DURA CLINICAL STUDY PROTOCOL

Revised February 8, 2018

Study Title: A Prospective Study of Recurrence Risk in Diabetic Foot Ulceration after Nerve Decompression WIRB Protocol #20122035

Initial Protocol Date: Dec. 2, 2012

Study Phase: Phase IIA

Study Design: Multi-center, randomized, placebo controlled, non-blinded, clinical response trial evaluating changes in the clinical outcome, recurrence risk of healed diabetic foot ulcer(DFU) after intervention for bilateral leg surgical nerve decompressions(ND). Part B - Prospective non-randomized clinical response trial of bilateral leg nerve decompression in candidates declining randomization.

Sponsor: The Extremity Nerve Research Foundation (ENRF) of the Association of Extremity Nerve Surgeons (AENS)

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1. Background

Nerve decompression(ND) at specific fibro-osseous extremity tunnels has been consistently reported in retrospective, subjective outcome, observational studies to improve pain and sensation in patients with diabetic sensorimotor polyneuropathy (DSPN)[1] and in Hansen's Disease.[2] Two retrospective medium and long term observational, objective outcome reports of DFU recurrence after ND in previously ulcerated feet have found >80% reduction of annual ulcer recurrence risk.[3,4] Zhang's large prospective, non-randomized report confirmed this impression.[5] Previous literature reported 25% and greater risk of DFU.[6-8] Given that almost all amputations in neuropathic DFU are preceded by an open or penetrating wound, ND has potential for substantially reducing the cost of diabetic foot care and the devastating cascade of ulcer recurrence, local infection, osteomyelitis, gangrene, sepsis, amputations, diminished life expectancy and early demise.[9] This effect would be produced entirely by prevention of

recurrences. Academic skepticism of subjective outcome ND studies[10] for painful DSPN has impeded widespread adoption of the ND technique, despite patient satisfaction and the potential for great benefits in reduced costs for pain treatment. The objective, but retrospective and uncontrolled results of the prior studies of ND in DFU need to be confirmed with Level 1 protocols. This would address the current academic skepticism and clinician indifference with quantitative, objective evidence of patient benefit and economic implications. Rozen has now done this Level 1 trial for DSPN pain with an excellent result..[11]

The published literature has some studies of DSPN in diabetes which have used objective outcome measures. Aszmann reported protection of the operated foot from ulceration and amputation in comparison to the contralateral leg in a long term follow-up of unilateral decompression for pain in IWGDF (International Working Group on the Diabetic Foot) high risk group 2.[12] Ducic has demonstrated prospectively that neuropathy patients improve their balance performance on the Mat Scan Measurement System test when both legs have had nerve decompression.[13,14] Rosson has shown that in DSPN, the medial ankle fibro-osseous tunnels of the posterior tibial nerve and its medial calcaneal, medial and lateral plantar branches can have pressures elevated to a level that endangers function and nerve survival.[15] A prospective patient registry found ND cases to have low objective rates of ulceration, re-ulceration, hospitalization for foot problems, and subsequent amputation as well as subjective sensory recovery and pain relief.[16] Anderson has demonstrated that ND of the common peroneal nerve in painful DSPN is usually followed within one or two minutes by improvement in the muscle evoked potential EMG value.[17]

This study will investigate high risk DSPN patients (IWGDF group 3) with a recently healed neuropathic plantar DFU, randomized to standard non-operative care or to bilateral ND plus standard care, and measure the subsequent appearance of a foot ulcer. The intent is to determine whether the risk of DFU recurrence changes after ND at lower extremity fibro-osseous tunnels. Candidates qualified for the study but declining randomization and preferring ND will be entered in a prospective arm which will be analyzed in comparison to historical norms.

Study Objectives

2.1 Primary Objective

To prospectively measure, after recent primary DFU wound healing, the subsequent appearance of a plantar DFU, comparing DSPN cases receiving standard care as placebo to the intervention case of standard care plus bilateral surgical nerve decompression ND.

2.2 Secondary Objective

1) Evaluate concurrent changes in Michigan Neuropathy Screening Index (MNSI), sensibility to vibration and touch, and pain by Visual Analog Pain Scale score (VAPS) in ND and standard care groups..

2) Quantify the risk of operative wound infection, delayed healing or dehiscence of surgical wounds in this setting.

3) Compare relative risk of ulcer formation for operated and non-operated legs in cases who might decline the contralateral procedure after their initial unilateral ND.

4) Analyze any relationship between ankle dorsiflexion range and ulcer recurrence risk.

5) Examine correlations between nerve decompression and objective measurements of foot circulation, autonomic sudomotor sweating function, falls, balance and gait.

