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Effect of lower extremity nerve decompression in patients with painful diabetic peripheral neuropathy: The DNND randomized, observation group- and placebo surgery-controlled clinical trial

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Short running head:

Nerve decompression in diabetic neuropathy

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Trial registration

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Abstract:

Objective:
Evaluate the effect of nerve decompression on pain in patients with lower extremity painful Diabetic Peripheral Neuropathy (DPN).
Summary Background Data:
Currently, no treatment provides lasting relief for patients with DPN. Benefits of nerve decompression remain inconclusive.
Methods:
This double-blinded, observation- and same-patient sham surgery-controlled randomized trial enrolled patients aged 18-80 years with lower extremity painful DPN who failed one-year of medical treatment. Patients were randomized to nerve decompression- or observation-group (2:1). Decompression-group patients were further randomized and blinded to nerve decompression in either right or left leg and sham surgery in the opposite leg. Pain (11-point Likert score) was compared between decompression and observation groups and between decompressed versus sham legs at 12 and 56 months.
Results:
Of 2987 screened patients, 78 were randomized. At 12 months, compared with controls (n=37), both right-decompression-group (n=22) and left-decompression-group (n=18) reported lower pain (mean difference for both, -4.46; [95% CI, -6.34 to -2.58 and -6.48 to -2.45 respectively]; P<0.0001). Decompressed and sham legs equally improved. At 56 months, compared with controls (n=14), pain was lower in both the right-decompression-group (n=20) (mean difference, -7.65; [95% CI, -9.87 to -5.44]; P<0.0001) and left-decompression-group (n=16) (mean difference, -7.26; [95% CI, -9.60 to -4.91]; P<0.0001). Mean pain score was lower in decompressed versus sham legs (mean difference, 1.57 [95% CI, 0.46 to 2.67]; P=0.0002).
Conclusion:
Although nerve decompression was associated with reduced pain, the benefit of surgical decompression needs further investigation since ~~a~~ placebo effect may be responsible for part or all of these effects.

INTRODUCTION

Pain is among the most disabling symptoms in diabetic peripheral neuropathy, occurring in approximately 10% to 20% of patients with diabetes mellitus and 40% to 60% of those with documented neuropathy.(1-3) Nearly 50% of patients with type 1 and type 2 diabetes will develop neuropathy, accounting for over 200 million patients worldwide and 20 million in the United-States.(4) Symptoms of diabetic peripheral neuropathy cost the United-States an estimated $3.65 billion annually in lost productive time.(5) To date, the only modifiable treatment is glycemic control, possibly decreasing incidence in type 1 diabetes but not type 2 diabetes,(6) while having no effect on its progression in patients with pre-existing diabetic peripheral neuropathy.(7)

The pathophysiology of pain in diabetic peripheral neuropathy is unclear but has been attributed to both peripheral and central nervous pathways.(8) Several studies report higher prevalence of compression neuropathies in patients with diabetes mellitus (14%) and diabetic peripheral neuropathy (30%) compared to the general population (2%).(9)

According to a 2017 Agency for Healthcare Research and Quality report, no pharmacologic or nonpharmacologic treatment provides lasting relief for established diabetic peripheral neuropathy pain.(10) While several early uncontrolled studies suggested that lower extremity nerve decompression may be of benefit,(11, 12) these were not randomized and were considered unproven by a 2006 American Academy of Neurology practice advisory.(13) A 2014 randomized controlled Lower Extremity Nerve Entrapment (LENS) trial reported significant pain reduction at 12 months,(14) but was critiqued for its limited methods reporting.(10)

To address this lack of evidence, the Diabetic Neuropathy Nerve Decompression (DNND) trial was designed as a randomized, patient- and rater-blinded, observation-control group and same-patient sham-controlled trial to rigorously assess the effect of nerve decompression in legs of patients with painful DPN and suspected nerve compression on two primary outcomes, pain, and quality-of-life at 12 months as well as long-term effect on pain at 56-months.

METHODS

Trial design and participants

The DNND trial was a single-center randomized, patient- and rater-blinded, observation-control group and same-patient sham surgery-controlled design (See Figure S1, Supplemental Digital Content 1, http://links.lww.com/SLA/F10, which demonstrates trial design flow). The goal of an identical no-surgery observation-control group under the same trial conditions was to serve as a control for the natural history of painful diabetic neuropathy and to decrease the chance of interpreting results as regression to the means.

Initially designed for two-year recruitment and one-year follow-up, both were extended to five-years after institutional review board approval, due to slower than anticipated enrollment. Referral sources included self, community, and academia. (See the Trial Protocol and Statistical Analysis Plan, Supplemental Digital Content 1, http://links.lww.com/SLA/F10).

Major inclusion criteria included patients between ages 18 to 80 years with type 1 or type 2 diabetes mellitus, symptoms consistent with symmetrical sensory or sensorimotor diabetic polyneuropathy, nerve conduction studies and clinical examination consistent with length-dependent symmetric polyneuropathy, failure to respond or tolerate single or multimodal pain-relieving medications for one-year (See Methods section, Supplemental Digital Content 1, http://links.lww.com/SLA/F10, for more details), positive Tinel sign over suspected areas of compression, and full understanding of the study. Major exclusion criteria included medical contra-indications for surgery, HbA1c (%) ≥ 12, previous lower extremity amputations, history of foot ulcers, symptoms of radiculopathy or sciatic type pain, substance dependency, and pregnancy. A full list of exclusion and inclusion criteria is provided (See Table S1, Supplemental Digital Content 1, http://links.lww.com/SLA/F10). Screening consisted of three phases. A short phone-screening was followed by a more comprehensive screening, requiring one or two research visits (1A; 1B) which included a history and physical exam by a peripheral nerve surgeon and physiatrist followed by a detailed study explanation. Eligible patients could consent in either visit. The third screening, permitted only after consent and group randomization (See Methods section, Supplemental Digital Content 1, http://links.lww.com/SLA/F10, for more details) included blood tests and a neurology screening visit performed by a neuromuscular neurologist (1C), and nerve conduction studies (bilateral tibial motor, fibular motor, sural sensory and superficial sensory nerves). Patients with HbA1c (%) ≥ 12 were referred to their physician, providing the opportunity to repeat screening procedures once corrected. Aside from surgery and routine post-operative visits, both groups were similarly evaluated at 3, 6, 9, and 12 months for changes in pain, quality-of-life, foot exam, pain medications, neurological exam, and labs (See Table S2, Supplemental Digital Content 1, http://links.lww.com/SLA/F10). Pain medications were managed by the patients' primary physicians who were not involved in the study. Trial staff only recorded medication changes over time. (See Methods section, Supplemental Digital Content 1, http://links.lww.com/SLA/F10, for more details). Additional pain assessments were performed at an average of 56 months. During recruitment, patients from both groups were given the option at the end of the study to undergo nerve decompression in non-decompressed legs or remain in their original assignments under original study conditions for a study extension involving a 10 year follow up.

