneal nerve. Surgery was performed within eight weeks after randomisation. The contralateral limb was treated with usual care and served as control: 'within-patient comparison'. Pain, sensibility, use of pain medication, aspects of the tibial nerve visualised with ultrasound, nerve conduction studies, postural stability and quality of life were assessed pre-operatively, 3, 6 and 12 months post-operatively.

3. Pain and sensibility

To evaluate pain, a Visual Analogue Scale (VAS) was used. The VAS is a straight line, using a 10-point scale ranging from 0 to 10, with 0 being no perceptible pain and 10 being intolerable pain. Patients draw a point on the line pre-operatively, 3, 6 and 12 months post-operatively, corresponding with the intensity of their pain at that moment. Both legs were scored separately. Sensibility was tested with a 5.07 (10g) Semmes Weinstein monofilament and two-point discriminator at nine predetermined plantar sites of the foot.

At baseline, there was no significant difference between the mean VAS-scores in the control and intervention leg (both means were 6.1, $p > 0.1$). At 3 months post-operatively, a significant decrease in VAS-score was noted in both the intervention and control leg. The mean VAS-score at 12 months was 3.5 (95% CI 2.5 – 4.4) for the intervention group and 5.3 (95% CI 4.4 – 6.2) for the control group, $p < 0.001$. Overall, 73.7% of the subjects improved in VAS in the operated leg, of which 35.7% decreased more than 5 points on VAS, 26.3% of the subjects had no effect or a worsening in VAS in the operated leg.

The Semmes Weinstein Monofilament Testing (SWMT) did not show significant differences at baseline; the mean score of the intervention group was 4.0 vs. 3.6 in the control group (p 0.24). At 3 months post-operatively, the SWMT score was 5.4 (95% CI 4.3 – 6.6) in the intervention group, a significant increase compared with the control and baseline scores (4.0 [p 0.002] and 4.0 [p 0.001], respectively). At 12 months of follow-up, however, the total SWMT score in the intervention group lowered to 4.6 (95% CI 3.3 – 5.6), not significantly different from the control group (4.1, 95% CI 3.1 – 5.1) and baseline measurements (4.0, 95% CI 3.0 – 4.9).

At baseline, intervention and control leg outcomes of two-point discrimination were not significantly different (p 0.75). After 12 months, the comparison between the intervention and control leg revealed no significant improvement in the ability to distinguish between two points.

We concluded that decompression of the nerves of the lower extremity in patients with painful DPN significantly decreases pain symptoms 3, 6 and 12 months after intervention. Tactile sensibility improved significantly in the first 3 months, but not at 12 months of follow-up.

4. Use of pain medication

We determined whether surgical decompression of nerves in the lower extremity, in patients suffering from painful DPN, would reduce the amount of pain medication taken by patients. Secondary we evaluated the physicians' adherence to the recommendations of the Dutch Guideline for polyneuropathy ('Richtlijn

Polyneuropathie', 2005), it's accuracy in respect to the European Federation of Neurological Societies (EFNS) Guideline and the therapy adherence of patients.
Prescription data for pain medication were collected from 1-1-2005 up until 1-8-2013 and evaluated for all patients. Pre-operative prescriptions were compared with prescriptions at 3, 6 and 12 months post-operatively. The Medication Possession Rate (MPR) was used for evaluation of therapy adherence per patient.
Six months post-operatively significantly less medication was used compared to before surgery and 3 months afterwards. The twelve months post-operative results were no longer significant. Of the prescriptions 44% did not meet the recommendations of the Dutch guideline for polyneuropathy; for pregabalin this was 29%. Therapy adherence was suboptimal at an MPR<79%.
We concluded that only at six months after surgical decompression of the nerves in the lower extremity in patients with painful DPN, patients used significantly less pain medication. The Dutch guideline contains incomplete data in respect to the EFNS guidelines, and recommendations are only marginally adhered to. Therefore this guideline should either be revised or physicians should focus on the EFNS guidelines. Therapy adherence, in patients with painful DPN, regarding pain medication is suboptimal.

