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Surgical peripheral nerve decompression for the treatment of painful diabetic neuropathy of the foot – A level 1 pragmatic randomized controlled trial

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ABSTRACT

Aims: To assess the efficacy of surgical decompression of lower extremity nerves for the treatment of painful diabetic peripheral sensorimotor polyneuropathy (DPN).
Methods: People with painful diabetic neuropathy were randomized single-blind to a lower extremity decompression surgery (n = 12) or observation (n = 10) for 1 year.
Results: Pain was the primary outcome assessed with 2 measures. The McGill pain visual analogue scores over time changed within the groups (p for time < 0.0001), and changed differently over time within the groups (p for group × time = 0.0138). The NeuroQoL pain sensitivity analysis significantly changed from baseline to 12 months comparing intervention to control (p = 0.0079), and the joint effect of group and time on pain scores was statistically significant (p for group × time = 0.0009). At the study end-point of 12 months, intervention group participants had over 3 times the odds of rating their pain as "better" compared to "unchanged" or "worse" in the control group (p = 0.0177).
Conclusions: Surgical decompression of lower limb nerves was an effective treatment for decreasing pain in patients with DPN and superimposed nerve compressions.

1. Introduction

The incidence of diabetic peripheral sensorimotor polyneuropathy (DPN) approaches 50% in individuals with diabetes mellitus, prevalence increasing with duration of disease [1,2]. Although sometimes asymptomatic, this condition often causes burning pain, and decreased tactile sensation of the foot [3,4]. Estimates of the prevalence of pain in individuals with DPN range from 21% to 50% [5,6]. Painful DPN is debilitating, adversely impacting many aspects of a patient's quality of life including mood, mobility, social relations, work, sleep, leisure activities and overall enjoyment of life [7–10]. Good glycemic control is partially effective in the primary prevention of neuropathy, and in patients with type 1 diabetes mellitus in whom neuropathy develops is sometimes helpful in ameliorating symptoms [4,11]. Multiple treatments are available, including anticonvulsants, antidepressants, opioids, transcutaneous electrical nerve stimulation, spinal cord stimulation, and topical creams and sprays [3,12–14].

Surgical treatment, namely decompression of lower extremity nerves at known sites of compression, has also been advocated for several years – for the amelioration of pain, improvement of sensation and for the prevention of ulceration. However, the quality of studies has generally been

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poor, predominantly non-blinded case series. This led to the issuance of a Practice Advisory by the American Academy of Neurology in 2006, "There are inadequate data concerning the efficacy of decompressive surgery for the treatment of diabetic neuropathy. Given our current knowledge, this treatment is unproven" [15]. The Academy recommended further research to evaluate this method of treatment. The American Diabetes Association also asserted that they "strongly support trials to determine whether these surgical procedures are beneficial" [16].

The purpose of this study was to determine whether nerve decompression surgery is effective in the treatment of painful DPN. The format was a single-blinded pragmatic randomized controlled trial, and the primary outcome measures were pain and neuropathy-specific quality of life. This trial was designed to inform patients and clinicians of the benefits and risks of this surgical intervention at an individual level. Pragmatic randomized controlled trials use primary outcomes which are patient-oriented or clinician-oriented, focus on effectiveness over efficacy, and aim for high external validity (i.e., generalizability to normal clinical practice) at some expense of internal validity [17,18]. In recent years, there has been a call for more pragmatic trials [17,19,20].

2. Methods

2.1. Trial design and participants

Between October 2009 and March 2014, we conducted a pragmatic, single-blinded, parallel-group randomized controlled trial using a 1:1 allocation ratio with blinded assessment of outcomes. The study was conducted in Sault Ste. Marie, Ontario, Canada, a site of the Northern Ontario School of Medicine. Interviews, enrollment procedures, pre- and post-surgical care for the intervention group, and evaluations on all patients were conducted at associated clinics and offices. Surgery was conducted at the Sault Area Hospital, an accredited public hospital.

The study was approved by the Laurentian University Research Ethics Board for the Northern Ontario School of Medicine and the Joint Group Health Centre/Sault Area Hospital Research Ethics Board, both in accordance with the Tri-Council Policy Statement 2 issued by the Panel for Research Ethics for the Government of Canada. All participants provided written informed consent, and had the ability to withdraw participation from the study at any time. Patients were recruited via a letter to all local and regional medical practitioners soliciting patient enrollment, through flyers posted on information boards at local stores providing such public service, and notices on local electronic bulletin boards, all approved by the research ethics boards.