Diagnostic criteria for diabetes mellitus included HbA1c > 6.5 or history of DM and use of either insulin or oral hypoglycemic medications. Diagnosis of diabetic peripheral neuropathy included symptoms of numbness, pain, tingling, burning, with or without weakness progressing proximally in a stocking-glove distribution. Evidence of sensory loss below the ankles to either small- or large-fiber modalities was required on neurological examination. Nerve conduction studies had to demonstrate abnormalities in both legs consistent with diabetic polyneuropathy including the sural nerve that is infrequently compressed. A positive Tinel sign in at least two of three suspected compression areas, the common peroneal nerve at the fibular neck, tibial nerve at the medial malleolus, and deep peroneal nerve on the dorsum of the foot, was required for inclusion.

The study was approved by the UT Southwestern institutional review board and was monitored by the institutional Data and Safety Monitoring Board during the 5-year recruitment period and additional 5-year follow-up periods. An executive committee comprised of neurologists, endocrinologists, a physiatrist, peripheral nerve surgeon, clinical coordinators, and technicians met every 6 months to discuss ongoing trial issues. A yearly progress report, including recruitment and adverse events, was submitted and study extensions were obtained. Related major adverse events were reported immediately and included wound dehiscence, bleeding, or infections necessitating surgical intervention, and nerve injury. Minor events included bruising, swelling, mild infections, and wound dehiscence that responded to leg elevation, oral antibiotics, and local care.

Randomization and masking

A computerized random-number generator assigned patients in a 2:1 ratio to either surgery (decompression group) or no-surgery (observation-control group). Cross overs were prohibited. Surgical patients were further randomized and blinded to leg; one leg was assigned to nerve decompression surgery (decompressed leg) and the other to sham surgery (sham leg). Leg randomization was provided to the surgeon in a numbered, opaque, sealed envelope, opened only after patient intubation. Both legs had mirror incisions and were dressed similarly prior to extubating. Recovery staff were blinded to leg assignment, and patients remained blinded during the entire study. At baseline and subsequent 3-month visits, patients independently filled numerically coded pain and SF-36 questionnaires that were entered into the database by an individual blinded to the randomization assignments. Additional, 56-month blinded pain evaluations were performed via phone by an experienced clinical coordinator uninvolved with the trial and unaware of group or extremity assignment. Final analyses were performed by the co-author in the Peter O'Donnell Jr. School of Public Health and Department of Psychiatry, who had no patient contact and after long-term assessments were complete.

Interventions

Surgery was performed under general anesthesia. Decompression included the common peroneal nerve at the fibular neck, deep peroneal nerve in the foot dorsum, and tibial, medial and lateral plantar nerves at the medial malleolus. On the sham side, three mirror incisions extended only into subcutaneous fat to avoid perineural scarring. Both groups received diabetic foot care instructions according to American Diabetes Association guidelines (See Interventions section, Supplemental Digital Content 1, http://links.lww.com/SLA/F10, for more details). Research funds paid for all costs other than surgical interventions which were billed to insurance.

Outcomes

The two primary outcome measures were changes in pain and quality-of-life at one year. Pain was measured with a Likert scale of 0 (no pain) to 10 (maximal pain).(15) A 30% or greater reduction was considered clinically significant as suggested by Farrar et al.(16) Comparisons were performed between 1) right decompression versus left decompression versus observation-control groups and 2) decompressed versus sham legs within the surgical group. Quality-of-life was assessed with the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36; range, 0 to 100, with higher scores indicating better quality of life) analyzing both the physical and mental-health components and their respective sub-scales. The 56-months pain assessment was completed under the original trial conditions of blinding and prior to any data analysis. Changes in use of pain medication was also analyzed (See Methods section, Supplemental Digital Content 1, http://links.lww.com/SLA/F10, for more details).

Statistical analysis

The sample size estimate was based on the primary outcome measure of an 11-point (0 to 10) Likert pain scale. Using an effect size based on a 30% reduction in pain score and an estimated standard deviation of 3.0 in each group, we estimated a total of 66 patients in the decompression groups and 33 in the observation-control group were required to achieve a power of 0.88 while maintaining a significance level of 0.05 using a Mann-Whitney U test (PASS, 2004). We planned to accrue 200 patients in order to account for loss of patients to follow up during the study.

The final strategy for analysis was developed after the trial was completed but before the examination of data. Since the Likert Pain Scale used in this study, also described as a “number production scale”, provides interval level measurement(17), parametric statistical analyses were feasible. After verifying the assumptions for parametric statistical analyses, a more comprehensive, longitudinal modeling of these data was possible. (See the Protocol and Statistical Analysis Plan, Supplemental Digital Content 1, http://links.lww.com/SLA/F10, for more details). Eligible patients with 2 or more measured time intervals who withdrew after randomization, were included in the full 12-month analysis set for pain and quality-of-life according to intention-to-treat principles. Comparable per-protocol analyses were performed. SAS v9.4 and SPSS v25 were used for all statistical analyses.