5. Ultrasound Findings

Pre- and 6 months postoperatively all subjects underwent ultrasound examination of the tibial nerve and flexor retinaculum at the ankle using a Philips iU22 with a 15-7 MHZ transducer. The short and long axis of the tibial nerve were measured at two specific locations: the medial plantar branch of the tibial nerve under the flexor retinaculum and the tibial nerve cranial to the flexor retinaculum; 3 cm proximal to the malleolar calcaneal line. Measurements were performed by drawing an ellipse around the nerve, after which the software calculated the minor and major axis and the cross sectional area (CSA).
To compare the results with the normal population, a control group consisting of 38 healthy subjects, aged 18-90 years with no symptoms or medical history of arterial insufficiency was enrolled.
The mean and standard deviations for the CSA, Thickness/Width (T/W) ratio and thickness of the retinaculum were assessed.
Results suggested that the CSA in the tarsal tunnel is significantly larger in patients with painful DPN (8.4 $mm^2 \pm$ 3.9) than in healthy controls (6.4 $mm^2 \pm$ 1.3) $p=0.007$. The T/W ratio in patients with painful DPN is 0.64 and in controls 0.59, $p=0.03$. Patients with DPN have a significantly thicker retinaculum (1.1 mm) than controls (0.84 mm), $p<0.005$. Difference between baseline and follow-up in the operated leg was

1.49 mm^2 and in the control leg 1.82 mm^2, p=0.67, which means that no significant differences in CSA in the tarsal tunnel at baseline and at follow-up after tarsal tunnel release were observed between the painful DPN group and the control group.
Although no effect on CSA after surgery was found, this part of the study demonstrates a larger and swollen tibial nerve and thicker flexor retinaculum at the ankle in patients with diabetic polyneuropathy compared to healthy controls.

6. Nerve conduction studies

Pre- and 12 months postoperatively, nerve conduction studies (NCS) were performed bilaterally, using a Viking Select EMG apparatus. Motor NCS were performed in the (i) deep peroneal nerve (recording: extensor digitorum brevis muscle (EDB), (ii) deep peroneal nerve (recording: anterior tibial muscle) and (iii) tibial nerve (recording: abductor hallucis muscle). Per nerve, we analyzed: amplitude, area, and duration of the negative compound muscle action potential (CMAP) part, distal motor latency (DML), motor nerve conduction velocity (MCV) per segment, and area-drop per segment.
Sensory NCS was performed for the superficial peroneal nerve. We analyzed amplitude of the sensory nerve action potential (SNAP) and sensory conduction velocity (SCV).
At baseline, there were no important differences in NCS outcomes between the intervention and control legs.
Univariate analysis 12 months postoperatively revealed the following differences: Of the peroneal nerve, the distal CMAP amplitude measured at the EDB of the intervention legs decreased significantly from 3.1 2.6 to 2.1 1.8 mV ($p \leq 0.001$). The distal motor latency measured at the EDB of the intervention legs increased from 4.3 1.1 to 4.7 1.2 ms ($p \leq 0.01$). The area drop in the lower leg measured at the EDB of the control legs decreased from 11 11 to 6 8 % ($p \leq 0.05$). The distal CMAP amplitude measured at the anterior tibial muscle of the control legs increased from 4.8 1.5 to 5.2 1.3 mV ($p \leq 0.05$). For the tibial nerve, the distal CMAP duration decreased significantly from 5.1 1.6 to 4.6 1.8 ($p \leq 0.05$) in the control legs.
To analyse the overall effect of the decompression a multivariate analysis of variance was performed on all variables; this analysis showed no significant differences among the studied variables.
Our results suggest that nerve decompression had no influence on NCS variables twelve months after surgery.

7. Stability

We used a sensitive pressure mat, the Matscan Measurement System, to investigate the effect of decompression of nerves in the lower extremity on static balance in patients with painful DPN. Barefoot plantar pressures were measured during 30 seconds. 900 Individual sway frames were recorded and merged into a movie. Sway was reflected by five variables: i) the total length of the path travelled by the center of pressure (Distance), ii) the maximum anterior-to-posterior center of pressure movement (AP length), iii) the maximum left to right (or medial to lateral) center of pressure movement (LR length). iv) An elliptical area in which the center of pressure trajectory moved during the measurement was defined 'Area' and v) 'Variability' was defined as the standard deviation of individual movements of the center of pressure between frames during the recording. Weight-bearing 'WB' was the mean amount of weight (in percentage) a patient put on one leg in 30 seconds compared to contralateral leg. All tests were performed under the same conditions by one single examiner blinded for operation side.

Of the original 42 patients of the LENS cohort, 39 Patients met inclusion criteria and were enrolled for stability testing.

Postoperatively no significant differences for sway variables and weight-bearing were seen compared to preoperative measurements. As expected, visual perturbations (eyes closed) increased sway of the centre of pressure for all variables, except LR length six months after surgery. Preoperatively, this increase was more evident and statistically significant in four out of five sway variables. Six months after surgery, only one sway variable, Distance, was significantly longer. At one year follow up, mean sway differences were more comparable to preoperative measurements: three out of five sway variables, (Distance, Variability and AP length), were significantly increased in patients with eyes closed.