Eligible patients were ≥18 years of age, with the presence of diabetes mellitus type 1 or 2 in accordance with the Canadian Diabetes Association 2003 Clinical Practice Guidelines, and had good diabetic control with hemoglobin A_{1C} (HbA1c) less than 8.0% (64 mmol/mol) [21]. Eligible patients were experiencing symptoms of paresthesia (including burning pain) or numbness present symmetrically in both feet, determined to be on a peripheral nerve basis clinically and using nerve conduction studies interpreted by a consultant neurologist. Included patients rated their average daily pain ≥5 on the 10-point McGill Pain Questionnaire visual analogue item [22,23] and had a total neuropathy score (TNS) ≥ 2 [24]. Exclusion criteria included other etiology diabetes mellitus or neuropathy; symptomatic lumbosacral spine or lower extremity vascular disease; previous foot ulceration or amputation; HbA1c ≥ 8.1% (65 mmol/mol); significant ankle edema, venous stasis, morbid obesity, or previous surgery/injury which would be incompatible with appropriate wound healing. Adults lacking capacity to consent, pregnant women, prisoners, non-English speakers who required an interpreter and those unwilling or unable to participate in the full study follow-up were excluded.

Initial screening for compliance with inclusion and exclusion criteria was via a telephone interview; potential candidates were then forwarded to the enrollment nurse, who then confirmed eligibility and guided willing candidates through the remainder of the enrollment screening process. The last step was a consultation with the study neurologist which included nerve conduction and electromyography testing to confirm the presence of DPN. Patients completing the screening protocol who met all of the inclusion criteria and who did not have any of the exclusion criteria were deemed eligible for enrollment in the study. All enrolled participants continued to receive standard medical management of diabetes and neuropathic pain from their usual medical practitioners throughout the study, without restriction or intervention by the study investigators or team members. Patients' usual practitioners were not involved in the study.

In total, 163 potential subjects were screened, 140 were excluded, 23 were randomized, and 22 were analyzed. One participant withdrew from the study at the point of randomization, so did not contribute any data to the study and was excluded from the analysis (Fig. 1).

2.2. Intervention group

Intervention group patients underwent the identical surgical procedure – decompression of the common peroneal, tibial, and deep peroneal nerves [25]. Surgery was performed at an accredited Canadian hospital, in the main operating theater, under a spinal or general anesthetic.

2.3. Control group

Control group patients continued to receive usual care through their primary care physician and/or endocrinologist. They were not restricted in any way in the management of their neuropathy throughout the course of the study. No advice or care was given by any member of the study team to the control subjects or to their practitioners.

2.4. Measures

All patients (control and intervention groups) were followed-up at three, six and twelve months. At each visit, patients were administered the short-form McGill Pain Questionnaire [22,23] and the Neuropathy-Specific Quality of Life Scale

