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Case Reports and Series

Clinical evaluation of an innovative nerve termination cap for treatment and prevention of stump neuroma pain: Results from a prospective pilot clinical study

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A B S T R A C T

Following nerve injury or transection, a disorganized sprouting of axons can result in painful neuroma formation due to disruptions and damage in the peripheral nerve tissue. Currently, there are various neuroma treatments; however, nonsurgical treatment is inconsistent and there is a high rate of residual pain postoperatively. This study reports results from the pilot phase of a multicenter clinical study on the use of Axoguard Nerve Cap® (nerve cap, Axogen) for capping the distal nerve stump after surgical resection of Morton's neuroma. Fifteen adults were enrolled (12 females and 3 males) with a painful, symptomatic neuroma in at least one nerve in the foot that could not be repaired to a distal target after resection. All participants received standard neurectomy resection of the affected nerve segment, followed by placement of the nerve cap over the distal nerve stump. Participants were followed for one year post-operatively and outcomes for pain, symptomatic neuroma recurrence, and quality of life (using the Patient-Reported Outcomes Measurement Information Systems), Foot Health Status Questionnaire, and Work Productivity and Activity Impairment were collected and compared to baseline, pre-surgical levels. Participants experienced a clinically significant reduction in pain at 3 months post-surgery that was sustained throughout the 12-month study follow-up. Additionally, clinical improvements were observed across all quality of life metrics. These results are promising, and future studies may provide further evidence by using a comparative group using the standard of care for neuroma management.

Introduction

Morton's neuroma is a compressive neuropathy related to a perineural fibroma of the common plantar interdigital nerve.[1] Morton's neuroma results from compression and constant irritation at the plantar aspect of the transverse intermetatarsal ligament, primarily in the third intermetatarsal space owing to the narrowness in this space compared with other intermetatarsal spaces.[1,2] Morton's neuroma is the second most common compressive neuropathy[3] and is present in females at a rate of 4-15 times that observed in males.[1]

In Morton's neuroma, the compression and repetitive trauma to the nerve leads to changes in vasculature, endoneurial edema and thickening of the bursa leading to perineurial fibrosis.[1] Histopathologic changes in the nerve can be noted by fibrosis in and around the nerve accompanied by axonal disruption and proliferation of Schwann cells and fibroblasts.[1] Examination by MRI often demonstrates a dumbbell-shaped soft tissue lesion, which is evidence of neuroma in continuity.[1] The tangled bulbous mass of the neuroma can cause significant pain, likely due to interactions between the axons as well as traction between the nerve and scar tissue.[4] Common symptoms include pain on the plantar aspect

Abbreviations: FHSQ, Foot Health Status Questionnaire; MCID, Minimal Clinically Important Difference; MME, Morphine Milligram Equivalence; PROMIS, Patient-Reported Outcomes Measurement Information System; SIS, Small Intestine Submucosa; VAS, Visual Analog Score; WPAI, Work Productivity and Activity Impairment

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of the forefoot, characterized by a feeling of 'walking on a pebble', numbness of the toes, and sharp or burning pain radiating proximally towards the leg.[1,5]

These neuromas may be managed through conservative and surgical intervention. Commonly used conservative management consists of physiotherapy, activity modification, footwear modification, injections, and other treatments.[5,6] These non-invasive treatments may mitigate symptoms for many patients; however, when these treatments do not meet the goals and expectations of the patient, then surgical options are considered. While there are many surgical techniques,[7] the most common surgical treatments for Morton's neuroma are nerve decompression or traction neurectomy.[2] In traction neurectomy, the affected segment of the nerve is placed under tension, cut, and removed.[2] Upwards of 70-80% of patients achieve favorable results from this procedure[8-10]; however, up to 37% of patients report residual pain and as many as 8% of patients report a worsening of their pain after neurectomy.[10] Such recurrent pain is commonly due to the formation of a stump neuroma at the terminal end of the cut nerve.[11] Recently, several additional techniques have risen in popularity which are noted to inhibit the formation of a painful neuroma, including targeted muscle reinnervation, burying the nerve stump into muscle or bone, and capping of the distal nerve stump.