6) Measure in the prospective cohort the DFU recurrence risk for comparison to published recurrence risk for non-ischemic DFU.

3. Research Design

3.1 Summary of Study Design

This is a phase IIA, multi-center, randomized, non-blinded, placebo controlled, clinical response trial evaluating risk of recurrence of diabetic foot ulcer (DFU) after nerve decompression(ND) compared to a control DFU group. Eligible patients will be randomized (1:2) to either a standard non-operative "best care" or to "best care" plus bilateral lower extremity multiple nerve decompression by the methods of Dellon. One hundred twenty patients will be recruited from 6 clinical practices around the country. Participants will have a history of recently healed (within 18 months) unilateral or bilateral plantar neuropathic diabetic foot ulcer (IWGDF risk group 3), adequate circulation, HgbA1c levels of under 8.5, and must agree to undergo, if selected, nerve decompression surgery with the goal of evaluating risk of DFU recurrence. The effects of nerve surgery on reducing the occurrence of subsequent foot ulcer and patients' tolerance of ND will be measured, and compared for approximately 24 months to the results for patients receiving the usual care for healed foot ulcers, but no ND. Other outcomes evaluated will include the objective and subjective measures in 2.1 and 2.2 above. Participants qualified for the study, but preferring surgical nerve decompression and unwilling to be randomized to usual care may be enrolled in the discrete prospective arm for separate analysis and reporting.

3.2 ***Treatment***

The study will track patients for about *2 years* after enrollment or operative ND. Each patient will have about *8* study visits, at quarterly intervals, as recommended for aftercare of healed DFU. ND cases will have at least 3 additional visits for the outpatient surgery and surgical aftercare. The control group will have all the usual non-operative aftercare provided for patients of the clinical practice with a healed plantar DFU. The intervention group will have the same care routine, but in addition will have both legs operated as an outpatient to open and decompress specific anatomic areas where nerve is commonly trapped. These entrapment areas are fibro-osseous tunnels surrounding the common peroneal nerve below the lateral knee, the tibial nerve and its branches at the medial ankle, the superficial peroneal nerve in the leg as it exits the anterior or lateral compartment fascia into a subcutaneous location, and the dorsal branch deep peroneal nerve under extensor pollicis brevis tendon. Any development of skin wound or ulcer will be required to be immediately reported to the patient's footcare clinic and therapy for skin healing will be initiated straightaway.

4. Study Population

4.1 Overview Men and women from 18 to 80 years of age inclusive diagnosed with diabetes and DSPN nerve damage (neuropathy), adequate circulation, having recently healed a plantar foot ulcer and meeting all inclusion and no exclusion criteria, are eligible for enrollment. Communication will be in English, and vulnerable cases will be excluded.

4.1.1 Participating Physicians

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4.2 Inclusion Criteria

1) A clinical diagnosis of type 1 or 2 diabetes, male or female, ages 18-80
2) A recent history (= or < 18 months) of one or more healed DFU

3) Have a hemoglobin A1C within the past 6 months prior to entry date.

4) At least one palpable foot or ankle pulse or ABI >0.8 bilaterally.

5) Diagnosis of DSPN

6) Most recent Hgb A1c < 8.5%

7) Ankle edema absent or mild

8) Be willing to have noninvasive neurosensory, Neuropad, Sudoscan or SPY testing, and to complete neuropathy and pain status questionnaires

9) Abnormal Rydel-Seiffer tuning fork, vibrometer or Vibratip vibration sensibility, Semmes-Weinstein monofilament, Ipswich Touch Test, Discriminator 2-point sensation or PSSD sensory testing in peroneal and/or posterior tibial sensory areas

10) Be willing, if assigned to the surgery group, to undergo soft tissue nerve decompression (external neurolysis) outpatient surgery at 4 anatomic entrapment locations of common peroneal and posterior tibial nerves and distal branches

11) Be willing to commit to regular participation in follow-up exams and questionnaires.

12) Be willing to provide a complete list of Rx & OTC medications and any herbal remedies being actively used.

13) Be willing to provide a past medical history.

4.3 Exclusion Criteria

1) Evidence of significant peripheral arterial disease including past surgical or medical vascular intervention, absent lower extremity pulses or ABI< 0.8, symptoms of claudication, rest pain or ischemia related ulceration.

2) Evidence of exacerbating lower extremity peripheral nerve pathology including past medical or surgical intervention, alcohol abuse(more than 2 drinks/day on average), untreated thyroid disorders, B12 or Folate deficiency, sero (-)/(+) spondyloarthropathies, hepatic disease, advanced renal disease, current lumbosacral radiculopathy or nerve compression, toxin exposure including chemotherapeutic agents, familial polyneuropathy or diagnosis of other neuromuscular disorders.