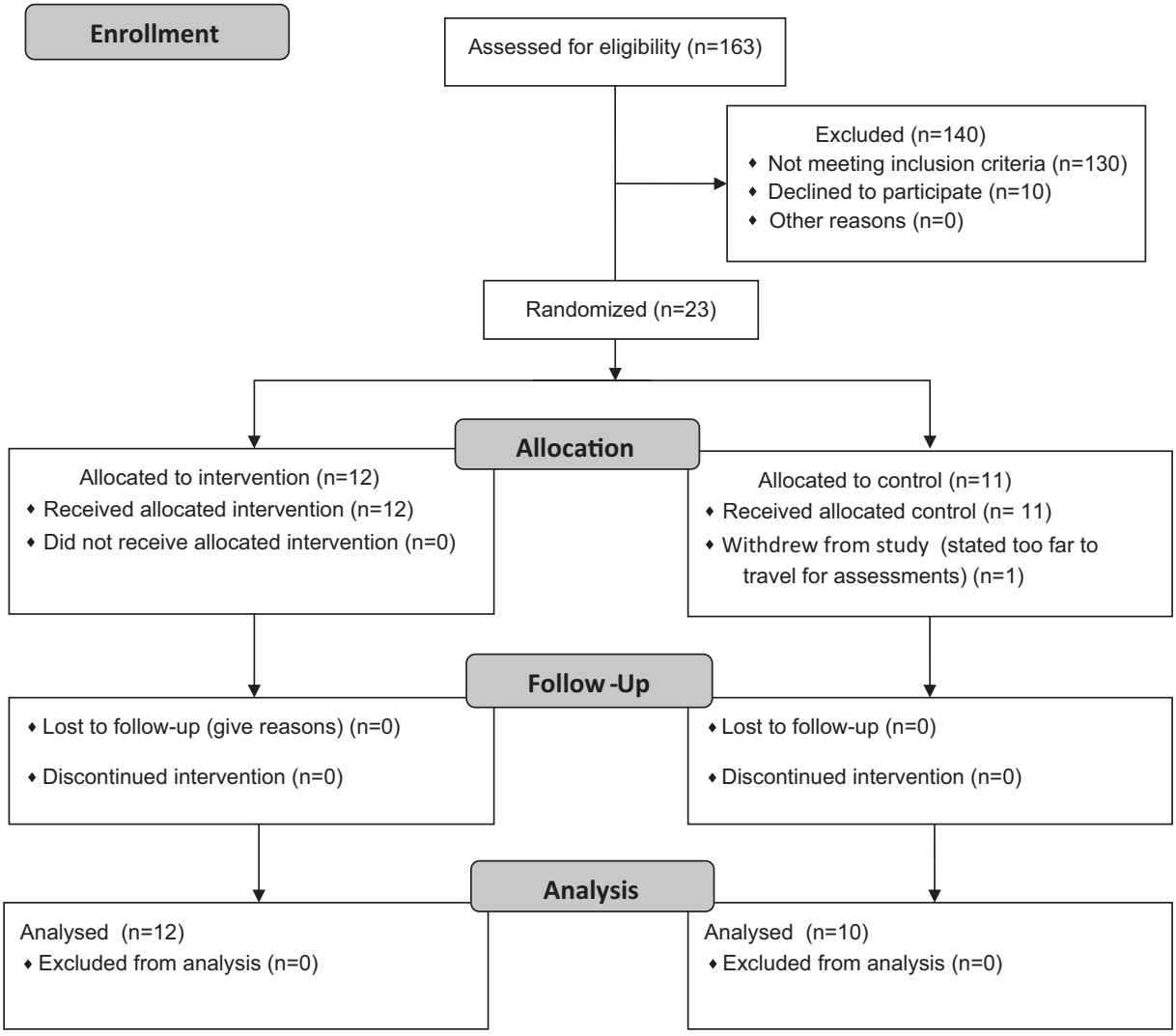

Fig. 1 – Patient flowchart.

(NeuroQoL) by the study nurses trained in proper administration of these measures [26].

The McGill Pain Questionnaire is a validated measure which assesses pain character and overall pain using a visual analogue item with a 10-point Likert scale (0 = none, 10 = worst possible pain). It has been used in previous studies of diabetic peripheral neuropathy [27–35].

The NeuroQoL is a validated, 35-item quality of life instrument developed specifically for patients with peripheral neuropathy [26]. It consists of several hierarchical domains which assess somatic experiences (including pain), sensory-motor experiences and functional, social and emotional experiences associated with diabetic peripheral neuropathy as well as quality of life.

At the baseline and 12-month visits, the study nurse assessed patients for signs and symptoms of neuropathy using the Total Neuropathy Score (TNS) [24]. The TNS is a collection of ten signs and symptoms which are each rated on a 0 to 4 scale, where higher total TNS scores indicates more severe signs and symptoms of neuropathy. Nerve conduction study component results are incorporated into the TNS, as performed by a certified neurologist. Patients were also assessed for two-point discrimination, two-point static pressure thresholds, and one-point static pressure thresholds at the same four lower extremity locations using the Pressure-Specified Sensory Device (PSSD) (Sensory Management Services, Baltimore, Maryland).

The assessment nurse was blinded regarding group allocation of participants for the TNS and PSSD assessments. Prior to each assessment, participants in both groups placed occlusive bandages at the 3 potential surgical sites, guided by a photograph of correctly applied bandages. Positioning was checked by study staff, who reminded patients to never disclose their study group status to the assessment nurse immediately prior to each assessment.

At study end, we asked all participants to simply rate their pain as “worse”, “no change” or “better”.

2.5. *Outcomes*

The primary outcomes under investigation in this pragmatic randomized controlled trial were:

1. Improvement in the change in pain scores using the 10-point scale of the McGill Pain Questionnaire, comparing scores at 12 months to scores at baseline.
2. Quality of life, using the neuropathy-specific quality of life domain and the overall quality of life domain from the NeuroQol.