Nerve termination by capping of the nerve stump is a technique that isolates the axons from external forces and contains any disorganized growth within the internal chamber, reducing the likelihood of symptomatic neuroma development. An off-the-shelf device for containing the cut nerve stump to prevent symptomatic neuroma formation has the potential to improve outcomes. A recent rodent study showed that off-the-shelf chambered nerve caps reduced axonal swirling, supported a higher ratio of regenerating axons to collagen, and improved animal pain behavior to a mechanical stimulus compared to a non-treated nerve stump.[12] These results are promising and provide a rationale for using an off-the-shelf small intestine submucosa (SIS) chambered nerve cap for the prevention of neuromas and their associated pain; however, clinical trials to corroborate these findings are necessary to understand the patient-perceived improvement in pain.

This study evaluates outcomes from the pilot phase of a multicenter clinical study on the use of Axoguard Nerve Cap® (nerve cap, Axogen Corporation, Alachua, FL) to prevent stump neuroma pain following standard neurectomy for the treatment of neuromas in continuity of the foot. This study population provides a suitable model in which symptomatic neuromas frequently occur and are associated with significant morbidity.[6] Owing to the considerable mechanical and compressive forces placed on the foot and ankle during ambulation, recurrence of symptomatic neuroma after neurectomy is common and presents with limited treatment options. The purpose of this study was to determine if Axoguard Nerve Cap, an FDA cleared chambered nerve cap manufactured from decellularized porcine SIS extracellular matrix, can reduce pain and prevent the development of symptomatic or painful neuroma formation after neurectomy. Endpoints of this study were changes in Visual Analog Scores (VAS), rate of symptomatic neuroma recurrence, Patient-Reported Outcomes Measurement Information Systems (PROMIS), changes in pain medication, and quality of life assessments up to one-year post-operative.

Material and methods

Study design

This multi-phase, randomized, controlled, prospective clinical trial is registered on Clinicaltrials.gov (# NCT03940963). The pilot phase described in this paper was an open-label study with all participants receiving the chambered nerve cap (Axogen Corporation, Alachua, FL). The study protocol and informed consent forms received favorable review and approval from appropriate governing Institutional Review Board/Independent Ethics Committees prior to study initiation. This pilot phase included 15 adults (12 females and 3 males) with symptomatic neuroma in at least one nerve in the foot that could not be repaired to a distal nerve segment (these and other patient details can be found in the supplementary materials). This female to male ratio was used to reflect the sex differences in Morton's neuroma prevalence. Each author contributed data from at least one participant in this study, thereby controlling for surgeon bias. Participants were treated between November 2018 and June 2020.

Inclusion and exclusion criteria

Participants were included if they signed informed consent prior to study procedures; were male or non-pregnant female ≥18 years of age; reported baseline pain scores of >65 mm on a 100 mm VAS at screening; and had a documented diagnosis of symptomatic neuroma in at least one nerve in the foot that was confirmed by diagnostic criteria for symptomatic neuroma (pain with at least 3 of the following characteristics: burning, sharp, shooting, electric, paresthesia, numbness, or cold intolerance; symptoms in a defined neural anatomic distribution; history of nerve injury or suspected nerve injury; and at least one of following criteria: positive response to local anesthetic injection; ultrasound or MRI confirmation of neuroma). Participants also had to be candidates for surgery to address a symptomatic neuroma; have sufficient healthy soft tissue available to adequately cover the nerve cap; in the surgeon's opinion be likely to achieve complete resection of the symptomatic neuroma and be able to undergo implantation with the nerve cap; and be willing and able to comply with all aspects of the treatment and evaluation schedule over a 12-month duration.

Participants were excluded if they had undergone surgical treatment for pain from symptomatic neuroma in the target nerve(s) on three or more occasions; had a life expectancy of less than 12 months; had a history of or planned radiotherapy in the area of the neuroma; were contraindicated for soft tissue implants (this included but was not limited to any pathology that would limit the blood supply, compromise healing or indicate the presence of a local infection); had a history of chronic ischemic conditions of the extremity; had a diagnosis of Type 1 Diabetes Mellitus or uncontrolled Type 2 Diabetes Mellitus (at the discretion of the investigator); had a history of diabetic neuropathy; were undergoing or expected to undergo treatment with chemotherapy, radiation therapy, or other known treatment that affects the growth of neural and/or vascular tissue; were immunosuppressed, immunocompromised or have planned immunosuppressive therapy within 12 months following the study procedure; had a history of congenital neuropathy or compressive neuropathy affecting the target limb; or had a history of prior surgical management of more proximal compressive neuropathies not related to the symptomatic neuroma that affected the target limb. The full CONSORT flow diagram is available in the supplementary materials.