To compare pain scores between the decompression groups and the observation group, mixed models analysis of covariance (ANCOVA) was used. Analyses were conducted using a modified intention-to-treat that included cases with 2 or more measurements, and two per-protocol analyses, one group following the protocol to 12 months (PPA12) and the other to 56 months (PPA56). For both modified intention-to-treat analysis and per-protocol analysis, 5 or 6 time points were examined. For 5 time points, we included 0, 3, 6, 9, and 12 months which represented the length of the original study. For 6 time points, an additional measurement was obtained at 56 months to examine long-term intervention effects. The factors for the mixed models ANCOVA included group (right decompression, left decompression, and control), leg (right vs left), and time. All 2- and 3-way interactions were included in these analyses. Covariates included those collected at baseline: age at consent, sex, HbA1c, body mass index

(BMI), duration of neuropathy, and duration of diabetes. In addition, HbA1c and BMI measures were available at each time point (including 56 months); these time varying covariates were included with other baseline measures. Covariates remained in the model if $P<0.15$. Subject was considered a random effect. The covariance structures fit to these data include compound symmetry, heterogeneous compound symmetry, autoregressive (1), heterogeneous autoregressive (1), Toeplitz, and unstructured. An iterative process was used to determine the significant covariates ($P<0.15$) for the final model. The structure with the best fitting covariate structure (smallest Akaike Information Criterion [AIC]) was selected for the statistical results and the least squares means. When an effect was found significant, pairwise post hoc comparisons were conducted, using a Bonferroni adjustment to the p-value and 95% Confidence Intervals. A Bonferroni adjustment is used to reduce the chance of obtaining false-positive results (Type I Errors) when post hoc, multiple pair wise tests are conducted.

To compare pain between the decompressed and sham legs within the surgical groups only, a similar model to the one described above was performed and includes the factors time (5 or 6 time points), surgery (decompression vs sham), the interaction of surgery-by-time and all potential covariates. Subject was again a random effect.

SF-36 measurements included the Physical Component Summary score, the Mental Component Summary score, and their respective sub-scales. A similar mixed models ANCOVA was used to analyze the data with 1 between effect (group: surgical vs observation), one within effect (time: baseline, 3, 6, 9, 12 months), and a group-by-time interaction.

An exploratory analysis was performed on the use of medications provided to alleviate pain. The Medication Quantification Scale Version III (MSQIII) which co-quantifies 3 relevant aspects of medications prescribed for chronic nonmalignant pain: drug class, dosage, and detriment, was calculated at baseline, 12 months, and at 56 months (LTFU) for 67 patients. Analyses similar to the mixed models ANOVA were conducted with a one within effect of time (baseline, 12 months, and 56 months) and one between effect of group (observation-control vs surgical).

RESULTS

Recruitment details are provided in Figure 1. Recruitment spanned from 2008 to 2013 at a single academic center. Of 2987 screened patients, 714 were diagnosed with diabetic peripheral neuropathy in the second screening phase, after which 138 (19.3%) were randomized - 92 to surgery and 46 to the observation-control group. In the third screening phase, an additional 51 surgical and 19 observation-control subjects were excluded or withdrew, leaving 41 surgical and 27 observation-control patients enrolled in the trial, representing 33.7% (68/202) of all eligible patients and 9.6% (68/710) of all DPN patients.

At 12 months, 40 (98%) surgical patients (1 died 2 months postoperatively of unrelated causes) and 27 (100%) observation-control patients completed the protocol. 10 eligible observation-control patients with similar baseline characteristics, who originally declined participation, agreed for the 12-month evaluation. Therefore, at twelve months, the modified intention-to-treat analysis consisted of 40 (22 right and 18 left) surgical and 37 observation-control patients; the per-protocol analysis consisted of 40 surgical (22 right and 18 left) and 27 observation-control patients. The 56-month modified intention-to-treat analysis included 36 (90%; 20 right and 16 left) surgical and 14 (38%) observation-control patients. Reasons for withdrawal or exclusion after assignment to group are provided. (Figure 1 and Table S3 in Supplement 1, Supplemental Digital Content 1, http://links.lww.com/SLA/F10). Baseline characteristics were similar in both groups (Table 1) as well as diabetes and neuropathy characteristics (Table 2). The HbA1c longitudinal modified intention-to-treat analysis for both 5 and 6 time points was non-significant for all effects (time, group, and time-by-group interaction) (Figure S2, Supplement 1, Supplemental Digital Content 1, http://links.lww.com/SLA/F10).

All analyses for 12 and 56 months were performed using a modified intention-to-treat principle. The per-protocol analyses showed similar results (See Figure S3, Supplemental Digital Content 1, http://links.lww.com/SLA/F10). Covariates, gender, HbA1c, BMI, and duration of diabetes had no effect on results in either group.

In the 12-month pain analysis, the main effects of time, group, and time-by-group interaction were significant ($P< .001$), and age was a significant covariate ($P= .0064$).

Compared with baseline, pain at 12 (and 3, 6, 9) months was significantly lower in both decompression groups (right-decompression-group: mean change, 5.30; 95% CI, 3.84 to 6.75; $P< .0001$; left-decompression-group: mean change, 5.56; 95% CI, 3.95 to 7.16; $P< .0001$), but remained unchanged in the observation-control group (mean change, 0.68; 95% CI, -0.45 to 1.80; $P> .9999$). Compared with the observation-control group, pain at 12 (and 3, 6 ,9) months was significantly lower in both decompression groups (right-decompression-group: mean difference, -4.46; 95%; CI, -6.34 to -2.58; $P< .0001$; left-decompression- group: mean difference, -4.46; 95% CI, -6.48 to -2.45; $P< .0001$). (Figure 2A and Table 3). When comparing decompressed with sham legs, after accounting for the covariate age ($P= .0206$), time ($P< .0001$) was the only significant effect for pain. Compared with baseline, pain at 12 months was significantly lower in both decompressed (mean change, 5.33; 95% CI, 3.71 to 6.94; $P< .0001$), and sham legs (mean change, 5.50; 95% CI, 3.80 to 7.20; $P< .0001$), but there was no difference between the decompressed and sham legs (mean difference, 0.13; 95% CI, -0.45 to 0.72, $P= .6430$) (Figure 2B and Table 3).

Over the 12-month period, the decompression group showed significant improvement compared with the observation-control group in the SF-36 physical component summary, bodily pain subscale, and general health subscale (group-by-time interaction, $P= .0026$, $P= .0002$, and $P= .0049$, respectively). Group main effects were found for the Physical Function subscale with the surgical group significantly higher than the observation-control group ($P= .0132$) and both groups improved significantly over time on the Role Physical subscale (time main effect, $P= .0114$). No significant differences were found in the mental component summary aside from the Vitality subscale which improved in the decompression group (mean change 4.15) while the observation-control group worsened over time (mean change -3.20) (interaction of group-by-time, $P= .0136$). (See Figure S4, Supplemental Digital Content 1, http://links.lww.com/SLA/F10, for detailed analysis of the SF-36 results).