Secondary outcomes included improvement in the TNS score (which includes pin and vibration sensibility), improvement in tactile sensibility using PSSD measurements, and change in nerve conduction studies at study end. All secondary outcomes were assessed comparing the difference in scores at 12 months to scores at baseline, between the groups.

2.6. Sample size

Although published results of clinical trials in painful DPN indicate wide variation in placebo response, a randomized controlled trial of 165 patients showing efficacy of gabapentin for pain reduction was considered for our sample size calculation [27]. The mean change in the pain score was 2.5 points [27]. Considering this and drawing on the expertise of our study's steering committee which included an endocrinologist, neurologist, neurosurgeon, plastic surgeon, and family physicians, we selected a minimally important difference in pain of 2.5 units on the McGill Pain Questionnaire's 10-point visual analogue item to be considered a positive response. Given a standard deviation of 3 in pain scores, a power of 80% and a two-tailed alpha of 0.05, the power calculation indicated that 24 subjects would be needed for each study group, for a total sample size of 48 subjects.

2.7. Randomization

Randomization was performed using a computer-generated randomization list and sequentially-numbered, sealed opaque envelopes, prepared in advance of enrollment commencement by a third party and kept in a secure locked location. Once individual patient enrollment was completed, the next envelope in the sequence was opened by the enrollment nurse in front of the appropriate study patient, and the enrollment group was recorded. The enrollment nurse was not involved in assessment of outcomes. Patients were randomized using a permuted block design of 4 in a 1:1 ratio.

Patients were aware of their allocation status, but investigators were blinded and assessment of outcomes was blinded. The surgeon performing surgical decompression (TJB) on intervention group patients was not involved in assessment of outcomes. The clinical epidemiologist (LAF) was involved in data analysis and was not involved in the randomization of participants and did not directly assess patient outcomes.

2.8. Statistical methods

Data were initially explored graphically and summarized using means and standard deviations for continuous variables, and counts and proportions for categorical variables. All continuous variables were visually inspected for normality using normal quantile plots and tested for goodness of fit to ensure data were from the normal distribution using the Shapiro-Wilk W test.

The primary outcome of pain was analyzed using an independent two-tailed *t*-test to assess the mean change in the McGill Pain Questionnaire visual analogue item scores from baseline to 12 months, comparing intervention to control. The mean change with its associated 95% confidence interval and *p*-value were calculated. To assess for differences on the visual analogue item within and between the groups over time, a repeated measures analysis using MANOVA was then performed. Using the same methods, we conducted a post-hoc sensitivity analysis to assess the change in neuropathy-specific pain scores at baseline and 12 months using only the NeuroQoL's pain domain.

The primary outcome of quality of life was analyzed with the same procedure, using the overall quality of life and neuropathy-specific quality of life domains from the NeuroQol.

Independent two-tailed *t*-tests were also used to assess secondary outcomes, including change in TNS score and improvement in tactile sensibility using the PSSD. Using ordinal logistic regression, we assessed for a change in peroneal amplitude and a change in sural amplitude on nerve conduction studies between the intervention and control groups at study end (12 months). Peroneal and sural amplitudes were rated by the consultant neurologist on a scale of 0 to 4 as follows: 0 = normal or <5% of lower limit of normal (LLN); 1 = 76 to 95% of LLN; 2 = 51 to 75% of LLN; 3 = 26 to 50% of LLN, 4 = 0 to 25% LLN. A score of 0 was used as the reference group.

We used ordinal logistic regression at study end to assess for differences between the groups when patients simply rated their pain as worse (reference group), unchanged or better.

All analyses were based on intention-to-treat protocol and conducted with two-tailed alpha set to 0.05. Statistical analyses were performed using JMP version 10.0 (Cary, NC). For MANOVA analyses, the sphericity test using the Mauchly Criterion was non-significant, so we report *p*-values derived from unadjusted univariable *F*-tests. Missing data were handled using multiple imputation.

3. Results

Baseline characteristics are reported in Table 1. Overall, baseline characteristics were similar between the groups. The intervention group participants had diabetes for a greater number of years, had slightly worse glycemic control, and were more likely to be taking an oral antihyperglycemic agent and a neuropathic pain agent compared to the control group.