Surgery

Upon inclusion in the study, participants underwent surgical intervention for identification and removal of the Morton's neuroma followed by subsequent placement of the nerve cap. Following incision and exposure per institutional standard of care, the affected nerve segment was transected and removed with placement of the nerve cap as follows. Briefly, the nerve cap was hydrated in sterile normal saline per the manufacturer's instructions for use. An entubulation stitch was placed through the nerve cap approximately 2 to 3 mm from the bifurcation outside to inside with an epineurial stitch to the native nerve matching the distance of the provisional entubulation stitch, which was then returned through the lumen of the nerve cap completing the boxed stitch. The nerve cap was gently moved onto the nerve stump. The entubulation stitch was tied to the dorsal surface of the nerve cap. The semi-translucent material allowed for visualization of the nerve stump and allowed verification that the nerve stump did not extend beyond the bifurcation within the nerve cap. A second epineurial suture at the edge of the nerve cap 180 degrees from the first suture was placed at the

surgeon's discretion. The nerve cap was anchored through the distal end tab and secured within the interosseous muscle belly within the intermetatarsal space at the surgeon's discretion.

VAS

To measure VAS, participants were asked to rate their pain on a continuous 100 mm long scale. The measured distance in millimeters (mm) from the origin (which indicates "no pain") was recorded as the pain level at time of questioning. VAS was reported at baseline, and 1-, 3-, 6-, 9-, and 12-months.

PROMIS

PROMIS for Pain Interference (PROMIS Short Form v1.1 – Pain Interference 8a), Pain Intensity (PROMIS Scale v2.0 – Pain Intensity 3a), Pain Behavior (PROMIS Scale v2.0 – Pain Behavior 20a), Physical Function (PROMIS Short Form v2.0 – Physical Function 6b), Fatigue (PROMIS Short Form v1.0 – Fatigue 8a), and Sleep Disturbance (PROMIS Short Form v1.0 – Sleep Disturbance 8a) were assessed.[13] PROMIS is a set of self-reported measurements for comparing patient status relative to the general population. PROMIS measures were scored with a T-score metric where the reference population had a mean score of 50 and standard deviation (SD) of 10. All 15 patients provided every PROMIS metric score except for Sleep Disturbance, which had only five patients participate at baseline and four patients at 6-12 month follow-up. PROMIS scores were reported at baseline, two weeks, and 1-, 3-, 6-, 9-, and 12-months.

Foot health status questionnaire (FHSQ)

The FHSQ is a standard 13-item questionnaire used to record foot health and foot health impact on quality of life.[14] The 13 items are divided among four subscales: foot pain, foot function, footwear, and foot health. FHSQ scores were reported at baseline, and 1-, 3-, 6-, 9-, and 12-months.

Work productivity and activity impairment (WPAI)

The WPAI questionnaire was used to assess impact on work productivity.[15] The WPAI questionnaire consists of four sections: Absenteeism (work time missed), Presenteeism (impairment at work), Work Productivity Loss, and Activity Impairment. WPAI scores were based on a percentage of days. Higher WPAI percentages represent increased impairment. WPAI scores were reported at baseline, and 1-, 3-, 6-, 9-, and 12-months.

Opioid use

The overall quantity and class of pain medications taken by study participants was collected at baseline and all study follow-up visits to assess potential changes in type and frequency of pain medications taken, with particular focus on opioid pain medications. Pain medication was reported by subjects in daily pain medication diaries. All opioid medications taken by participants throughout the study were converted into a Morphine Milligram Equivalence (MME) for standardization across medication type to assess changes in opioid medication usage.

Minimal clinically important difference (MCID)

When analyzing patient-reported outcomes, it is important to evaluate not only the change in the overall metric, but to associate the level of change noticeable or meaningful to the patient. Such a change is termed the MCID and represents the smallest change in an outcome that a single patient would identify as important. The MCID values used in this study were taken from previous published reports on relevant clinical populations. References for each subscale's MCID threshold are available in the supplementary materials.