At 56 months, compared with baseline, pain was significantly lower in both decompression groups (right-decompression-group: mean change, 6.71; 95%CI, 5.20 to 8.22; $P< .0001$; left-decompression-group: mean change, 6.57; 95%CI, 4.89 to 8.25; $P< .0001$), while non-significantly worsened in the observation-control group (mean change, -1.11; 95%CI, -2.73 to 0.51; $P> .9999$). Compared with the observation-control group, pain was significantly lower in both decompression groups (right-decompression-group: mean difference, -7.65; 95% CI, -9.87 to -5.44; $P< .0001$; left-decompression-group: mean difference, -7.26; 95% CI, -9.60 to -4.91; $P< .0001$). (Figure 2C, Table 3).

When comparing decompressed with sham legs at 56 months, after accounting for the significant covariates age ($P= .0004$) and duration of neuropathy ($P= .0489$), there was a significant interaction of time-by-surgery ($P= .0034$), and main effects of time ($P= .0001$) and surgery (decompression vs. sham) ($P= .0449$). At month 56, the mean pain score in the decompressed leg was significantly lower than in the sham leg (mean difference, 1.57, 95% CI, 0.46 to 2.67; P= .0002) (Figure 2D, Table 3). Number of patients with more than 30% reduction by group and time are provided in Table S4, Supplement 1, Supplemental Digital Content 1, http://links.lww.com/SLA/F10.

In the pain medications exploratory analysis, the MSQIII showed that the surgical group had higher means at baseline, and lower means at 12 and 56 months compared to the observation-control group but mixed models ANOVA analyses examining MSQIII was found to be non-significant for the interaction of time by group (p=0.0638), time (p=0.0989) and group (p=0.5278) (See Figure S5, Supplemental Digital Content 1, http://links.lww.com/SLA/F10).

No related major complications were observed in either surgical or observation-control group. 23 minor complications were noted in the decompressed legs, 5 in the sham legs, and none in the observation legs. Mild cellulitis was observed in 7 decompressed and 3 sham extremities and responded to oral antibiotics. Wound dehiscence was observed in 12 decompressed and 2 sham legs and successfully treated conservatively. No patients dropped out of the study due to adverse events (Table 4).

DISCUSSION

The DNND trial evaluated the effect of lower extremity nerve decompression in patients with diabetic peripheral neuropathy and suspected nerve compressions on pain and quality of life. At the original timeline endpoint of 12 months, pain was significantly less in the decompression groups when compared with the observation-control population, but no difference was observed between the decompressed and sham legs. The SF-36 physical component summary significantly improved from baseline to 12 months in the surgical groups while no improvement was observed in the observation-control group.

At 56 months pain continued to significantly improve in the decompression groups when compared with the observation-control population, albeit the number of patients in the observation-control group was significantly reduced. The decompressed legs continued to improve while the sham legs did not, resulting in significantly less pain in decompressed legs when compared with sham legs.

The improvement in pain levels experienced by subjects in the sham leg at 12 months, and to a lesser degree at 56 months, was less expected, and raises the concern of a placebo effect, especially considering that no difference was observed between the sham and decompressed legs at 12 months, the original trial timeline endpoint. Additionally, although the goal of the observation-control group was to reduce the chance for interpreting changes in the decompression groups as regression to the means or reflection of diabetic peripheral neuropathy natural history,(18) observation-control patients could not be blinded, risking a negative treatment bias. Placebo effect may have also involved both decompressed and sham legs; patients were aware they underwent decompression in one extremity but were blinded to the actual side.

A placebo response is observed across trials of pain disorders, studies that typically rely on patient-reported outcomes for the primary efficacy measure.(19) Expectation from surgery, medical visitation ritual, selection and reporting biases may also affect outcomes. In our trial design, we made efforts to reduce such effects. The randomized groups were similar in baseline characteristics. Covariates such as age, gender, neuropathy duration, diabetes duration, BMI, and HbA1C levels did not affect outcomes over time. Glycosylated hemoglobin levels were similar across populations through the entire trial. To decrease selection bias, we did not allow crossovers. Placebo effects that could arise from close supervision in a trial protocol were possibly further minimized in the long-term results when all subjects had little to no contact with the study team for nearly four years. While a three-arm trial was considered, 90 minutes of general anesthesia to perform a 10-minute sham procedure was difficult to justify.

Although hypothetical and not to be considered in the interpretation of this data nor rule out a placebo effect, several interesting findings should provide a basis for further studies. The gradual but continued pain reduction observed in the decompressed leg throughout the study may suggest that changes are time dependent, possibly paralleling neural regeneration which is slower in patients with diabetes.(20, 21) Similar results have been reported previously in a 5-year follow-up observation-control study after nerve decompression in diabetes mellitus patients.(22) Additionally, sensory mirroring of both hyperalgesia and hypoalgesia has been reported in clinical and basic science experiments. Cross signaling mechanisms at the dorsal root ganglion(23-27) and activation of descending pain modulatory pathways impacting dorsal horn transmission of afferent nociceptive information have been suggested.(28) Such mechanisms may explain findings observed in clinical experiments(29) and clinical trials such as the 2014 LENS study,(14) in which unblinded patients reported long-term improvement in a knowingly unoperated contralateral extremity. Similarly, improved gait and balance after nerve decompression has been reported in several animal (30-32) and clinical trials (33, 34) respectively, may have also resulted in decreased pain in both legs. Also, the deeper incision on the decompressed side closer to the nerves when compared with the more superficial sham side incision, may have caused increased local perineural inflammatory response and changes in blood flow, possibly affecting perceived pain in the first 1 to 2 years after surgery until inflammation subsides, making early differentiation between the sham and decompressed limbs difficult. Finally, temporal improvement ranging from one-month to one-year in pure placebo arms have been described,(35, 36) but the non-fluctuating pattern of pain reduction observed in the first year that persisted for nearly another 4 years is not wholly consistent with this literature but may also reflect a potential lengthy effect of placebo previously undescribed in the literature. While surgical complications in the decompressed extremity were higher than in the sham side, all patients healed with conservative care without needing additional surgery. No patients dropped out of the study due to adverse events.

Interestingly, patients in the surgical group stated the pain in the contralateral sham leg was not significant enough to pursue decompression and agreed to maintain blinding for a long-term 10 year follow up study. Two control patients underwent decompression after completing the trial (See Table S3, Supplemental Digital Content 1, http://links.lww.com/SLA/F10).

Limitations

Several inherent methodological difficulties are worth mentioning.

