Nerve Decompression After Diabetic Foot Ulceration May Protect Against Recurrence

A 3-Year Controlled, Prospective Analysis

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Background: Nerve entrapment, common in diabetes, is considered an associated phenomenon without large consequence in the development of diabetes complications such as ulceration, infection, amputation, and early mortality. This prospective analysis, with controls, of the ulcer recurrence rate after operative nerve decompression (ND) offers an objective perspective on the possibility of frequent occult nerve entrapment in the diabetic foot complication cascade.

Methods: A multicenter cohort of 42 patients with diabetic sensorimotor polyneuropathy, failed pharmacologic pain control, palpable pulses, and at least one positive Tinel's nerve percussion sign was treated with unilateral multiple lower-leg external neurolyses for the indication of pain. All of the patients had healed at least one previous ipsilateral plantar diabetic foot ulceration (DFU). This group was retrospectively evaluated a minimum of 12 months after operative ND and again 3 years later. The recurrence risk of ipsilateral DFU in that period was prospectively analyzed and compared with new ulcer occurrence in the contralateral intact, nonoperated control legs.

Results: Operated legs developed two ulcer recurrences (4.8%), and nine contralateral control legs developed ulcers (21.4%), requiring three amputations. Ulcer risk is 1.6% per patient per year in ND legs and 7% in nonoperated control legs ($P = .048$).

Conclusions: Adding operative ND at lower-leg fibro-osseous tunnels to standard postulcer treatment resulted in a significantly diminished rate of subsequent DFU in neuropathic high-risk feet. This is prospective, objective evidence that ND can provide valuable ongoing protection from DFU recurrence, even years after primary ulcer healing. (J Am Podiatr Med Assoc 104(1): 66-70, 2014)

The peripheral nerve entrapments commonly found in diabetic sensorimotor polyneuropathy (DSP)[1] are considered an associated phenomenon without large consequence in the development of diabetes complications such as ulceration, infection, amputation, and early mortality. Reports in the past 2 decades that suggest nerve entrapment is involved in DSP complications are not widely accepted due to their use of subjective outcome measures subject to bias and placebo issues. Diabetic foot ulceration (DFU) problems continue to be serious and frequent complications of DSP. Ulcers can initiate a complication cascade leading from chronic wounds to local and regional infections, gangrene, systemic sepsis, life-altering amputations, and associated early mortality. No high-level scientific evidence has demonstrated effective methods for initial ulcer prevention.[2,3] Only plantar temperature monitoring and activity restriction[4] have demonstrated benefit in decreasing recurrence rates for patients with high-risk neuropathic DFU denoted as International Working Group on the Diabetic Foot very-high-risk group 3 (Table 1).

However, temperature monitoring requires ongoing patient commitment and a support infrastructure that is rarely available. Several published papers[5-7] and anecdotal reports of only rare cases of ulceration or recurrence after external neurolysis at fibro-osseous tunnel sites for pain relief have suggested that nerve decompression (ND) might prevent the ulcer complication cascade while also ameliorating the subjective pain and numbness symptoms that are primary patient concerns. This

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Table 1. International Working Group on the Diabetic Foot Risk Groups for Foot Ulceration

Group	Risk Level	Description
Group 0	Low	No sensory neuropathy
Group 1	Intermediate	DSP plus sensory neuropathy
Group 2	High	DSP sensory neuropathy plus PVD or foot deformity
Group 3	Very high	DSP plus previous foot ulcer or amputation

Abbreviations: DSP, diabetic sensorimotor polyneuropathy; PVD, peripheral vascular disease.

study further tests that hypothesis with a prospective analysis of ulcer recurrences over 3 years in 42 patients with DFU and unilateral ND, using the never-ulcerated, contralateral nonoperated legs as matched controls.