Statistics

The number of events (n), mean, SD, and standard error of the mean (SEM) were used to summarize continuous data. All descriptive statistics in the Results section are mean ± SD. Paired t-tests were conducted to examine the degree of changes in key outcomes. All statistical testing was two-sided and was performed using an overall significance (alpha) level of 0.05.

Results and discussion

Safety

This study evaluated the safety and performance of the nerve cap in the surgical management of symptomatic neuromas, specifically recurrence of stump neuroma after Morton's neuroma removal. In this study, there were no instances of adverse events, serious adverse events, or subject deaths attributed to the nerve cap. Additionally, no additional product risks were identified that required modification of the product's risk assessment indicating that the nerve cap product is safe to use when placed over the distal nerve stump following traction neurectomy.

VAS

At baseline, participants reported a mean VAS pain score of 80.1 ± 10.0 mm (Fig. 1). The reported scores continually dropped after baseline measurements with decreases to 10.9 ± 25.2mm at three months ($p<0.0001$) and 1.7 ± 4.2 mm at 12 months ($p<0.0001$). The MCID for VAS pain score has been established between 14 and 22 mm. These results indicate that participants not only saw a nearly complete reduction in pain at the end of this study, but the reduction in overall pain levels was also a noticeable and meaningful change. Most importantly, no patients experienced neuroma recurrence as determined by VAS pain score.

PROMIS

Six different PROMIS outcomes were assessed: pain interference, pain intensity, pain behavior, physical function, fatigue, and sleep disturbance. Three different PROMIS scores involved pain outcomes (Pain

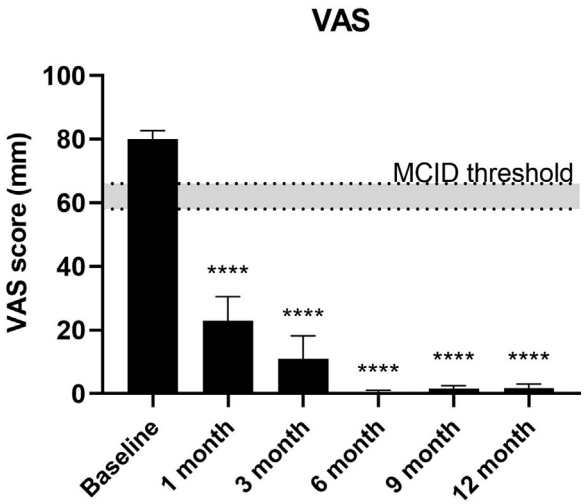

Fig. 1. VAS pain scores showed significant reductions at each time point. Scores below the MCID threshold are considered clinically meaningful. Data are represented as mean + SEM; **** $p<0.0001$.

Interference, Pain Intensity, and Pain Behavior). Pain Interference measures the impact of pain on participant outcomes such as impact on every day social, work, recreational, and other activities. PROMIS Pain Interference baseline scores were recorded at 62.6 ± 8.4 (Fig. 2A). Scores at three months and 12 months were recorded at 43.5 ± 7.1 ($p<0.0001$) and 41.5 ± 2.8 ($p<0.0001$), respectively. The MCID values for PROMIS Pain Interference have been established between 1.5 and 6 points, indicating that participants in this study saw a clinically important reduction in pain interference in their daily lives after one month.

PROMIS Pain Intensity scores measure the severity of pain of the participant population. PROMIS Pain Intensity had reported baseline scores of 53.8 ± 6.0 (Fig. 2B). Scores were recorded at 35.3 ± 7.8 ($p<0.0001$) and 33.0 ± 5.2 ($p<0.0001$) at three and 12 months, respectively. The MCID values for PROMIS Pain Intensity have been established between 5.5 and 10.9 points, indicating that these participants, on average, saw substantial clinically important reductions in pain intensity after one month.

PROMIS Pain Behavior assesses external behavioral changes caused by pain, both verbal/nonverbal and voluntary/involuntary. The baseline PROMIS score for Pain Behavior was 59.1 ± 5.9 (Fig. 2C). After three and 12 months, reported scores dropped to 38.9 ± 9.0 ($p<0.0001$) and 33.9 ± 3.3 ($p<0.0001$), respectively. The MCID value for PROMIS Pain Behavior has been established at approximately 3.2 points, indicating these participants saw clinically relevant reductions in pain behavior after one month.