The first primary outcome was a change in McGill pain visual analogue scores between 12 months and baseline, comparing the intervention group to the control group. The mean change between the groups at 12 months was -0.53 points (95% CI −2.95 to 1.89; $p = 0.6459$), not statistically significant. Repeated measures analysis using MANOVA did not demonstrate any significant differences between the groups across the study ($p = 0.1617$), but pain scores did change over time within the groups (p for time <0.0001), and the pain

Table 1 – Baseline characteristics of intervention and control groups.

Variable	Intervention (n = 12)	Control (n = 10)
Age (years), mean (SD)	64 (6.38)	68 (7.13)
Sex, n (%)		
Male	6 (50)	4 (40)
Female	6 (50)	6 (60)
Race, n (%)		
White	11 (92)	9 (90)
Aboriginal	1 (8)	1 (10)
Smoker, n (%)	0	0
Alcohol consumption, n (%)	6 (50)	5 (50)
Exercise, n (%)		
Never	2 (17)	1 (10)
Rarely	1 (8)	4 (40)
Sometimes	4 (33)	3 (30)
Frequently	5 (42)	2 (20)
Diabetes, n (%)		
Type 1	0	1 (10)
Type 2	12 (100)	9 (90)
Duration of diabetes (years), mean (SD)	11.63 (9.63)	7.14 (3.08)
HbA1c, mean (SD) % [mmol/mol)]	6.8% [51(3)]	6.4% [46(4)]
Oral antihyperglycemic agents, n (%)	11 (92)	7 (70)
Insulin, n (%)	3 (25)	2 (20)
Neuropathic pain agent, n (%)	8 (67)	3 (30)

Legend: SD = standard deviation.

scores changed differently over time within the groups (p for group × time = 0.0138) which is apparent in Fig. 2.

Using the NeuroQoL pain item as a sensitivity analysis, the mean change from 12 months to baseline comparing intervention to control was −3.33 (95% CI: −5.67 to −0.99; p = 0.0079). Once again pain was not different between the groups across the study (p = 0.3107). In this analysis, pain scores did not change over time within the groups (p for time = 0.4443) but the joint effect of group and time on pain scores was statistically significant (p for group × time = 0.0009).

The second primary outcome was quality of life using the NeuroQoL. Comparing intervention to control, the mean change in overall quality of life was −0.27 points (95% CI: −1.02 to 0.48; p = 0.4571) from baseline to 12 months, and the mean change in neuropathy-specific quality of life was −0.64 points (95% CI: −1.68 to 0.40; p = 0.2107). No statistically significant differences within or between the groups across the study were detected using repeated measures MANOVA.

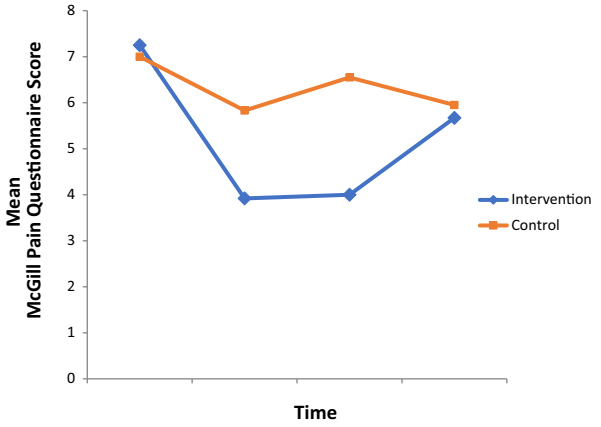

Fig. 2 – Mean McGill pain questionnaire score versus time.

Enrollment was terminated after the interim analysis as the intervention was deemed to be beneficial on the primary outcome analysis.

Results of secondary outcomes are reported in Table 2. There were no significant differences between the groups for the secondary outcomes. Using ordinal logistic regression at 12 months, the intervention group was less likely to have poor nerve conduction studies after surgery compared to the control, with odds ratios approximately 0.3 for sural and peroneal amplitudes, although this did not reach statistical significance (OR for sural amplitude = 0.30; 95% CI: 0.06 to 1.53; p = 0.1470 and OR for peroneal amplitude = 0.28; 95% CI: 0.05 to 1.42; p = 0.124).

At the end of the study, participants in the intervention group were significantly more likely to have indicated that overall their pain was "better" as opposed to "worse" or "unchanged" compared to the control group (OR 3.27; 95% CI: 1.32 to 9.87; p = 0.0177).