First, comparing, and interpreting data between the observation-control group to the surgical groups is difficult. Although identical in baseline characteristics and exposed to the same variables as the surgical group, the observation-control group could not be blinded to treatment, thus introducing an inherent non-treatment bias. Only a third pure sham surgery arm could overcome such limitations.

Second, is lack of objective evidence of compression. Surgeon intraoperative observation of macroscopic evidence of compression is inaccurate, frequently impossible, and risks observerbias. While clinical diagnostic accuracy of diabetic peripheral neuropathy was high (120/124; 96.8%) when subjects were evaluated by neurologists with expertise in neuropathy, diagnosing lower extremity nerve compression is more challenging, especially in the setting of diabetic peripheral neuropathy. The Tinel sign has been advocated,(37, 38) claiming positive predictive value of 80% in identifying nerve compression but is not uniformly accepted. Similarly, nerve conduction studies assist in diagnosing lower extremity neuropathy but offer limited value in identifying focal lower extremity nerve compressions, especially in the setting of neuropathy.(39) Likewise ultrasound measures of compression have not been validated. Additionally, lack of objective measurements of pain necessitated the use of patient-reported outcomes as primary outcomes which admittedly increases further exposes to biases.(40) Third, only 3% of trial patients had type 1 diabetes mellitus and patients with preexisting ulceration prevalent in more advanced disease were excluded, raising questions about the application of these results on those populations. Fourth, while men, women, White and Black patients were represented fairly equally in this study (in contrast to the majority of large clinical trials involving diabetes mellitus in which most participants are white males), Hispanic and Asian populations were under-represented (See Table S5, Supplemental Digital Content 1, http://links.lww.com/SLA/F10, for Generalizability of Study Participants). Fifth, the number of enrolled patients was lower than that planned in the original sample size. When the analysis was changed from a comparisons of groups at one time point to comparing groups over several time points simultaneously, power improved. Finally, selection bias must also be considered. Of the 202 eligible patients, only 68 (19.3%) were enrolled, likely due to a rigorous visitation protocol and stringent exclusion criteria. While prohibiting crossovers likely reduced selection bias it also increased withdrawals and lengthened recruitment.

Conclusions

Although nerve decompression decreased pain and improved quality of life at one year relative to no surgery, pain reduction was similar in both the decompressed and sham legs, raising the question that some or all of these benefits may represent placebo effects. Therefore, the current data does not provide definitive evidence for benefit of surgical decompression in painful diabetic peripheral neuropathy. The continued pain reduction observed at nearly five years after surgery in the decompressed group and legs when compared to the control-observation group and sham legs, respectively, is interesting and should provide a basis for further research.

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Transparency: The lead author (SMR) affirms that the manuscript is an honest, accurate and transparent account of the study being reported, and follows the CONSORT guidelines for the reporting of clinical trials. No important aspects have been omitted, and any discrepancies from the study as planned have been explained and provided with the protocol and statistical analysis plan appendix.

Participating clinical sites: University of Texas Southwestern Medical Center; Parkland Hospital

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Ethical approval: This study was approved by the institutional review board of the University of Texas, Southwestern Medical Center, Dallas, Texas, USA (IRB Number: 082007-100) as well as by the institutional review board of each participating center, and informed consent was obtained from all patients.

Data Sharing: All requests for data should be submitted to SMR (shai.rozen@utsouthwestern.edu) after publication of the study. This data may include only de-identified participant data due to continued long-term follow-ups on trial surgical patients who continued to be masked and control patients and will require a signed data share agreement. The protocol, analysis plan, and informed consent documents are provided in the supplementary appendices and may be available upon request.

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Figure 1. Eligibility, Randomization, and Follow-up

* 2 patients chose to undergo nerve decompression after completion of the 12-month evaluation. They were not included in the 56-month evaluation of either control or decompression groups since crossovers weren't permitted.

DPN – Diabetic Peripheral Neuropathy; DPN (+) – Patient with working diagnosis of diabetic peripheral neuropathy; DPN (-) – Patients with lack of diagnosis of diabetic peripheral neuropathy; GSW – gunshot wound; CAD – coronary artery disease; CHF – congestive heart failure; mITT – modified intention to treat; PPA – per protocol analysis

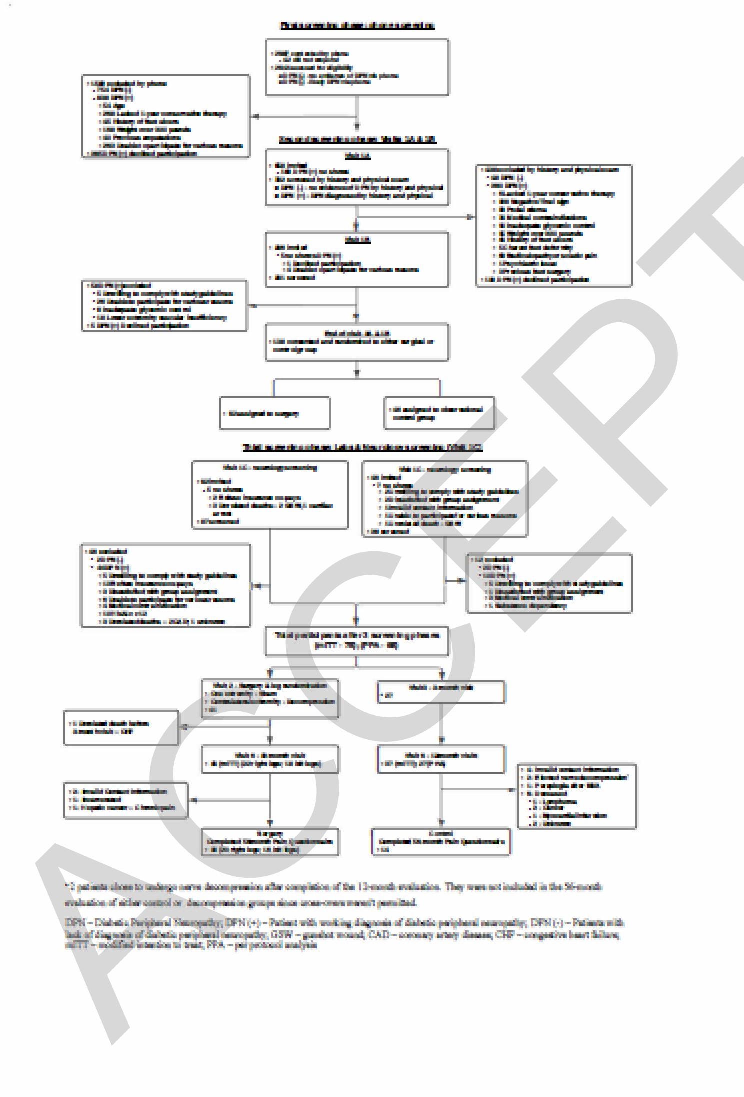
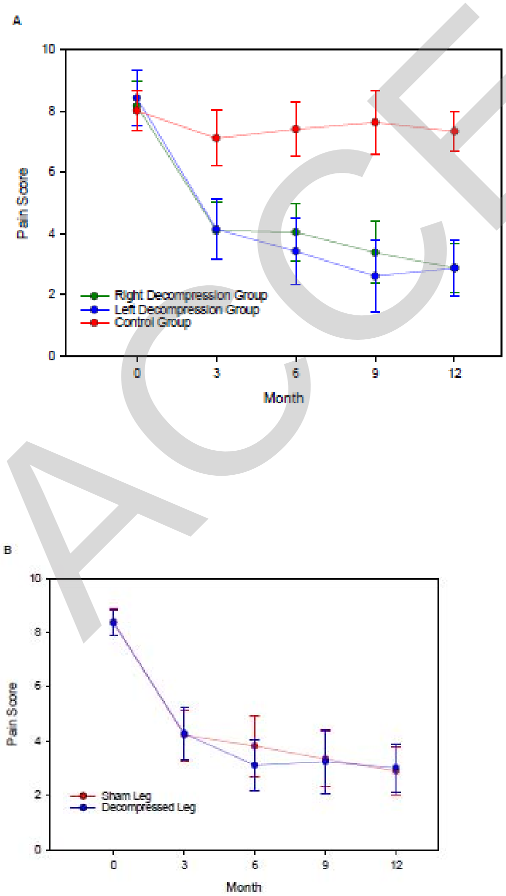