Three additional PROMIS scores measured quality of life metrics. Physical Function measures self-reported capabilities during physical activities. At baseline, scores of 37.5 ± 7.2 were reported indicating the participants saw a reduction in physical capabilities relative to the general population prior to treatment. After three and 12 months, scores of 53.0 ± 8.9 ($p=0.0002$) and 57.0 ± 4.5 ($p<0.0001$) were reported, respectively (Fig. 3A). The MCID values for PROMIS Physical Function have been established between 1.9 and 6 points, indicating these participants saw clinically meaningful increases in physical function after three months. Physical function scores were significantly worse than baseline at two weeks.

The PROMIS Fatigue assessment measures a range of symptoms relating to fatigue such as feelings of tiredness and exhaustion impacting participant daily activities and function. A baseline score of 51.6 ± 9.3 was reported for the PROMIS Fatigue assessment, with reductions to 41.4 ± 12.1 ($p=0<0.01$) and 37.2 ± 6.2 ($p<0.001$) at three and 12 months, respectively (Fig. 3B). The MCID values for the PROMIS Fatigue outcome have been established between 3 and 5 points, supporting that this decrease in fatigue scores was clinically meaningful to the patients.

PROMIS Sleep Disturbance assesses quality and depth of sleep. Baseline scores of 52.1 ± 8.5 were reported. Note that only five of the participants in the study were assessed at baseline for PROMIS Sleep Disturbance. At three months, these scores had statistically remained the same at 42.6 ± 14.5 ($p>0.05$) but decreased to 33.3 ± 8.9 at 12 months ($p<0.01$; Fig. 3C). The MCID for PROMIS Sleep Disturbance scores is approximately 2 points, indicating these participants saw clinically relevant improvements in sleep quality after one month.

FHSQ

The FHSQ was used to assess foot health-specific participant outcomes. The FHSQ is divided into four subscales: Foot Pain, Foot Function, Footwear, and Foot Health. Each subscale is reported as a value between zero (very poor foot health) and 100 (optimal foot health). At