One patient in the intervention group developed a postoperative surgical site infection at the tarsal tunnel decompression site. This was treated with oral antibiotic therapy (cephalexin) and daily wound care. The infection resolved and the wound healed in 10 days, and no discernable consequences other than a slightly widened scar were detected.

Table 2 – Secondary outcome measures.

Secondary Outcome	Measure	Mean Difference	95% Confidence Interval	*p*-value
Peripheral Neuropathy	TNS	−2.41	(−5.70, 0.88)	0.9292
Tactile Sensibility	PSSD	−0.34	(−5.90, 5.23)	0.5500

4. Discussion

To date, the treatment of painful diabetic neuropathy of the lower limbs with surgical nerve decompression has been controversial and judged unproven. This level 1 pragmatic, single-blinded, parallel-group randomized controlled trial was designed to address the methodologic concerns of previous studies. This is the first randomized clinical trial reported using a single-blinded between group study design. We selected primary outcomes of pain and quality of life with the understanding that they are patient- and clinician-oriented measures, and are important considerations in therapeutic options and shared decision-making.

This study employed a single-blinded approach where the investigators and outcome assessors were not aware to which group research subjects were allocated. The subjects were aware of their allocation status; the only practical way to blind them would have been to subject the control subjects to sham surgery. Neither of the Canadian research ethics boards overseeing this study permitted a sham surgery control group.

The conceptual basis for applying surgical decompression for the treatment of neuropathy of a metabolic nature deserves comment. Upton and McComas in 1973 first introduced the hypothesis of the double crush syndrome – axonal compression at one site increases susceptibility to developing symptoms of nerve compression when those same axons are compressed at a second site [36]. This hypothesis was altered by Dellon to conceptualizing the 'first crush' or insult to the nerve as the diabetic state, and the second crush as a physical peripheral nerve compression [37]. This was illustrated in a laboratory model of rats with streptozotocin-induced diabetes subjected to physical nerve compression with a 1.0 cm silastic band, a validated model of induced peripheral nerve compression [38]. Subsequently in 1992 the first of a series of clinical reports suggested efficacy of lower limb nerve decompression at known sites of susceptibility, namely the common peroneal nerve at the fibular head, the tibial nerve and its terminal branches at the tarsal tunnel and distally, and the deep peroneal nerve on the dorsum of the foot [39]. Recently, investigations have documented an increased cross-sectional area in ultrasonographic measurements of the tibial nerves of diabetic patients, which may increase their susceptibility to physical compression [40]. Hence at its most basic, the hypothesis can be restated that in patients with diabetes mellitus, the metabolic insult of the disease renders their peripheral nerves susceptible to compressive neuropathy, and hence those patients may experience an amelioration of their symptoms by means of surgical nerve decompression.

In this study, analysis of the primary outcome of pain demonstrated significantly different McGill pain visual analogue scores over time within the groups ($p = 0.0138$), which favoured decompression surgery. Further, we demonstrated that pain scores changed differently over time (Fig. 2). It appeared that pain reduction after surgery was greatest at three and six months in our study, but waned at twelve months when measured with the McGill visual analogue scale. However, our sensitivity analysis using the NeuroQol pain item demonstrated a statistically significant change of more than 3 points in pain scores at study end (12 months) compared to baseline in univariable analysis ($p = 0.0079$). We did not observe a significant change from baseline using the McGill visual analogue scale at 12 months. This discrepancy could suggest that the NeuroQol pain domain is a more accurate measure of neuropathic pain than the McGill visual analogue scale, or that the two measures reflect the construct of neuropathic pain differently.

At the end of the study, intervention group participants had over 3 times the odds of rating their pain as "better" compared to unchanged or worse ($p = 0.0177$).

Together, these results demonstrate that surgical decompression of lower limb nerves is an effective treatment for decreasing pain from DPN, at least in the first year after surgery. This is an important finding because patients with DPN commonly seek medical treatment for the amelioration of pain.

Although we did not detect any statistically significant results in the secondary outcomes, the intervention group was less likely to have poor nerve conduction studies after surgery compared to the control, with odds ratios approximately 0.3 for sural and peroneal amplitudes. In addition, we did not detect an improvement in quality of life using the NeuroQoL instrument. This may be due to small sample size, or reflect a limitation of this measurement tool in this setting. This issue needs to be explored in future studies. A shortcoming of this study was the small sample size. The study was approved for enrollment of 48 patients, 24 in each arm. However, as a surgical interventional study on humans, the research ethics boards demanded an interim analysis at half enrollment, and recruitment termination if a significant difference in primary outcome measures was detected. In the current study, 23 patients were randomized, and the interim analysis was performed. The finding of a significant difference between groups over time in both primary outcome measures caused the termination of enrollment, which unfortunately reduced statistical power.