Figure 2. Pain at 12 and 56 months*

Panel A shows pain scores up to 12 months in both the decompression and control groups. Compared to baseline, pain significantly improved in the decompression groups while no improvement was seen in the control group. When comparing groups, pain was significantly lower in the decompression groups compared to the control group at 12 months and at 3-, 6-, and 9-month intervals. Panel B shows pain scores up to 12 months in both decompressed and sham legs. Compared to baseline pain significantly improved in both, but no between difference was observed. Panel C shows pain scores up to 56 months in both the decompression and control groups. In the decompression groups pain continued to improve and compared to baseline was significantly improved. In the control group, pain worsened. When comparing groups, pain was significantly lower in the decompression groups versus the control group at 56 months. Panel D shows pain scores up to 56 months in both decompressed and sham legs. Pain continued to improve in both legs but was significantly less in the decompressed legs when compared to the sham legs.

Likert pain scores ranged from 0-10, with higher scores indicating more severe pain. I bars denote 95% confidence intervals.

* The 12-month mITT analysis included 40 subjects in the decompression group and 37 subjects in the control group. The 56-month mITT analysis included 36 subjects in the decompression group and 14 subjects in the control group.



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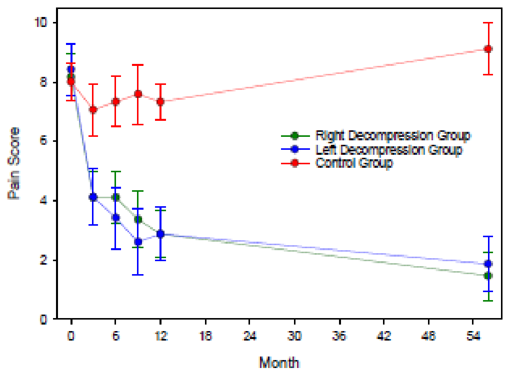
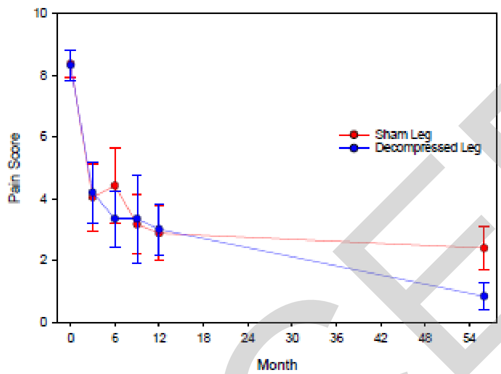


Pain Score
Month
Right Decompression Group
Left Decompression Group
Control Group

D



Pain Score
Month
Sham Leg
Decompressed Leg

Table 1. Baseline characteristics of nerve decompression and control groups in the mITT analysis. *

Characteristic:	Nerve decompression group mITT - 40	Control group mITT-37
Age in years	51·73 + 13·30	54·62 + 9·86
Female, n (%)	21 (52·5%)	15 (40·5%)
Race or ethnic group, n (%) †		
Black	16 (40·0%)	21 (56·8%)
Non-Hispanic White	15 (37·5%)	12 (32·4%)
Hispanic	9 (22·5%)	4 (10·8%)
Health Coverage, n (%)		
Medicare	5 (12·5%)	6 (16·2%)
Medicaid	3 (7·5%)	2 (5·4.0%)
VA	3 (7·5%)	5 (13·5%)
County	24 (60·0%)	20 (54·1%)
Commercial	5 (12·5%)	4 (10·8%)
Referral Source, n (%)		
Academic physician	6 (15·0%)	4 (10·8%)
Academic Self	5 (12·5%)	1 (2·7%)
Community Self	28 (70·0%)	30 (81·1%)
VA Self	1 (2·5%)	2 (5·4%)
Body-mass index ‡	32·94 + 7·71	31·83 + 7·33
Pain score in leg §		
Right leg	8·50 + 1·54	7·86 + 1·78
Left leg	8·25 + 1·55	8·08 + 1·59
SF-36 physical component summary score[¶]	31·51 + 8·99	32·27 + 9·14
Physical Functioning	32·35 + 11·73	29·25 + 11·12
Role Physical	33·93 + 10·78	35·37 + 12·29
Bodily Pain	30·61 + 6·86	32·50 + 7·56
General Health	36·21 + 10·06	37·43 + 12·4
SF-36 mental-component summary score[ǀ]	41·14 + 10·75	41·02 + 12·21
Vitality	38·83 + 9·05	40·24 + 10·61
Social Functioning	33·45 + 11·38	35·74 + 12·36
Role Emotional	35·73 + 11·54	35·75 + 12·47
Mental Health	42·32 + 11·49	39·42 + 13·22
Medication Quantification Scale Version III[Ψ]	20.14 + 11.05	18.67 + 10.26

* Plus-minus values are means ± SD. There were no significant differences in the baseline characteristics between the nerve decompression and control groups.
† Race and ethnic group were self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Pain was assessed on a rating scale of 0 to 10, with higher scores indicating more severe pain.