Research Design and Methods

An institutional review board–approved retrospective cohort study previously reported that annual ulcer recurrence risk after ND for pain was 4.6% at a mean of 2.5 years[7] and 2.3% at 5 years.[8] These risk figures are more than 80% lower than the literature leads us to expect. Demographic data are shown in Table 2 for that DFU/ND cohort of 75 previously ulcerated legs in 65 patients with DSP. Figure 1 shows the timelines and results for the three differing reports on members of the cohort. The 55 patients in the initial cohort who underwent only unilateral decompression offer an opportunity to compare the ulceration behavior of operated and nonoperated legs of the same individual subsequent to ND. The inclusion criteria for this current subset cohort of 42 members were painful DSP, failed medical control of pain, a positive Tinel's sign, adequate circulation with at least one palpable pulse or an ankle-brachial index greater than 0.8, an intact contralateral leg, and previous ipsilateral DFU. External neurolysis for decompression of lower-extremity nerves as recommended by Dellon[9] for painful neuropathy had been accomplished at four fibro-osseous tunnel locations (tarsal, abductor, common peroneal, and dorsal foot deep peroneal). The 55 patients in the ND/DFU cohort who underwent only unilateral decompression offer an opportunity to compare the ulceration behavior of operated and nonoperated legs of the same individual subsequent to ND.

In this case, the nonoperated leg can serve as a control perfectly matched for duration and severity of metabolic disease and DSP neuropathy, tissue metabolic milieu, International Working Group on the Diabetic Foot risk group, past and current medical treatment, activity level, sex, age, race, and time since operative decompression. Risk factors such as foot deformity, large-vessel circulation, and plantar skin pressure concentrations might be asymmetrical between legs. Thirteen of 55 patients with unilateral ND in the retrospective study were excluded for a control, nonoperated leg with previous amputation or a subsequent vascular procedure or ND, leaving 42 patients for prospective analysis. Events of demise during the study period are included. We here analyze the ulcer occurrence risk of operated and nonoperated legs of those patients with unilateral ND during the 3 years between initial publication[7] and last report.[8] Ulcer-free survival of the operated legs and their contralateral mates over 3 years was illustrated with Kaplan-Meier curves and was compared statistically with the Fisher exact test.

Table 2. Initial Demographic Data for 75 Legs of 65 Patients With Diabetes, Previous Diabetic Foot Ulceration, Adequate Circulation, Failed Medical Pain Control, a Positive Tinel's Nerve Percussion Sign, and Subsequent Lower-Extremity Nerve Decompressions (NDs)

Characteristic	Value
Age (years)	
Mean	74.5
Range	42–86
Type 1/2 diabetes (%)	13/87
Duration of diabetes known to patient (mean [years])	13.5
Duration of follow-up after operative ND (years)	
Mean	2.49
Range	1–13
Open ulcer at time of surgery (No.)	4
Ulcer healed without recurrence (No.)	4
Postoperative complications resolved with local care (No.)	3
Delayed wound healing (No.)	3
No. of operated legs by treating surgeon's training	
Plastic surgery (n = 2)	18
Orthopedic surgery	4
Podiatric medicine (n = 2)	53

Results

These legs demonstrated annual recurrence rates much lower than the 25% or greater reported in the