Overall, the results of this pragmatic randomized controlled trial support surgical nerve decompression in the treatment of painful DPN. The results are similar to the first randomized clinical trial reported on this surgery by Macaré van Maurik et al in the Netherlands [41]. They reported, using a within-patient comparison design, a significant improvement in visual analog pain scores in the operative

leg over 1 year compared to the control leg. Nonetheless, larger studies will be required to replicate these findings in other populations, such as in the context of a multicentre randomized controlled trial. Our study was not designed or powered to assess the effectiveness of decompression surgery on outcomes such as change in sensation, reduction in diabetic ulcers or amputations, so future investigations will need to address these important considerations. Finally, it is not clear which validated pain measures are most sensitive at properly capturing neuropathic pain associated with diabetic neuropathy; further research is needed to determine this.

Conflict of interest

The authors report no conflicts of interest relevant to this article.

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Author contributions

T.B. conceived of the study, contributed to its design, performed the surgery, and wrote the manuscript. C.B. and A.B. recruited patients, researched data, and reviewed/edited the manuscript. L.F. wrote the manuscript, researched data, and performed the data analysis. T.B. and L.F. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Prior presentation

This study was presented as an oral presentation at the American Society for Peripheral Nerve Annual Meeting, Scottsdale, AZ, 15–17 January 2016, and the Canadian Society of Plastic Surgeons 70th Annual Meeting, Ottawa, Canada 14–18 June 2016.

Footnote

Clinical trial reg. no. NCT01006915, clinicaltrials.gov.

REFERENCES

[1] Dyck PJ, Katz KM, Karnes JL, Litchy WJ, Klein R, Pach JM. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy study. Neurology 1993;43:817–24.

[2] Young MJ, Boulton AJM, McLeod AF, Williams DRR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the UK hospital clinic population. Diabetologia 1993;36:150–6.

[3] Boulton AJ. Management of diabetic peripheral neuropathy. Clin Diab 2005;23(1):9–15.

[4] Vinik A, Casellini C, Nevoret ML. Diabetic neuropathies. In: De Groot LJ, Beck-Peccoz P, Chrousos G, Dungan K, Grossman A, Hershman JM, Koch C, McLachlan R, New M, Rebar R, Singer F, Vinik A, Weickert MO, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2015 Aug. p. 23.

[5] Abott CA, Malik RA, van Ross ER, Kulkarni J, Boulton AJ. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes Care 2011;34(10):2220–4.

[6] Tesfaye S, Vileikyte L, Rayman G, Sindrup SH, Perkins BA, Baconja M, et al. Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management. Diabetes Metab Res Rev 2011;27:629–38.

[7] Schmader KE. Epidemiology and Impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. Clin J Pain 2002;18(6):350–4.

[8] Tesfaye S, Kempler P. Painful diabetic neuropathy. Diabetologia 2005;48:805.

[9] Sadosky A, Schaefer C, Mann R, Bergstrom F, Baik R, Parsons B, et al. Burden of illness associated with painful diabetic peripheral neuropathy among adults seeking treatment in the US: results from a retrospective chart review and cross-sectional survey. Diabetes Metab Syndr Obes 2013;6:79–92.

[10] Alleman CJ, Westerhout KY, Hensen M, Chambers C, Stoker M, Long S, et al. Humanistic and economic burden of painful diabetic peripheral neuropathy in Europe: A review of the literature. Diabetes Res Clin Pract 2015;109(2):215–25.

[11] Tkac I, Bril V. Glycemic control is related to the electrophysiologic severity of diabetic peripheral sensorimotor polyneuropathy. Diabetes Care 1998;21 (10):1749–52.

[12] Heydari M, Homayouni K, Hashempur MH, Shams M. Topical Citrullus colocynthis (bitter apple) extract oil in painful diabetic neuropathy: A double-blind randomized placebo-controlled clinical trial. J Diabetes 2016;8(2):246–52.

[13] Javed S, Alam U, Malik RA. Burning through the pain: treatments for diabetic neuropathy. Diabetes Obes Metab 2015;17(12):1115–25.

[14] de Vos CC, Meier K, Zaalberg PB, Nijhuis HJ, Duyvendak W, Vesper J, et al. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. Pain 2014;155(11):2426–31.

