SHORT REPORT

Protocol for a Randomised Controlled Trial Investigating Decompression for Leprous Neuropathy (The DELN Protocol)

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Summary

Objectives: An expert group of peripheral nerve surgeons, reconstructive surgeons, and immunologists who have extensive experience with Hansen’s Disease convened to discuss the status of nerve decompression as a treatment for leprous neuropathy. The expert group recommended an international, multi-center randomised controlled trial (RCT). Subsequently, a study protocol called Decompression for Leprous
Neuropathy (DELN) was designed and further refined by multiple investigators worldwide.

**The DELN Protocol:** The DELN RCT seeks to determine the long-term effect of nerve decompression on sensibility, motor function, neuropathic pain, disability, and quality of life. The RCT would enroll patients with clinically diagnosed leprous neuropathy and positive Tinel signs in the upper and lower extremities. Patients would then be randomized to receive nerve decompression or not. Outcomes of interest include sensory function, motor function, pain, disability, and quality of life. The development of ulcers or amputations after surgery and the influence of corticosteroid therapy are also important outcomes that DELN seeks to determine.

**Conclusions:** The study Decompression for Leprous Neuropathy (DELN) is an international, multi-center RCT with the potential to produce high quality data to address whether nerve decompression for leprous neuropathy can conclusively improve patient outcomes. We invite discussion from all those involved in the peripheral nerve and leprosy communities.

**Introduction**

Even though the first written description of Leprosy (Hansen’s Disease) dates back to 1550 BC, Hansen’s Disease continues to exist as a profoundly damaging illness today. In 2014, there were at least 213,899 new cases globally; underreporting likely affects this figure. Globally, an estimated 4 million people are afflicted with physical disabilities due to Hansen’s disease. The physical disabilities present as paresthesias, muscle paralysis (e.g., lagophthalmos, foot drop, claw hands, and inability to blink), ulcers, and/or limb loss.

The World Health Organization (WHO) Hansen’s Disease disability grading system describes, for the hands and feet, Grade 1 disability as having anaesthesia with no visible deformity or damage; the determination for Grade 2 disability is based on having visible deformity or damage. Grade 2 disability is estimated to affect 6.6% of new cases in 2014. Global rates of Grade 1 disability are not reported, but several country-level studies indicate that 20.3% to 50.0% of new cases can suffer loss of sensation.

The physical disabilities and stigma characteristic of Hansen’s Disease can arguably be linked to the *Mycobacterium leprae*, which preferentially targets the peripheral nerves and incites immunological reactions. Nerve damage (i.e., nerve function impairment or leprous neuropathy) is one underappreciated aspect of this disease’s pathophysiology and may benefit from innovation in early detection and treatment in order to prevent the stigmatizing physical disabilities. We and others have noted that it is imperative that effective interventions be identified for preventing and treating leprous neuropathy.

Cross, in 2015, provided a timely review of the relevant literature examining the effectiveness of corticosteroid therapy. In brief, a recent systematic review that identified 5 randomized controlled trials (RCTs) with low risk of bias and moderate to low quality of evidence. A meta-analysis could not be conducted due to the small sample sizes and heterogeneity. The review concluded that there were no significant long-term (i.e., at 12 months) differences in nerve function improvement between the treatment and control groups. Two more RCTs examining the effectiveness of corticosteroids are currently underway.

Notably, two prospective cohort studies demonstrated that at least 30% of patients with leprous neuropathy did not improve. Given the significant proportion of patients who do...
not improve while on corticosteroid therapy, it would be prudent to investigate the effectiveness of other treatment options.

As previously described in detail, the mechanism of nerve damage is likely that bacterial colonisation of the superficial peripheral nerves (i.e. via phenolic glycolipid-1 and/or lipoarabinomannan) predisposes the nerves to ischemia from inflammation, trauma, and/or mechanical stressors such as nerve compression at specific locations of anatomic narrowing (e.g. fibrous tunnels and near the joints).\textsuperscript{8,24–32} Immune reactions may exacerbate the damage. These assaults on the nerve lead to loss of sensation and motor function, which are characteristic of Hansen’s Disease.