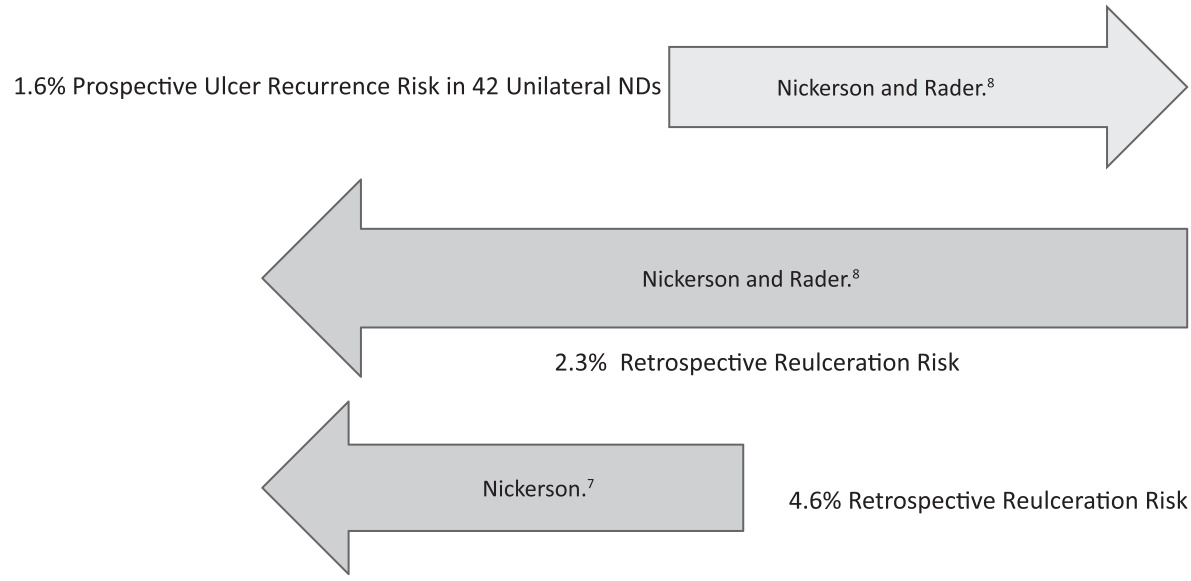

Figure 1. Retrospective reports of short- and long-term (5-year) ulcer recurrence behavior after nerve decompression (ND) of the 75 legs with previous diabetic foot ulceration and the prospective behavior of patients with unilateral ND during the 3 years between the short- and long-term evaluations.

literature in the short- and medium-term.[4] Legs treated with ND had a lower rate of subsequent ulceration than control legs. Operated legs experienced two ulcer recurrences (4.8%), and nine contralateral legs developed ulcers (21.4%), requiring three amputations, during the 3 years of prospective review. The two recurrences on operated legs were at the second metatarsal head (same site) and the plantar hallux (new site). No information is available about loss of ankle dorsiflexion as a possible contributor to recurrence. The initial retrospective report patients[7] had a mean of 2.5 years (range, 1–13 years) of follow-up after ND, and this current prospective study period covers the ensuing 3 years, a mean of 35.8 months (range, 16–53 months). Short follow-up times represent patient demise. Ulcer risk in that period is 1.6% per patient per year in ND limbs and 7% in nonoperated control legs. Using the Fisher exact test of a hypothesis that ND will have no effect on subsequent ulcer occurrence, the null hypothesis is rejected. This finding supports the conclusion that ND is effective in changing ulcer recurrence risk ($P = 0.048$). The hazard ratio of ulcer occurrence being in the nonoperated leg is 5.5 (95% confidence interval, 3.6–7.0). Figure 2 presents the ulcer-free survival of operated and control legs with a Kaplan-Meier graph.

Discussion

Operated leg values for annual ulcer recurrence risk are low compared with the level 1 prospective study control groups of Lavery et al[4] and previous retrospective case study literature, which lead us to expect annual recurrence risk for neuropathic DFU of at least 25% using best foot care methods. The prospective analysis of matched leg controls and the use of ulcer occurrence as an objective outcome measure address the potential confounding problems of placebo effects, surgeon or patient bias, and the necessity for blinding of observers. These issues have been suggested to be design weaknesses of the retrospective, subjective, and pain and sensibility reports in the ND/DSP literature. Availability of the matched, nonoperated contralateral leg as a control

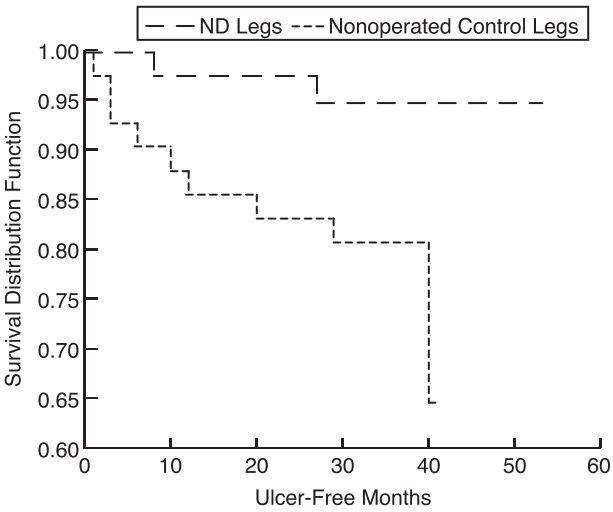

Figure 2. Kaplan-Meier curve illustrates the ulcer-free survival of 42 nerve decompression (ND) operated and nonoperated legs of patients with neuropathic International Working Group on the Diabetic Foot risk group 3. The initial data collection point is at least 1 year (mean, 2.5 years) subsequent to diabetic foot ulceration wound healing and unilateral operative ND.

for many known and pertinent variables is a particular strength in rebutting that critique.