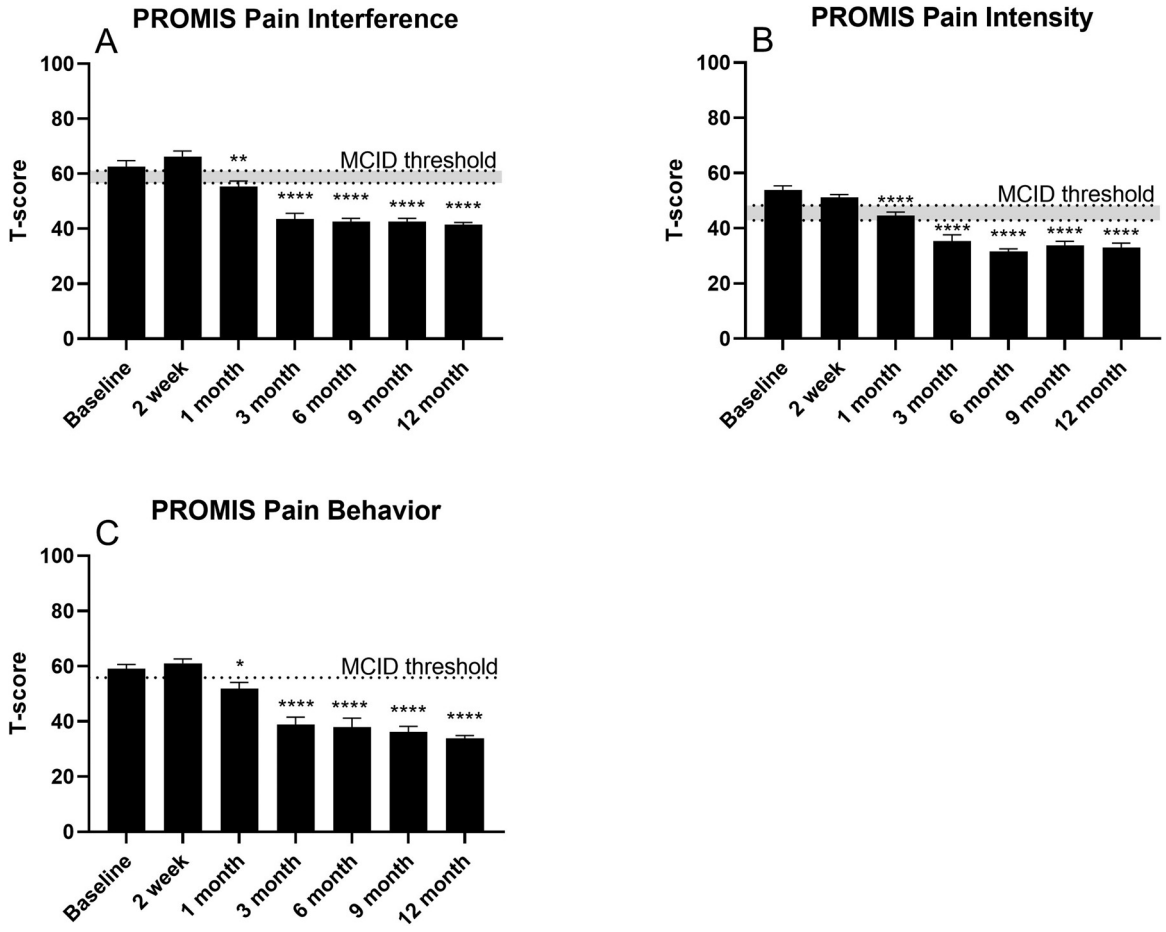

Fig. 2. PROMIS Pain Interference (A), Pain Intensity (B), and Pain Behavior (C) scores all showed significant reductions at one month and at each later time point. Scores below the MCID threshold are considered clinically meaningful. Data are represented as mean + SEM; *p<0.05, **p<0.01, ****p<0.0001.