Surgical nerve decompression (ND), or neurolysis, has been used for several decades to relieve the ischemia and compression in leprous neuropathy. Studies have demonstrated that, after ND, at least 50\% of leprous neuropathy cases demonstrate sensory improvement, and motor recovery can occur in as many as 89\% of cases (under review).\textsuperscript{8,33,34} Ulcer healing and pain relief have also been reported.\textsuperscript{33} However, high quality studies that investigate the effectiveness of nerve decompression are seriously lacking. A systematic review determined that the only 2 RCTs suitable for inclusion were of such low quality that robust conclusions could not be made about the efficacy of nerve decompression on leprous neuropathy.\textsuperscript{35}

**Workshop and Protocol Development**

Sensing that a study with high quality and high-level of evidence would be welcome, we convened an expert group of peripheral nerve surgeons, reconstructive surgeons, and immunologists who have extensive experience with Hansen’s Disease. The first meeting occurred during November 11–14, 2015 in Denver, Colorado, USA with support from the Association of Extremity Nerve Surgeons.

Initial statistical and study design consulting was provided by the Johns Hopkins Institute for Clinical and Translational Research (ICTR), which is funded in part by Grant Number UL1 TR 001079 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH) and the NIH Roadmap for Medical Research.

**Workshop Results and the DELN Protocol**

The expert group recommended an international, multi-centre RCT that would produce high quality data with regards to the outcomes of nerve decompression for leprous neuropathy. Subsequently, a study protocol was designed and further refined by multiple investigators worldwide. The proposed name for this study is Decompression for Leprous Neuropathy (DELN).

In brief, the envisioned RCT would primarily seek to determine the long-term effect of nerve decompression on sensibility. The RCT also seeks to determine the long-term effect of nerve decompression on motor function, neuropathic pain, disability, and quality of life. Other objectives of the study are listed in Figure 1.

The RCT would enroll patients with clinically diagnosed moderate to severe leprous neuropathy and positive Tinel signs\textsuperscript{36,37} in the upper or lower extremities. The degree of leprous neuropathy would be determined using the Pressure Specified Sensory Device\textsuperscript{TM}
Patients would then be randomised to receive surgery or no surgery. We opted to allow each centre to treat patients randomised to the ‘no surgery’ group using standard medical therapy instead of prescribing a standard therapy for all centres. Randomisation would occur within each surgical centre according to a pre-established randomisation procedure that ensures balance between study groups with regards to the type of Hansen’s, the location (i.e. upper or lower extremity) of the affected nerve(s) with leprous neuropathy, and the degree of neuropathy.

Outcomes of interest include sensory function, motor function, pain, disability, and quality of life. Additionally, the development of ulcers and/or amputations and the influence of pre-enrollment neuropathy and corticosteroid therapy are important aspects that we seek to capture and analyse. At regular time points after randomisation (i.e. 3, 6, 12, and 18 months), as well as prior to randomisation, standard questionnaires will be administered and non-invasive examinations will be conducted (Table 1).

Table 1. Measurement Methods for Outcomes of Interest

<table>
<thead>
<tr>
<th>Outcomes of Interest</th>
<th>Measurement method(s)</th>
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<tbody>
<tr>
<td>Motor function</td>
<td>Voluntary Motor Testing (VMT)</td>
</tr>
<tr>
<td></td>
<td>Pinch Device (AcroPinchTM) (PD)</td>
</tr>
<tr>
<td></td>
<td>Rotterdam Intrinsic Hand Myometer (RIHM)</td>
</tr>
<tr>
<td></td>
<td>Paper Grip Test (PGT)</td>
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<tr>
<td>Sensory function</td>
<td>Semmes-Weinstein Monofilament (SWM)</td>
</tr>
<tr>
<td></td>
<td>Pressure Specified Sensory Device™ (PSSD)</td>
</tr>
<tr>
<td>Pain</td>
<td>Numeric Pain Rating Scale (NPRS)</td>
</tr>
<tr>
<td>Disability</td>
<td>Quick – Disabilities of the Arm, Shoulder and Hand Score (Q-DASH)</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>12-Item Short-Form Health Survey (SF-12v2®)</td>
</tr>
<tr>
<td></td>
<td>World Health Organization Quality of Life-BREF (WHOQOL-BREF)</td>
</tr>
</tbody>
</table>

Figure 1. Select Objectives of the DELN RCT.
These data, along with other clinical and demographic data (Figure 2), will be recorded in case report forms and entered into a HIPAA-compliant database.