These results are similar to those of Aszmann et al,[5] who reported that amputation or ulceration after unilateral lower-extremity ND was frequent in the nonoperated legs (30%) and absent in the operated legs (0%) of 50 patients with DSP at a mean of 4.5 years. Those patients, lacking any data about foot deformity, were International Working Group on the Diabetic Foot risk group 1 or 2, having neuropathy but without impaired circulation or the ulceration history of risk group 3.

This report differs from other reports[5-8] of low ulcer recurrence risk after ND in taking initial observations not at the time of ulcer healing or ND surgery but at the time of original cohort assembly for the previous retrospective analysis.[7] That baseline data point of original cohort examination was a mean of 2.5 years after surgical external neurolysis. Hence, the 3-year evaluation period for this report of ulcer-free survival in these legs is shorter than both the total postulcer healing and postoperative ND periods. This study design allows analysis of the data to be prospective, objective, and placebo controlled and strengthens the scientific evidence from level 3 (retrospective cohort study) to level 2 (prospective, controlled interventional clinical outcome study).

There are recognized weaknesses due to the retrospective medical record review that originally defined the study group. Medical records lack independent subjective or objective neuropathy evidence aside from the existence of diabetes, pain, and at least one previous foot ulceration in the operated leg. Another weakness is the lack of contemporaneous laboratory confirmation of diabetes, although all of the patients were taking oral or parenteral medical diabetes treatments at the time of operation. Yet, the multiplicity of signs and symptoms and the absence of confounding factors support the diagnosis of DSP by the guidelines of the 2005 statement on diabetic neuropathies by the American Diabetes Association.

It could be argued that analysis of ulcer risk in a remote follow-up interval, beginning at least 12 months after initial ulcer healing and surgical intervention, is not comparable with the extensive ulcer recurrence literature. But the difference in ulcer occurrence rates of the index foot and the contralateral nonoperated control limb is statistically significant and so must be given some credence. We are not aware of any evidence that ulcer or recurrence risk subsides with time. The comparatively poor performance of the nonoperated control legs as predicted by the literature suggests that the high ulceration risk of International Working Group on the Diabetic Foot group 3 continues unabated in the long-term.

Traditionally, DSP has been viewed as irreversible and progressive. Prevention of neuropathy complications has focused on educating providers and patients about risks and self-care, and using custom footwear or inserts to reduce pressure concentrations. This study's demonstration of lower complication incidence accompanying surgical neurolysis implies that ND provides an important modification of the degree of DSP or other etiologic factors that eventuate in DFU.

The finding that ND produced greater than 80% risk reduction for foot ulcer development in high-risk legs implies an opportunity for large reductions in future occurrences of soft-tissue infections and amputations because almost all lower-extremity amputations in DSP are preceded by an open wound.[10] Might no ulcer wound imply that there will be no amputation? This investigation cannot answer that question since cases were selected for adequate circulation parameters. But neurally mediated effects on small vessels in peripheral vascular disease is a potential mechanism through which ND may deliver protection. Studies are under way evaluating this possibility.

The cost-benefit economics of applying ND to the large population with neuropathic DFU is currently unknown. The high costs of ulcer care might be reduced by up to 80% if these recurrences were avoided. Forestalled expenses of major amputation and its aftercare would compound savings, to say nothing of the value of productivity and quality of life preserved. How such savings would balance against the cost of providing ND to appropriate patients with DFU is yet to be calculated, but it will be an important consideration should level 1 evidence-based studies confirm ND to have a protective effect versus recurrent and initial DFU.

This result adds to the objective outcome reports by Aszmann et al,[5] Ducic et al,[11] Rosson et al,[12] Dellon et al,[6] Nickerson and Rader,[7,8] and now Zhang et al[13] finding ND of value in improving various parameters and avoiding complications of DSP. This list now includes ulceration and recurrence, amputation, balance, sonographic nerve englargement, nerve conduction deficits, fibro-osseous tunnel tissue pressure, nerve conduction velocity, foot-related hospitalizations, and short- and long-term ulcer recurrence risk. It is consistent with a hypothesis of frequent subclinical nerve entrapment in DSP, not regularly recognized by standard electrophysiologic testing, but responsible for some fraction of symptoms and complications and importantly, amenable to therapeutic ND. This result cannot be explained by the hypothesis of metabolically induced length-dependent axonopathy alone and challenges that currently regnant paradigm. Prospective randomized controlled trials seem strongly advised to test this prospect for the avoidance of many serious and life-threatening diabetes foot complications via a simple, safe, and effective surgical procedure.

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