3) Hgb A1c > 8.0 may delay enrolment

4) Previous lower extremity nerve or lumbar disc surgery.

5) Concurrent operative foot procedures.

6) Severe ankle edema

7) Unwillingness to provide consent for nerve decompression procedure

STUDY DATA

5.0 Sources of Data

Data will be collected from patient medical records, clinical interviews, physical examinations and laboratory testing

5.1 Data collected will include:

- Demographic information: age, gender, weight, height, BMI
- Diabetes: Type 1 or 2, and known duration of disease
- Initial Hgb A1c at study inception
- Prior ulcer count & location, each foot
- Range of ankle motion, dorsiflexion & plantar flexion
- MNSI Michigan Neuropathy Screening Index score
- VAPS Visual Analog Pain Scale score
- Charcot Foot neuro-osteoarthropathy history, with deformity?
- Claw toes, hammertoes, fixed position?
- Quantification of analgesics, narcotics being used
- History of falling events
- Vibrometry or Rydel-Seiffert tuning fork result, 10 gm 5.07 SWM @ 4 plantar sites & toe pads + dorsal 1st web, Ipswich Touch Test, Discriminator 2-point sensation, PSSD where available
- Tinel's sign or tenderness @ common peroneal nerve tunnel, tarsal tunnel, abductor tunnels, dorsal deep peroneal nerve
- Circulation status, one or more palpable arterial foot pulse (PT, dorsalis pedis, peroneal), ABI if absent
- UTHSC stage of most recent DFU wound
- Time since healing & location for most recent healed ulcer, and # of prior ulcers
- Time duration of ND surgical procedure
- Anaesthesia method; Local, spinal, general, tourniquet?
- Perioperative antibiotic, dose, route, duration.

- Wound healing troubles post-op ND, location, dehiscence, clinical infection, antibiotics p.o., antibiotics parenteral, hospitalization.
- Surgical site infection, by clinical criteria- heat, rubor, pain, swelling, wound drainage; culture?
- Wound dehiscence w/o infection
- Post-op ulcer occurrences, date, interval since ND
- Site of recurrence; same vs new, previously ulcerated leg or not, time to healing of recurrence
- Treatment for new ulcer, TCC, other, healing time?
- Vascular complications or interventions, designate limb
- Amputations, level, ischemia, revascularization, site
- Foot related hospitalizations- sepsis, gangrene
- Other footcare regimen changes, bilaterality
- Other foot procedures concurrent to ND proscribed
- Changes in neuroactive medications, narcotics or other analgesics
- Demise, with or without recurrence, date.
- SPY exam data by indocyanine green fluorescence circulation, and gait and balance evaluations (limited to sites with SPY availability).
- Autonomicaly controlled sudomotor skin sweating function evaluated by non-invasive Sudoscan or Neuropad technology (at selected sites)

5.2 **Therapeutic Intervention:** Multiple peripheral nerve releases via external neurolysis, as described by Dellon[18,19], of

1. Common peroneal n. at fibular neck
2. Superficial peroneal N. at fascial ostium in distal leg.
3. Deep peroneal n. under Extensor Pollicis Brevis
4. Posterior Tibial n. at medial ankle retinaculum
5. Medial and lateral plantar nn. at abductor tunnels
6. Medial calcaneal n. at medial heel
7. Epineural neurolysis of any of these nerves found thickened and fibrotic.

This procedure is similar to open carpal tunnel surgery for the hand.

***5.3* Primary Outcome Measure** DFU Occurrences and Recurrence risk of the control group and the intervention group will be calculated.

***5.4* Secondary Outcomes Measured**

- Wound healing difficulties- clinical infection of surgical wound , delayed non-infected healing, dehiscence.
- Relation of ulcers and restricted ankle dorsiflexion.
- Sensibility changes; vibration, SWM changes, light touch, two point discrimination, Tinel sign, PSSD
- Pain medication usage, VAPS changes
- Foot related hospitalizations, LE amputations and mortality will be recorded.
- Examine circulation changes with SPY indocyanine green circulation studies.
- Correlate surgical nerve decompression with falls, gait and balance studies.
- Correlate nerve decompression with autonomic nerve function as evaluated with SudoScan or Neuropad sweat studies.
- Recurrence risk of non-randomized, prospective cases

***5.5* Statistical analysis** Power calculations will define case numbers needed to differentiate between the widely accepted recurrence risk of at least 25% per patient year and a 10% risk, at the alpha level of $P = <0.05$ with 95% confidence.

Fischer's Exact Test will calculate scientific significance of ulcer recurrence risk differences between intervention and control groups. Null hypothesis, based on current academic opinion, is that multiple nerve LE decompressions in diabetic sensorimotor polyneuropathy (DSPN) patients with prior neuropathic DFU would not decrease the risk of ulcer recurrence.