¶ The physical-component summary of the SF-36 includes physical functioning, role–physical, bodily pain, and general health; scores range from 0 to 100, with higher scores indicating better quality of life.
‖ The mental-component summary of the SF-36 includes vitality, social-functioning, role-emotional, and mental health; scores range from 0 to 100, with higher scores indicating better quality of life.
Ψ The Medication Quantification Scale Version III co-quantifies 3 relevant aspects of medications prescribed for chronic nonmalignant pain: drug class, dosage, and detriment.

Table 2. Baseline diabetes and neuropathy characteristics of nerve decompression and control groups in the mITT analysis. *

Characteristic:	Nerve decompression group mITT - 40	Control group mITT-37
Type of Diabetes		
Diabetes Mellitus Type 1	2 (5%)	1 (2·7%)
Diabetes Mellitus Type 2	38 (95%)	36 (97·3%)
HbA1c	7·98 + 1·98	8·43 + 3·15
Duration of diabetes in years		
1-5 years	16 (40%)	12 (32·4%)
6-10 years	9 (22·5%)	11 (29·7%)
11-15 years	10 (25%)	6 (16·2%)
>16 years	5 (12·5%)	8 (21·6%)
Duration of Neuropathy in years		
less than one year	2 (5%)	2 (5·4%)
one year	4 (10%)	3 (8·1%)
two years	10 (25%)	6 (16·2%)
three years	7 (17·5%)	7 (18·9%)
four years	4 (10%)	4 (10·8%)
five years	7 (17·5%)	5 (13·5%)
six years	2 (5%)	2 (5·4%)
seven years	1 (2·5%)	3 (8·1%)
ten years	2 (5%)	1 (2·7%)
thirteen years	0 (0%)	1 (2·7%)
fourteen years	1 (2·5%)	0 (0%)
fifteen years	0 (0%)	2 (5·4%)
eighteen years	0 (0%)	1 (2·7%)
Duration of leg pain in years		
Right leg		
< 1year	2 (5·0%)	2 (5·4%)
1-5 years	31 (77·5%)	25 (67·6%)
6-10 years	5 (12·5%)	6 (16·2%)
11-15 years	2 (5·0%)	2 (5·4%)
16 years and longer	0 (0%)	2 (5·4%)
Left leg		
< 1year	2 (5·0%)	2 (5·4%)
1-5 years	31 (77·5%)	25 (67·6%)
6-10 years	5 (12·5%)	6 (16·2%)
11-15 years	2 (5·0%)	2 (5·4%)
16 years and longer	0 (0%)	2 (5·4%)

* Plus-minus values are means ± SD. There were no significant differences in the baseline characteristics between the nerve decompression and control groups.

Table 3. Pain and Quality of Life Outcomes with 56-month Follow-up*

Pain Score Changes from Baseline by Group									
	Right Decompression Group			Left Decompression Group			Observation Group		
Time in months	Mean Pain Score (95% CI)	Change from Baseline (95% CI)	P Value	Mean Pain Score (95% CI)	Change from Baseline (95% CI)	P Value	Mean Pain Score (95% CI)	Change from Baseline (95% CI)	P Value
Baseline†	8.18 (7.38 to 8.97)	NA	NA	8.44 (7.56 to 9.32)	NA	NA	8.01 (7.40 to 8.63)	NA	NA
3	4.11 (3.21 to 5.01)	4.07 (2.40 to 5.73)	< .0001	4.13 (3.18 to 5.08)	4.31 (2.55 to 6.07)	< .0001	7.07 (6.20 to 7.95)	0.94 (-0.68 to 2.56)	> .9999
6	4.12 (3.22 to 5.01)	4.06 (2.40 to 5.72)	< .0001	3.42 (2.39 to 4.46)	5.01 (3.10 to 6.92)	< .0001	7.34 (6.49 to 8.19)	0.67 (-0.90 to 2.25)	> .9999
9	3.37 (2.40 to 4.34)	4.81 (3.01 to 6.61)	< .0001	2.61 (1.50 to 3.72)	5.83 (3.77 to 7.88)	< .0001	7.60 (6.59 to 8.60)	0.42 (-1.44 to 2.27)	> .9999
12	2.88 (2.09 to 3.68)	5.30 (3.83 to 6.76)	< .0001	2.88 (2.00 to 3.76)	5.56 (3.93 to 7.18)	< .0001	7.34 (6.73 to 7.95)	0.68 (-0.46 to 1.81)	> .9999
56	1.47 (0.65 to 2.29)	6.71 (5.20 to 8.22)	< .0001	1.87 (0.96 to 2.78)	6.57 (4.89 to 8.25)	< .0001	9.12 (8.25 to 10.00)	-1.11 (-2.73 to 0.51)	> .9999

Pain Score Differences Between Groups‡						
	Right vs Left Decompression Group		Right Decompression vs Observation Group		Left Decompression vs Observation Group	
Time in months	Mean Difference (Adjusted 95% CI)	Adjusted P Value	Mean Difference (Adjusted 95% CI)	Adjusted P Value	Mean Difference (Adjusted 95% CI)	Adjusted P Value

Baseline†	-0.26 (-2.45 to 1.93)	> .9999	0.16 (-1.69 to 2.02)	> .9999	0.42 (-1.56 to 2.41)	> .9999
3	-0.02 (-2.44 to 2.40)	> .9999	-2.96 (-5.29 to -0.63)	.0009	-2.94 (-5.34 to -0.54)	.0019
6	0.69 (-1.84 to 3.22)	> .9999	-3.23 (-5.52 to -0.93)	< .0001	-3.92 (-6.40 to -1.43)	< .0001
9	0.76 (-1.97 to 3.48)	> .9999	-4.23 (-6.82 to -1.64)	< .0001	-4.98 (-7.76 to -2.21)	< .0001
12	0.00 (-2.19 to 2.19)	> .9999	-4.46 (-6.31 to -2.60)	< .0001	-4.46 (-6.44 to -2.47)	< .0001
56	-0.40 (-2.66 to 1.86)	> .9999	-7.65 (-9.87 to -5.44)	< .0001	-7.26 (-9.60 to -4.91)	< .0001