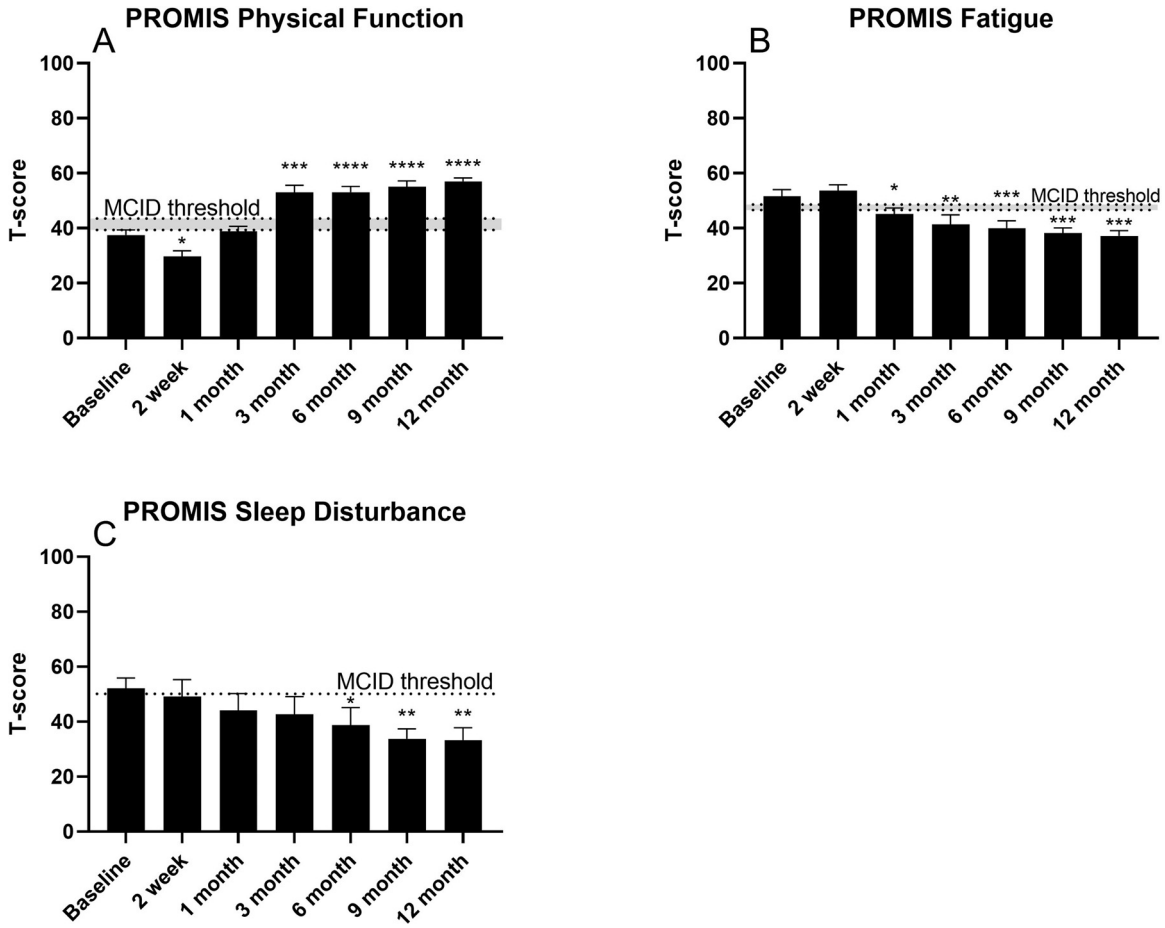

Fig. 3. PROMIS Physical Function (A), Fatigue (B), and Sleep Disturbance (C) scores showed significant changes at most time points. Scores above the MCID threshold are considered clinically meaningful for physical function. Scores below the MCID threshold are considered clinically meaningful for fatigue and sleep disturbance. Data are represented as mean + SEM; *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

baseline, FHSQ Foot Pain scores of 31.3 ± 21.8 were reported. After three and 12 months, these scores improved to 84.9 ± 22.4 (p<0.0001) and 93.8 ± 11.5 (p<0.0001), respectively (Fig. 4A). FHSQ Foot Pain MCID for this score has been established to be 13 points, indicating these participants saw clinically relevant improvements in foot pain following treatment.

The FHSQ Foot Function scores were 42.1 ± 31.0 at baseline with increases to 90.6 ± 21.6 (p<0.001) and 94.9 ± 13.4 (p<0.0001) at three and 12 months, respectively (Fig. 4B). Foot Function MCID of 7 points has been established for this subscale, indicating participants saw clinically important improvements in foot function at one month.

FHSQ Footwear scores of 20.6 ± 23.5 were obtained at baseline with changes to 61.1 ± 33.4 (p<0.01) and 69.7 ± 29.4 (p<0.0001) after three and 12 months, respectively (Fig. 4C). FHSQ Footwear MCID scores have been established at 2 points, indicating clinically important changes in the score over time.

FHSQ Foot Health scores at baseline were reported to be 25.0 ± 28.7 with scores of 64.6 ± 28.6 (p<0.01) and 75.0 ± 25.0 (p<0.01) following three and 12 months, respectively (Fig. 4D). FHSQ Foot Health score has an established MCID of 9, indicating clinically relevant improvements over the course of the study.

WPAI

The WPAI was used to measure the impact on participants' work productivity over time. WPAI Absenteeism measures the percent work time missed caused by the specific health problem. Baseline Absenteeism scores of 9.3 ± 24.0% were reported. At one month, these scores increased to 33.3 ± 50.0% (p>0.05); however, by three months, the scores had dropped to 0 ± 0% (p>0.05) with the score remaining at or near 0% for the duration of the study (12 months) indicating participants were able to attend work by three months post-surgery (Fig. 5A).

WPAI Presenteeism measures impairment while at work caused by the specific health problem. Baseline scores of 41 ± 43.6% were reported. At three and 12 months, scores dropped to 7.1 ± 12.5% (p>0.05) and 0 ± 0% (p<0.05), respectively (Fig. 5B). The MCID for WPAI Presenteeism score has been established as 20 points, indicating that clinically important differences in presenteeism were reported beginning at three months from baseline and continued over the course of the study.

WPAI Work Productivity Loss measures overall work impairment experienced by the participant caused by the health problem being studied. At baseline, a score of 45.1 ± 46.3% was reported. Following three months and 12 months, however, these scores dropped to 7.1 ± 12.5% (p<0.05) and 0 ± 0% (p<0.05), respectively (Fig. 5C). A MCID of 15 points has been established for WPAI Work Productivity Loss score, indicating participants saw clinically relevant improvements in work productivity by three months that continued for the duration of the study.