Kaplan-Meier graphing will demonstrate the survival rates without ulcer recurrence of the control group and the intervention cohort and, if there are unilateral surgery cases, operated vs. non-operated legs.

Simple percentage risk will be calculated for surgical site infection, hospitalizations for foot complications, and dehiscence or delayed healing .

6. Schedule of Assessments and Procedures

6.1 Visit 1 (Screening Examination)

All patients must sign and date the most current Institutional Review Board (IRB)/Ethics Committee's approved informed consent document before any study-specific assessments or procedures are performed. A screening examination (medical history, physical and neurological examination including vital signs, height and weight) will be performed. Patients will complete an MNSI and a VAPS questionnaire during their screening visit to evaluate severity of their neuropathic symptoms and pain. Assignment will be made randomly to the best care Non-surgical control group, or to surgical Intervention, bilateral ND group. Candidates declining randomization will be entered in the prospective trial arm. SPY circulation exam, gait and balance studies, and SudoScan or Neuropad evaluations will be accomplished at study entry, pre-operatively.

6.2 Visit 2a (Surgery Day, for Intervention cases)

Patients in the intervention group will undergo a ND procedure as an outpatient surgery. Legs will be operated either simultaneously, or sequentially at a later date according to surgeon's routine and preference.

6.3 Visit 2b (2-3 weeks post op, for Intervention cases)

Patients will have a visit with their surgeon to evaluate their recovery from surgery and for suture removal. .

6.4 Visit 2c- Week 5-6 (after peripheral nerve decompression, for Intervention cases)

Patients will have a follow up post-surgery exam, VAPS, sensibility and Tinel's testing

6.5 Visit 3- Week 12 for <u>All</u> patients

Assess and document all adverse events

Review all concomitant medications

SPY, SudoScan or Neuropad, gait and balance studies

6.6 Visit 4-9 6 Month visit and subsequent quarterly visits @ 9, 12,15, 18, 21 months

Assess and document all adverse events

Provide standard post-ulcer foot care and exam

Brief history and physical including neurological testing

Review all concomitant medications

Administer VAPS, sensibility and Tinel's testing @ Months 6, 12, and 18

SPY, SudoScan, gait and balance studies at 12 month visit

6.8 Visit 10 Last Visit 24 months

Assess and document all adverse events

Provide standard post-ulcer foot care and exam

Brief history and physical including neurological testing

Review all concomitant medications

Administer VAPS, sensibility and Tinel's testing, MNSI, PSSD

6.9 ***Interim visits*** Complications such as ulcer appearance, foot infection, swelling, redness, drainage, or inordinate pain should be immediately reported to the physician's office.

7.0 Safety Variables Surgical wound infections, nerve injury, wound dehiscence, non-surgical foot infections, hospitalization, sepsis, gangrene, critical limb ischemia.

7.1 Data and Safety Monitoring Board

Because the procedures and care in this study are not investigational, but an efficacy evaluation only, no safety monitoring board is required. There will, however, be a Data Monitoring Board (DMB) will consist of the Principal Investigator and Medical Monitor (Drs. Barrett & Nickerson). They will be responsible for periodic evaluations of the clinical trial. Unforeseen complication events will be part of that data review, and this board would move to report to the IRB such cases which would raise safety concerns. This board will meet after 15 surgical patients have completed 3 months of the study, then quarterly after that. The DMB will receive

case listings and data summaries. In addition, the DMB will receive SAE data (significant adverse event) monthly for review. If any safety concerns arise, the DMB will take appropriate measures to assure safety of study patients. If there are significant concerns the DMB will consider whether to abate the trial for safety; stop accrual and request follow up visits with the patients already enrolled, or continue with accruing the remaining patients at the time of the interim analysis.

7.2 Safety

For adverse events, a descriptive analysis will be given. Furthermore, the nature, incidence, severity (mild, moderate or severe) and causality will be reported and recorded for each adverse event.

7.3 Potential Risks and Procedures to Minimize Risks

All known potential risks are disclosed to study participants prior to their participation. No known additional risks apply to the Non-surgical control group. The potential risks associated with this study's Intervention group include anaesthesia events, injury to muscle/nerves/blood vessels during surgical decompression, wound infection or delayed healing, pain or discomfort during decompression and the postoperative period. In addition, although every attempt is made to protect all areas of the body from pressure on nerves, skin and bones, injuries to these areas could occur, particularly with prolonged cases. Perioperative antibiotics will also be given under the direction of each surgeon. Post op follow up visits will occur to minimize the risk of infection and ensure early recognition.

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