We concluded that there is no evidence that surgical nerve decompression influences postural stability in patients with painful DPN, even though results do suggest that sway measurements improve temporarily after surgery.

8. Quality of life

The objectives of this part of the study were to examine the effect of decompression of nerves in the lower extremity in patients with painful DPN on health related quality of life (HRQoL) and to determine minimal clinically important differences (MCID) after 12 months in pain- and quality of life scores.

Pre-Operatively, at 6 and 12 months, a Visual Analogue Scale (VAS) for pain and 36-Item Short-Form Health Survey (SF-36) and EuroQol 5 dimensions (EQ-5D) questionnaires were filled out. Additionally, an anchor question was administered,

asking patients what effect on their complaints they noticed after surgery.
The SF-36 has eight specific subdomains: physical functioning (PF), social functioning (SF), role limitations due to physical problems (RP), role limitations due to emotional problems (RE), bodily pain (BP), general health perception (GH), vitality (VT) and general mental health (MH).
All 5 EQ-5D domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) were evaluated based on the ratio of three possible responses to each domain. The EQ-VAS is a VAS ranging form 0 (worst imaginable health) through 100 (best imaginable health), where people may visually indicate the current state of their health.
MCID helps to ascertain if a statistically significant response is meaningful to actual patients. It represents the smallest improvement considered worthwhile for a patient. In painful DPN, a MCID for pain score measured with the Visual Analogue Scale (VAS) may specify the effect of treatment.
Both SF-36 and EQ-5D scores showed no significant improvement at 12 months post-operatively. The SF-36 questionnaire showed that the only significant difference after surgical decompression was found in the domain Bodily Pain at six months postoperatively (54.5 versus 46.4, $p< 0.05$). On further exploration of the domain, this effect seemed to come from a reduction in the severity of pain (58.1 versus 48.2, p 0.002), rather than pain being less of an obstruction in daily life (67.6 versus 64.3, not significant). There was no significantly positive effect 12 months after the procedure (50.5 versus 46.4, not significant).
Based on the responses to the anchor question "What was the effect of surgery on your: a. Operated leg, b. Control leg, c. Daily functioning", MCID values were calculated for the VAS, SF-36 domain scores and the EQ-5D index score.
An MCID was determined for the VAS (2.900), its MCID exceeded the corresponding Minimal Detectable Change MDC (2.052) with an area under the curve of 0.730 (0.569-0.892). According to this MCID value, the success-rate of lower extremity nerve decompression for markedly reducing pain (VAS difference 2.900) in our study population is approximately 42.5%.
Surgical decompression of nerves in the lower extremity in patients with painful DPN has no effect on HRQoL as measured through EQ-5D and SF-36 at 12 months follow-up. A clinically meaningful reduction in pain by surgical decompression was seen in 42.5% of patients with painful DPN 12 months after surgery.

CONCLUSIONS

The Lower Extremity Nerve entrapment Study (LENS) is the first randomized controlled trial with predefined endpoints on the effect of surgical decompression of nerves in the lower extremity in patients with painful diabetic polyneuropathy.
We proved that decompression of the tibial nerve and its three branches and the common peroneal, superficial peroneal and deep peroneal nerve, in patients with painful DPN significantly reduces pain, measured with the VAS, during the total follow up period of one year. In 42.5 % of the patients the alleviation of pain is clinically meaningful with a VAS reduction of 2.9 at 12 months. In spite of this result, no significant effect on quality of life was measured at the end of the study. The effect of surgery had only a temporarily positive effect on the use of pain medication. Correct prescription of pain medication according to the Dutch guideline by doctors and therapy adherence by patients were suboptimal.
Patients with painful DPN have a more swollen tibial nerve at the ankle site, at the same time the covering flexor retinaculum is thicker than in healthy people. No effect, however, on CSA was seen after decompression. Furthermore, one year after decompression no positive effect was seen in motor and sensory nerve conduction studies, which supports the non-significant differences at twelve months on stability and sensory tests.

Based on the results of this study, we suggest to add surgical decompression of nerves in the lower extremity in patients with painful DPN as a treatment modality when medication fails to achieve decrease of pain symptoms or when medication leads to intolerable side effects.

FUTURE PERSPECTIVES

In 2030, the number of patients with diabetes worldwide is estimated to reach 366 million; diabetes mellitus type 2 comprises 90% of cases. Approximately half of these patients will develop a form of DPN. Intense glucose control is seen as the only remedy to preserve sensory nerve function and medication is the treatment of choice against neuropathic pain.