[15] Chaudhry V, Stevens JC, Kincaid J, et al. Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Practice advisory: utility of surgical decompression for treatment of diabetic neuropathy. Neurology. 2006;66:1805–8.

[16] Cornblath DR, Vinik A, Feldman E, et al. Surgical Decompression for Diabetic Sensorimotor Polyneuropathy. Diabetes Care 2007;30(2):421–2.

[17] Zwarenstein M, Treweek S, Gagnier JJ, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. BMJ 2008;337:a2390.

[18] Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. J Chronic Dis. 1967;20:637–48.

[19] Liberati A. The relationship between clinical trials and clinical practice: the risks of underestimating its complexity. Stat Med 1994;13:1485–91.

[20] Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. JAMA 2003;290:1624–32.
[21] Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2003 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2003;27 (Suppl 2):S1–152.
[22] Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1(3):277–99.
[23] Melzack R. The short-form McGill Pain Questionnaire. Pain 1987;30(2):191–7.
[24] Cornblath DR, Chaudhry V, Carter K, Lee D, Seysedadr M, Miernicki M, et al. Total neuropathy score: validation and reliability study. Neurology. 1999;53(8):1660–4.
[25] Dellon AL. The Dellon approach to neurolysis in the neuropathy patient with chronic nerve compression. Handchir Mikrochir Plast Chir 2008;40(6):351–60.
[26] Vileikyte L, Peyrot M, Bundy C, Rubin RR, Leventhal H, Mora P, et al. The development and validation of a neuropathy- and foot ulcer-specific quality of life instrument. Diabetes Care 2003;26(9):2549–55.
[27] Backonja M, Beydoun A, Edwards KR, Shwartz SL, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA 1998;280(21):1831–6.
[28] Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology. 2004;63(11):2104–10.
[29] Beydoun A, Kobetz SA, Carrazana EJ. Efficacy of oxcarbazepine in the treatment of painful diabetic neuropathy. Clin J Pain 2004;20(3):174–8.
[30] Wallace MS, Rowbotham MC, Katz NP, Dworkin RH, Dotson RM, et al. A randomized, double-blind, placebo-controlled trial of a glycine antagonist in neuropathic pain. Neurology. 2002;59(11):1694–700.
[31] Kochar DK, Jain N, Agarwal RP, Srivastava T, Agarwal P, Gupta S. Sodium valproate in the management of painful neuropathy in type 2 diabetes – a randomized placebo controlled study. Acta Neurol Scand 2002;106(5):248–52.
[32] Eisenberg E, Lurie Y, Braker C, Daoud D, Ishay A. Lamotrigine reduces painful diabetic neuropathy: a randomized, controlled study. Neurology. 2001;57(3):505–9.
[33] Tesfaye S, Watt J, Benbow SJ, Pang KA, Miles J, MacFarlane IA. Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy. Lancet 1996;348(9043):1698–701.
[34] Stracke H, Meyer UE, Shumacher HE, Federlin K. Mexiletine in the treatment of diabetic neuropathy. Diabetes Care 1992;15(11):1550–5.
[35] Masson EA, Hunt L, Gem JM, Boulton AJ. A novel approach to the diagnosis and assessment of symptomatic diabetic neuropathy. Pain 1989;38(1):25–8.
[36] Upton AR, McComas AJ. The double crush in nerve-entrapment syndromes. Lancet 1973;302(7825):359–62.
[37] Dellon AL, Mackinnon SE, Seiler WA. Susceptibility of the diabetic nerve to chronic compression. Ann Plast Surg 1988;20(2):117–9.
[38] Mackinnon SE, Dellon AL, Hudson AR, et al. Chronic nerve compression – an experimental model in the rat. Ann Plast Surg 1984;13(2):112–20.
[39] Dellon AL. Treatment of symptoms of diabetic neuropathy by peripheral nerve decompression. Plast Reconstr Surg 1992;89:689–97.
[40] Riazi S, Bril V, Perkins BA, et al. Can ultrasound of the tibial nerve detect diabetic peripheral neuropathy? A cross-sectional study. Diabetes Care 2012;35(12):2575–9.
[41] Macare van Maurik JF, van Hal M, van Eijk RP, et al. Value of surgical decompression of compressed nerves in the lower extremity in patients with painful diabetic neuropathy: a randomized controlled trial. Plast Reconstr Surg 2014;134 (2):325–32.