Pain Score Differences Between Decompressed vs Sham Legs

	Decompressed Legs	**Sham Legs**	**Decompressed versus Sham Legs**	
Time in months	**Mean Pain Score (95% CI)**	**Mean Pain Score (95% CI)**	**Mean Difference (Adjusted 95% CI)**	**Adjusted P Value**
Baseline†	8.33 (7.85 to 8.82)	8.38 (7.93 to 8.84)	0.05 (-0.79 to 0.89)	> .9999
3	4.21 (3.21 to 5.20)	4.04 (2.94 to 5.15)	-0.17 (-2.08 to 1.75)	> .9999
6	3.35 (2.44 to 4.26)	4.43 (3.21 to 5.65)	1.08 (-0.91 to 3.07)	> .9999
9	3.35 (1.93 to 4.77)	3.17 (2.23 to 4.11)	-0.18 (-2.47 to 2.11)	> .9999
12	3.01 (2.17 to 3.84)	2.88 (2.01 to 3.75)	-0.13 (-1.65 to 1.40)	> .9999
56	0.83 (0.38 to 1.29)	2.40 (1.69 to 3.11)	1.57 (0.46 to 2.67)	.0002

SF-36 Physical Component Scale (PCS) Changes from Baseline and Difference Between Decompressed and Observation Groups¶

	Decompression Group			**Observation Group**			**Decompressed versus Observation**	
	Mean PCS Score (95% CI)	**Change from Baseline (95% CI)**	**P Value**	**Mean PCS Score (95% CI)**	**Change from Baseline (95% CI)**	**P Value**	**Mean PCS Score Difference (Adjusted 95% CI)**	**Adjusted P Value**
Baseline*	31.51 (28.66 to	NA		32.27 (29.30 to	NA		0.76 (-6.25 to 7.77)	> .9999

	34.37)			35.24)				
3	36.97 (33.82 to 40.11)	-5.45 (-10.11 to -0.80)	.0073	33.45 (29.37 to 37.53)	-1.18 (-7.57 to 5.21)	> .9999	-3.52 (-12.29 to 5.26)	> .9999
6	37.68 (34.29 to 41.07)	-6.16 (-10.94 to -1.38)	.0018	31.38 (27.32 to 35.43)	0.90 (-5.14 to 6.93)	> .9999	-6.30 (-15.30 to 2.70)	.9054
9	37.47 (33.68 to 41.25)	-5.95 (-11.91 to 0.01)	.0505	33.64 (28.55 to 38.73)	-1.37 (-9.66 to 6.91)	> .9999	-3.82 (-14.63 to 6.98)	> .9999
12	38.49 (35.35 to 41.63)	-6.98 (-11 to -2.95)	< .0001	31.79 (28.27 to 35.32)	0.48 (-4.28 to 5.24)	> .9999	-6.70 (-14.73 to 1.34)	.2700

* 56-month follow up was performed only for pain scores

† The baseline scores shown are the mean values in the group.

‡ Bonferroni post hoc adjustments have been made to P Values and 95% Confidence Intervals (95% CI).

¶ No differences between decompression and observation groups were seen in the Mental Component Scale

Table 4. Adverse events during the study per group and extremity

Adverse Events between 0-12 months			
	Surgery		**Control**
	Decompressed leg	**Sham leg**	
Total number of patients	41		37
Total related adverse events	23	5	**0**
Total related major adverse events	0	0	0
Total related minor adverse events	23	5	0
Edema	4¤	0	0
Superficial Infection	7^	3	0
Wound Dehiscence	12*	2	0
Total unrelated adverse events	8		5
Total unrelated major adverse events	6		3
Death			
Cardiovascular	1		0
Infection necessitating hospitalization	1$^{\beta}$		0
Chronic Kidney Disease $^{\psi}$	2		0
Cardiovascular $^{\chi}$	2		2
Non-Lethal Trauma	0		1$^{\upsilon}$
Total unrelated minor adverse events	2		2
Foot ulcer- no. of events	1$^{\tau}$	1$^{\sigma}$	2$^{\varpi}$
DVT- no. of events	0	0	1
Cellulitis- no. of events	0	0	1
Adverse Events between 12-56 months			
	Surgery		**Control**
	Decompressed leg	**Sham leg**	
Total number of patients	36		14
Total related adverse events	**0**	**0**	**0**
Total related major adverse events	0	0	0
Total related minor adverse events	0	0	0
Total unrelated adverse events	1		7
Total unrelated major adverse events	1		7
Death			
Malignancy	0		3
Cardiovascular	0		1
Unknown	0		2
Non-Lethal Trauma	0		1$^{\rho}$
Non-neuropathic chronic pain	1$^{\theta}$		0
Total unrelated minor adverse events	0		0

β Denotes patient who presented to emergency department with a urinary tract infection (unrelated major) and a paronychia in the toe (unrelated minor) after a pedicure in a spa 2 weeks after surgery.

ǂ Denotes patient who presented with post-operative bleeding on post operative visit 1 which resolved and a new event of wound dehiscence on post-operative visit 2. Event considered as a wound dehiscence event.

^ Patients were included in both surgical and sham counts who had bilateral infections. Two had both superficial infection and concomitant wound dehiscence during post-operative visit 1 and were therefore counted in both categories. One patient with concomitant infection and ecchymosis was counted as a single infection event.

* One patient had bilateral wound dehiscence and is counted in both sham leg and decompression leg totals.

¤ Edema incidence was counted as isolated events of edema in the absence of other complications.

φ Solely consists of gunshot wounds

χ Cardiovascular causes of major unrelated adverse events include cardiac arrest, congestive heart failure, and coronary artery disease

ψ Both cases were end-stage when reported

υ Patient was stabbed resulting in pneumothorax which resolved after hospitalization

ω Both events occurred in the same patient bilaterally

σ Occurred one-year post-op

τ Occurred 4 months post-op

ρ Denotes patient who was in a motor vehicle accident resulting in paraplegia

θ Denotes patient who developed chronic pain secondary to hepatocellular carcinoma