In 42.5% of our study population, decompression of lower extremity nerves resulted in relief of pain in a clinical meaningful way. A subset of patients does not respond to surgery. Other than a positive Tinel sign, no specific symptom, sign or test can

help us distinguish people who are likely to benefit from surgery. A linear regression module may reveal characteristics in the study population that influence the outcome positively (e.g. blood pressure or use of anti coagulants or laboratory parameters). It would be interesting to study such specific characteristics in future randomized studies on (painful) DPN and decompression of nerves. Investigation of (micro) vascular alterations after surgical decompression in this population has evoked our interest as well.
Since the VAS is a subjective score, critics may suggest that the effect of decompression is largely a placebo effect. A sham procedure would have identified the effect. In our opinion, however, a sham procedure would not have been ethical in this vulnerable patient group. An alternative may be found in Quantitative Sensory Testing (QST), which we added during the course of our study. QST can be a useful tool for detection of small fiber threshold alterations for thermal pain and sensation in future studies on surgical decompression, to avoid sham surgery.

Although surgical decompression decreases pain, DPN is not reversible. It is of utter importance to prevent complications such as neuropathy and to emphasize the importance of glucose control in diabetes mellitus to patients. Diabetes mellitus type 1 cannot be prevented, but there is evidence that lifestyle changes such as decrease in body weight and increase in physical activity can help prevent the development of type 2 diabetes and its complications, including peripheral diabetic polyneuropathy.

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Samenvatting, conclusie en toekomst perspectieven

Het doel van dit onderzoek: evaluatie van het effect van chirurgische decompressie van zenuwen in het onderbeen bij patiënten met pijnlijke diabetische polyneuropathie.

1. Introductie

In Nederland hebben ten minste 600.000 mensen diabetes mellitus (DM) en verwacht wordt dat dit aantal zal toenemen tot 737.000 patiënten in 2025. Symmetrische perifere diabetische polyneuropathie (DPN) is een bekende complicatie bij diabetes en kan wel bij 50% van de patiënten optreden. Meestal beginnen de klachten bij de voeten. De symptomen variëren van een branderig of jeukend gevoel tot pijn en doofheid. Door de afname van protectieve sensibiliteit is het risico op ulcera en amputaties in de onderste extremiteiten verhoogd. Medicatie om pijn te verminderen kan bij een beperkt aantal patiënten met diabetische neuropathie helpen, maar voorkomt de voortgang van de neuropathie niet.

In 1992 beschreef Dellon de eerste chirurgische decompressie van zenuwen bij DPN. Het mogelijke voordeel van deze procedure is onderwerp geweest van verschillende studies. In een systematische Cochrane review in 2008 werden geen gerandomiseerde studies gevonden naar de effectiviteit van chirurgische decompressie. Wel werden er positieve effecten beschreven ten aanzien van pijn, sensibiliteit, balans en zenuwgeleidingsonderzoek. Het gebrek aan een gerandomiseerde gecontroleerde studie naar het effect van decompressie van zenuwen in het onderbeen bij patiënten met pijnlijke diabetische neuropathie en de huidige beperkte mogelijkheden voor behandeling van pijn bij DPN, in combinatie met een groeiende populatie van patiënten met DM waren de aanleiding tot deze studie.

2. Opzet van de studie

Gedurende een periode van twee jaar werden 42 patiënten met pijnlijk DPN toegelaten tot de Lower Extremity Nerve entrapment Study (LENS). In deze studie werd het effect van decompressie van zenuwen in het onderbeen, namelijk de nervus peroneus communis, superficialis en profundus en de nervus tibialis met zijn drie takken naar de voet bij patiënten met pijnlijke DPN, onderzocht.

De patiënten hadden DM type 1 of 2, leeftijd 18-90 jaar, een positieve Tinel ter plaatse van de nervus tibialis, de nervus peroneus communis of superficialis, een enkel-arm index tussen 0.8-1.15, met een teen-arm index ≥0.7 en voelbare pulsaties ter plaatse van de arteria dorsalis pedis en arteria tibialis posterior. De patiënten ondergingen een operatie, na loting voor het te opereren been. Het contralaterale been, waarvoor de gebruikelijke zorg werd gehandhaafd, diende als controle. Pijn, sensibiliteit, gebruik van pijn medicatie, echografische aspecten van de nervus tibialis, zenuwgeleidingsonderzoek, stabiliteit en kwaliteit van leven werden pre-

operatief, drie, zes en 12 maanden postoperatief getest.