Our study seeks to enroll approximately 180 patients, which would allow for a difference to be detected based on the primary objective; this estimate also includes patients for five surgical centres and an estimated 30% attrition rate. The study would take approximately 3 years from institutional board approval to final data analysis and publication. Site visits, regular reports, and interim analysis are planned for in the protocol. Additionally, the protocol plans for the formation of a Data and Safety Monitoring Board and data storage on a HIPAA-compliant web-based server (e.g. REDCap) with hierarchical permissions. The protocol also describes policies regarding access to data, data sharing, and data analysis.

**Discussion**

There is a significant deficit in the existing literature regarding peripheral nerve decompression for the treatment of leprous neuropathy. Existing studies are highly variable in methodology of outcome assessment, and existing RCTs are low quality, making it difficult to come to robust conclusions about the efficacy of nerve decompression for leprous...
neuropathy. We and others have identified several flaws in the existing literature and have called for a well-designed and high quality RCT (under review) (Table 2).⁸,¹⁷,¹⁹,³⁵

Here, we have proposed and described a protocol for an RCT resulting from extensive discussion among an expert group with significant experience in the study of nerve decompression and leprous neuropathy. We considered sham surgery to be unethical due to impaired wound healing among those with Hansen’s Disease. Our RCT uses multiple outcome measures for redundancy and seeks to explore quality of life and cost-effectiveness, aspects that will improve the quality of our study and address flaws identified by Van Veen et al.³⁵

The visible deformities, disabilities, and stigma afflicting those with Hansen’s Disease is related to the leprous neuropathy. A well-designed and high quality RCT would be an important contribution to the literature. As evidence-based health care moves forward, high quality studies with high level of evidence will be crucial for making policy decisions. It is our hope that the DELN study will introduce high quality evidence so as to make an impact in the treatment of leprous neuropathy. The authors welcome discussion on the proposed study, which has the potential to improve clinical treatment of Hansen’s Disease.

### Competing Interest Statement

A. Lee Dellon, MD, PhD, holds a financial interest in the Pressure Specified Sensory Device™ described in this paper. All other authors verify that the answer to the question on competing interest form are all ‘No,’ and therefore have nothing to declare.

### Contributors and Guarantor

All authors contributed to this manuscript and act as guarantors of the work and conduct of the study. All authors give permission to publish. More information specific to contributions of each author are listed at the end of this manuscript.

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**Table 2. Benefits of the DELN RCT**

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<thead>
<tr>
<th>RCT Characteristics</th>
<th>Existing RCTs</th>
<th>DELN RCT</th>
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</thead>
<tbody>
<tr>
<td>Blinding (outcome assessor)</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Adequate Randomization</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Adequate Outcome Measures</td>
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<td>✓</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Cost Effectiveness</td>
<td>✗</td>
<td>✓</td>
</tr>
</tbody>
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E.L. Wan et al.⁵⁵⁸
Contributorship

Eric L. Wan: 1) substantial involvement in the development of the protocol; 2) drafting this manuscript and revising this manuscript critically for important intellectual content; and 3) final approval of the version to be published.

Andres F. Rivadeniera: 1) substantial involvement in the development of the protocol; 2) drafting this manuscript and revising this manuscript critically for important intellectual content; and 3) final approval of the version to be published.

Hector A. Serrano: 1) substantial involvement in the development of the protocol; 2) drafting this manuscript and revising this manuscript critically for important intellectual content; and 3) final approval of the version to be published.

Indra Napit: 1) substantial involvement in the development of the protocol; 2) drafting this manuscript and revising this manuscript critically for important intellectual content; and 3) final approval of the version to be published.

José Antonio Garbino: 1) substantial involvement in the development of the protocol; 2) drafting this manuscript and revising this manuscript critically for important intellectual content; and 3) final approval of the version to be published.

Jerry Joshua: 1) substantial involvement in the development of the protocol; 2) drafting this manuscript and revising this manuscript critically for important intellectual content; and 3) final approval of the version to be published.

Nora Cardona-Castro: 1) substantial involvement in the development of the protocol; 2) drafting this manuscript and revising this manuscript critically for important intellectual content; and 3) final approval of the version to be published.

A. Lee Dellon: 1) substantial involvement in the development of the protocol; 2) drafting this manuscript and revising this manuscript critically for important intellectual content; and 3) final approval of the version to be published.

Willem Theuvenet: 1) substantial involvement in the development of the protocol; 2) drafting this manuscript and revising this manuscript critically for important intellectual content; and 3) final approval of the version to be published.

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