3. Pijn en sensibiliteit

Om de pijn te evalueren werd de Visual Analogue Scale (VAS) gebruikt. De VAS is een rechte lijn die begint bij 0 en eindigt bij 10. Nul staat voor geen waarneembare pijn en 10 voor onhoudbare pijn. Patiënten zetten pre-operatief, drie, zes en 12 maanden postoperatief een streep op deze lijn op de plaats die overeenkwam met de intensiteit van hun pijn op dat moment. Beide benen werden apart gescoord. De sensibiliteit werd op negen plaatsen aan de plantaire zijde van de voet getest met een 5.07 (10g) Semmes-Weinstein monofilament en een 2-punts discriminator.

Pre-operatief was er geen significant verschil tussen de gemiddelde VAS-score van het controle en interventie been (beide gemiddelden waren 6.1, p>0,1). Drie maanden postoperatief was er een significante vermindering van de VAS score in beide benen. De gemiddelde VAS-score, 12 maanden post-operatief, was 3.5 (95% CI 2.5-4.4) voor de groep geopereerde benen en 5.3 (95% CI 4.4-6.2) voor de groep controle benen (p<0.001).

De VAS verbeterde in 73.7% van de geopereerde benen, 35.7% van deze groep had een verbetering van 5 punten op de VAS lijn, 26.3% van de groep geopereerde benen gaf geen effect of een verslechtering aan, gemeten met de VAS.

Semmes Weinstein Monofilament Testing (SWMT) toonde pre-operatief geen verschil; de gemiddelde score in de interventie groep was 4.0 vs 3.6 in de controle groep (p 0.24). Drie maanden post-operatief was de SWMT score 5.4 (95%CI 4.3-6.6) in de interventie groep, een significante toename in vergelijking met de controle groep en baseline scores waar respectievelijk 4.0 (p 0.002) en 4.0 (p 0.001) werd gehaald. Twaalf maanden post-operatief was de totale SWMT score in de interventie groep gedaald tot 4.6 (95% CI 3.3-5.6), geen significant verschil ten opzichte van de controle groep (4.1, 95%CI 3.1-5.1) en ten opzichte van de baseline (4.0, 95% CI3.0-4.9). De twee-punt discriminatie toonde pre-operatief geen significant verschil tussen de interventie en de controle groep (p 0.75). Twaalf maanden na de operatie werd er geen significante verbetering gevonden met deze test.

Wij concludeerden dat decompressie van de zenuwen in het onderbeen bij patiënten met pijnlijke DPN drie, zes en 12 maanden postoperatief significant minder pijn geeft. Tactiele sensibiliteit verbeterde significant in de eerste drie maanden, maar na 12 maanden was dit niet meer het geval.

4. Gebruik van pijnmedicatie

We hebben onderzocht of chirurgische decompressie van zenuwen in de onderste extremiteiten bij pijnlijke DPN de inname van medicatie tegen pijn reduceerde.

Daarbij evalueerden we de navolging van de 'Richtlijn Polyneuropathie' door artsen en de opvolging van de voorschriften door de patiënten.
Voorschriften van pijnmedicatie tussen 1-1-2005 en 1-8-2013 werden verzameld en geëvalueerd voor alle patiënten die deelnamen aan de LENS studie. Pre-operatieve voorschriften werden vergeleken met de voorschriften van drie, zes en 12 maanden post-operatief. Om de therapietrouw van patiënten te evalueren gebruikten we de Medication Possession Rate (MPR). Een MPR ≥80% wordt gezien als therapie trouw.
Zes maanden post-operatief werd er significant minder medicatie tegen pijn gebruikt vergeleken met de voorschriften pre-operatief. Twaalf maanden post-operatief was dit resultaat niet langer significant. Van de voorschriften voldeed 44% niet aan de aanbevelingen van de Nederlandse richtlijn; voor pregabaline, een aanvulling uit de Europese richtlijn bleek dat 29% te zijn. De therapietrouw was suboptimaal met een MPR<79%.
We concludeerden dat alleen zes maanden na chirurgische decompressie van de zenuwen in het onderbeen bij pijnlijke DPN patiënten significant minder pijnmedicatie gebruikten. De Nederlandse Richtlijn Polyneuropathie bevat incomplete informatie en is toe aan herziening. Aanbevelingen hieruit worden onvoldoende nageleefd. Patiënten zijn niet optimaal therapietrouw ten aanzien van pijnmedicatie gebruik.

5. Echografisch onderzoek

Pre-operatief en zes maanden postoperatief ondergingen alle patiënten echografisch onderzoek van de nervus tibialis en het flexor retinaculum ter plaatse van de mediale enkel. Het flexor retinaculum is de structuur die de tarsale tunnel, waarin de nervus tibialis loopt, afdekt en welke bij decompressie wordt gekliefd. Er werd gebruik gemaakt van een Philips iU22 met een 15-7 MHz transducer. De korte en lange as van de nervus tibialis werden gemeten op twee specifieke locaties: de mediale plantaire tak van de nervus tibialis onder het flexor retinaculum en de nervus tibialis boven het flexor retinaculum; 3 cm proximaal van de lijn tussen malleolus en calcaneus. De oppervlakte werd berekend door de computer nadat een ellips rond de zenuw werd getekend.
Om de resultaten te kunnen vergelijken onderging een controle groep met 38 mensen zonder diabetes mellitus of een geschiedenis van vaatinsufficiëntie met een leeftijd tussen 18-90 jaar hetzelfde onderzoek.
Het gemiddelde en de standaard deviatie voor de oppervlakte, verhouding hoogte-breedte (T/W ratio) en de dikte van het retinaculum werden bepaald.
De resultaten lieten zien dat de oppervlakte van de zenuw in de tarsale tunnel significant groter was in patiënten met pijnlijke DPN (8.4mm^2± 3.9) vergeleken met gezonde mensen(6.4mm^2± 1.3) p=0.007. De T/W ratio bij patiënten met pijnlijke DPN

is 0.64 en bij de controle groep 0.59, p=0.03. Patiënten met pijnlijke DPN hebben een significant dikker retinaculum (1.1mm) vergeleken met controles (0.84mm), p<0.005. Zes maanden postoperatief was er geen significant verschil in oppervlakte tussen beide benen ten opzichte van de baseline (p=0.67). Ondanks het feit dat chirurgie geen invloed heeft op de oppervlakte van de nervus tibialis in de tarsale tunnel toonde echografie aan dat bij patiënten met pijnlijke DPN er sprake is van een meer gezwollen nervus tibialis en een dikker flexor retinaculum vergeleken met de gezonde controle groep.

6. Zenuwgeleidingsonderzoek

Zenuwgeleidingsonderzoek (engels: nerve conduction studies (NCS)) werd pre-operatief en 12 maanden post-operatief verricht met een Viking Select EMG-apparaat. Voor stimulatie en afleiding werden standaard oppervlakte-electroden gebruikt. Motorisch NCS omvatte de n. peroneus profundus (afleiding: m. extensor digitorum brevis (EDB) en m. tibialis anterior (TA); stimulatie: enkel, 5cm distaal van het fibulakopje en 5cm proximaal van het fibulakopje) en n. tibialis (afleiding: m. abductor hallucis (AH); stimulatie: enkel en knieholte); variabelen waren: (i) amplitude, oppervlakte en duur van de negatieve piek van de distale CMAP, (ii) distale motorische latentie (DML), (iii) motor conduction velocity (MCV) per segment, en (iv) oppervlakte verval (proximaal t.o.v. distaal) per segment. Sensibele NCS werden van de n. peroneus superficialis verricht; variabelen waren de distaal opgewekte sensory nerve action potential (SNAP) en sensory nerve conduction velocity (SCV).

Pre-operatief waren er geen significante verschillen in NCS waarden tussen het interventie-been en het controle-been. Postoperatief toonde univariate analyse de volgende significante verschillen in het interventie-been. De distale CMAP amplitude van de EDB in het interventie-been verminderde van 3.1± 2.6 naar 2.1±1.8 mV (p≤0.001). De DML van de EDB van het interventie-been nam toe van 4.3 ±1.1 naar 4.7±1.2 ms (p≤0.01). Het oppervlakte verval van de EDB CMAP in het onderbeen van het controle-been verminderde van 11±11 naar 6± 8 % (p≤0.05). De distale CMAP amplitude van de TA van het controle-been nam toe van 4.8±1.5 naar 5.2±1.3 mV (p≤0.05). De distale CMAP duur van de AH in het controle been verminderde van 5.1± 1.6 naar 4.6±1.8 (p≤0.05). Al deze veranderingen waren minimaal en vielen binnen de inter-observer variatie.

Multivariate analyse toonde geen significante verschillen tussen de onderzochte variabelen.Onze resultaten suggereren derhalve dat zenuw decompressie geen invloed had op de NCS-variabelen 12 maanden na chirurgie.

7. Stabiliteit

Om het effect van chirurgische decompressie op stabiliteit te testen gebruikten we het Matscan Measurement System. Patiënten stonden gedurende 30 seconden met blote voeten op deze mat waarbij de plantaire drukken werden gemeten. 900 momenten werden met plaatjes vastgelegd en in een filmpje gezet. De beweging, het zwaaien op de benen, kon door middel van vijf variabelen worden bepaald: de totale bewegingsafstand, de voor-achterwaartse bewegingsafstand, de links-rechts bewegingsafstand, de oppervlakte van de verplaatsing van het centrale drukpunt en de variabiliteit (standaard deviatie van individuele bewegingen). Verder werd er gekeken of de patiënt zijn of haar gewicht op beide benen gelijk verdeelde.

Van de 42 patiënten die meededen aan de LENS studie, konden 39 patiënten het stabiliteitsonderzoek ondergaan.

Ten opzichte van pre-operatieve metingen werden er na 1 jaar geen significante verschillen gezien voor de verdeling van het gewicht van de patiënt alsmede de vijf verschillende variabelen. Zoals te verwachten werd de balans beïnvloed door visuele oriëntatie. Vrijwel alle bewegingen werden door het sluiten van de ogen vergroot. Zes maanden postoperatief was alleen de totale bewegingsafstand nog significant groter bij het sluiten van de ogen, echter een jaar na de operatie waren de metingen te vergelijken met de pre-operatieve waardes.

Wij concludeerden dat er geen bewijs is dat unilaterale decompressie van zenuwen in het onderbeen bij pijnlijke DPN de stabiliteit langdurig positief beïnvloedt.

8. Kwaliteit van leven

Dit hoofdstuk beschrijft het effect van decompressie van zenuwen in het onderbeen bij patiënten met pijnlijke diabetische neuropathie op de kwaliteit van leven en het bepalen van een minimaal klinisch merkbaar effect (MCID) voor pijn en kwaliteit van leven scores. Pre-operatief, zes maanden en 12 maanden postoperatief werden verschillende vragen lijsten door de patiënten ingevuld namelijk: de visual analogue scale (VAS) voor pijn en twee specifieke vragenlijsten om de kwaliteit van leven te toetsen: de SF-36 en EQ-5D. Voor de MCID beantwoordden patiënten een vraag met betrekking tot het effect dat de operatie had op hun klachten.

De SF-36 heeft de volgende subdomeinen: fysiek functioneren, rolfunctioneren fysiek, lichamelijke pijn, ervaren gezondheid, vitaliteit, sociaal functioneren, rolfunctioneren emotioneel en geestelijke gezondheid.

De EQ-5D heeft eveneens subdomeinen, namelijk: mobiliteit, zelfzorg, dagelijkse activiteiten, stemming, pijn en cognitie. De EQ-VAS is een visuele analoge schaal van 0 (slechtst voorstelbare gezondheid) tot 100 (best voorstelbare gezondheid) waarop mensen hun gezondheid op dat moment kunnen aangeven.

Met de MCID is het mogelijk om vast te stellen of een statisch significante uitkomst van betekenis is voor de patiënt; het toont de geringste ervaren verbetering voor de patiënt door de therapie aan en kan de uitkomsten van een operatie bij pijnlijke DPN nuanceren en specificeren. Op basis van de antwoorden op de sleutelvraag: " Wat was het effect van de chirurgie op uw a: geopereerde been, b: controle been, c: dagelijks functioneren", werd de MCID berekend voor de VAS, SF-36 domein scores en EQ-5d index scores.

De SF-36 en de EQ-5D toonden beide na 12 maanden geen significante verbetering aan. Zes maanden na de ingreep veranderde het domein 'lichamelijke pijn' significant (54.5 versus 46.4, $p<0.05$). Dit bleek bij nader onderzoek van het domein meer door een vermindering van de ernst van de pijn te zijn gekomen (58.1 versus 48.2, p 0.002) dan door de invloed van pijn op het dagelijks leven (67.6 versus 64.3, niet significant). Twaalf maanden na de procedure was er geen positief significant effect meer (58.1 versus 48.2).
De MCID voor de VAS werd bepaald en was 2.9; de MCID overschreed de minimaal waargenomen verandering (MDC) (2.052) met een 'gebied onder de curve' van 0.730 (0.569-0.892). Waarmee de succesratio van zenuwdecompressie in het onderbeen voor een merkbare pijnvermindering (VAS verschil 2.9) in onze studiepopulatie ongeveer 42.5% is.
Wij concludeerden dat chirurgische decompressie van zenuwen in het onderbeen bij patiënten met pijnlijke diabetische neuropathie 12 maanden postoperatief geen effect heeft op de kwaliteit van leven gemeten met de EQ-5D en de SF-36. Een klinische objectiveerbare pijnvermindering door zenuwdecompressie werd 12 maanden postoperatief gezien in 42.5% van de patiënten met pijnlijke DPN.

CONCLUSIES

De Lower Extremity Nerve entrapment Study (LENS) is het eerste gerandomiseerde gecontroleerde onderzoek naar het effect van chirurgische decompressie van zenuwen in het onderbeen bij patiënten met pijnlijke diabetische neuropathie met vooraf vastgestelde eindpunten.
Wij bewezen dat decompressie van de nervus peroneus communis, superficialis en profundus en van de nervus tibialis en zijn 3 takken bij patiënten met pijnlijke DPN leidt tot significante pijnvermindering gemeten met de VAS gedurende de gehele follow-up periode van een jaar. In 42.5% van de patiënten was de pijnvermindering klinisch merkbaar bij een VAS daling van 2.9 na 1 jaar. Ondanks dit resultaat werd

geen significant effect op de kwaliteit van leven gezien gemeten aan het eind van de studie. Chirurgie had slechts een tijdelijk effect op de inname van pijnmedicatie. Juiste voorschriften van medicijnen tegen pijn volgens de Nederlandse Richtlijn Polyneuropathie door artsen en de therapietrouw van patiënten waren suboptimaal. Zenuwgeleidingsonderzoek toonde een jaar na decompressie geen positief effect, dit ondersteunt de niet significante veranderingen voor stabiliteit's en sensibiliteitstesten na 12 maanden. Patiënten met pijnlijk DPN hadden een gezwollen nervus tibialis ter plaatse van de enkel, het flexor retinaculum was tegelijkertijd dikker ten opzichte van de gezonde populatie. Toch werd er een half jaar na het klieven van het retinaculum geen verandering gezien in de oppervlakte van de zenuw.
Op basis van de uitkomsten van deze studie stellen wij dat chirurgische decompressie van zenuwen in het onderbeen een toevoeging is voor de behandeling van pijnlijke DPN wanneer medicatie ontoereikend is of ongewenste bijwerkingen vertoont.

TOEKOMST PERSPECTIEVEN

In 2030 wordt het aantal mensen met diabetes mellitus geschat op 366 miljoen; in 90% van de gevallen zal dit gaan om diabetes mellitus type 2. Bijna de helft van de patinten ontwikkelt een vorm van DPN. Strikte glucose controle wordt gezien als de enige remedie voor het behoud van sensibiliteit en medicatie is het middel van eerste keuze bij neuropathische pijn.

42.5% van onze studiepopulatie gaf aan dat pijnvermindering tot minder klachten leidde; een aanzienlijk aantal van de patiënten reageerden niet op chirurgie. Er zijn, behalve een positief Tinel teken, geen specifieke symptomen of testen die de uitkomst van decompressie kunnen voorspellen. Een lineair regressie model kan karakteristieken aantonen die de uitkomst positief zouden beïnvloeden (bloeddruk, gebruik van bloedverdunners of laboratorium waarden). Het is interessant om zulke specifieke karakteristieken in toekomstige, gerandomiseerde studies naar (pijnlijke) diabetische neuropathie en decompressie van zenuwen te bestuderen. Visualisatie van mogelijke (micro)vasculaire veranderingen na chirurgische decompressie in deze populatie hebben ook onze aandacht gewekt.
Door de subjectiviteit van de VAS score, kan gesuggereerd worden dat het effect van decompressie grotendeels berust op een placebo effect. Een zogeheten ‘sham procedure’ waarbij wel een wond wordt gemaakt maar geen decompressie wordt uitgevoerd (simpel gezegd een nep operatie) zou een placebo effect hebben kunnen aantonen. Wij zijn van mening dat een dergelijke ingreep in deze kwetsbare

patiëntengroep niet ethisch zou zijn. Een alternatief kan mogelijk worden verkregen door een kwantitatieve sensorische test (QST). Hiermee kunnen in toekomstige studies veranderingen worden aangetoond in drempels voor thermische pijn en waarneming, waarmee een sham procedure kan worden vermeden.

Ondanks het feit dat chirurgische decompressie pijn vermindert is DPN niet omkeerbaar. Het is van het grootste belang om complicaties zoals neuropathie te voorkomen en het belang van glucose controle voor patiënten te benadrukken. Diabetes mellitus type 1 kan niet worden voorkomen, maar er is bewijs dat veranderingen in lifestyle zoals gewichtsreductie en toename van lichamelijke activiteit het ontstaan van diabetes mellitus type 2 en bijkomende complicaties, waaronder DPN, kan voorkomen.