WPAI Activity Impairment measures impairment in both paid and unpaid activities by the participant. At baseline, a score of 59.3 ± 35.6% was reported with the scores dropping to 6.7 ± 11.5% (p<0.001) and 1.8 ± 6.0% (p<0.0001) following three and 12 months, respectively (Fig. 5D). The MCID for WAPI Activity Impairment score has been established as an improvement of 20%, indicating participants saw clinically relevant improvements in their ability to perform paid and unpaid activities over the duration of the study.

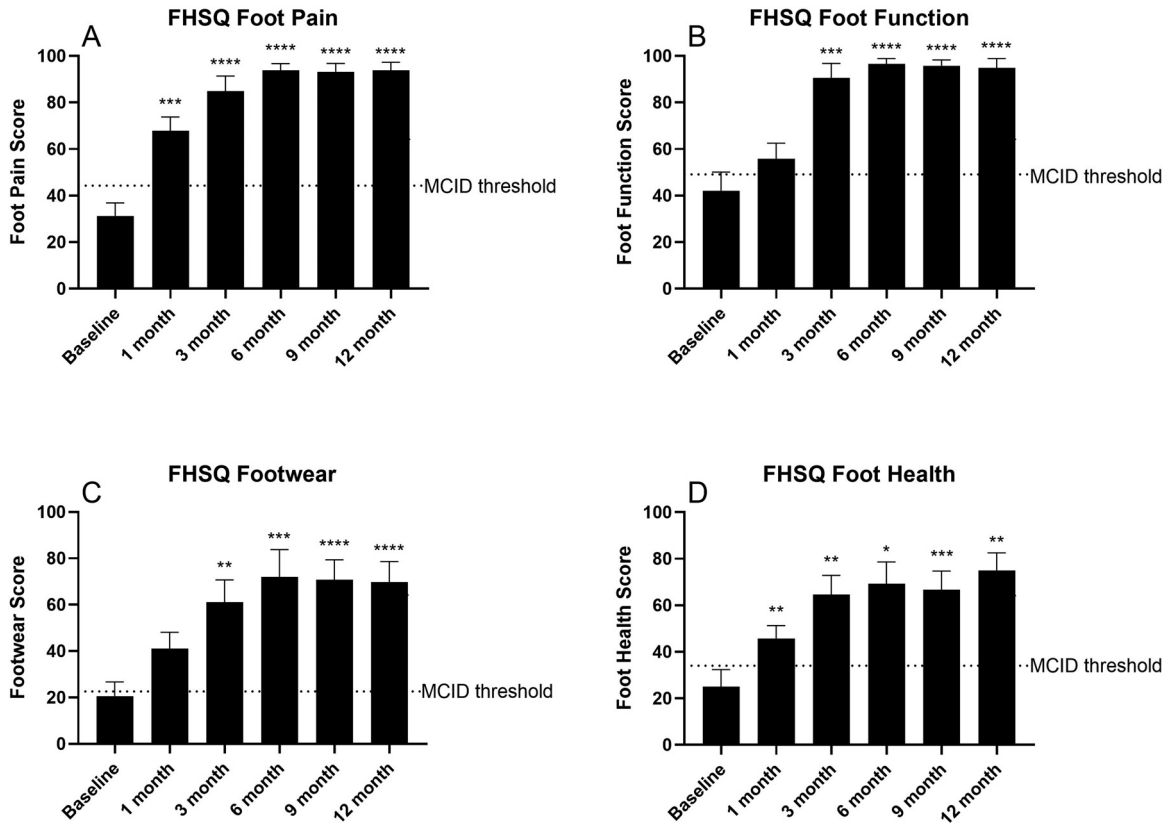

Fig. 4. FHSQ Foot Pain (A), Foot Function (B), Footwear (C), Foot Health (D) sores showed significant increases at nearly all time points. Scores above the MCID threshold are considered clinically meaningful. Data are represented as mean + SEM; *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

Opioid use

At baseline, eight of 11 (72.7%) participants did not report taking any opioid medications. For the three remaining participants, the average daily MME usage during the baseline period was 0.17, 5.00 and 9.00, respectively. All three participants that reported taking opioid pain medications at baseline reported taking no such medications by the 3-month visit and throughout the follow-up period.

Taken together, these results are promising; however, they are limited by a small sample size. In addition, this REPOSE clinical study pilot phase did not include a comparative evaluation of the efficacy of the nerve cap relative to a control. To overcome these limitations, a prospective clinical study will include increased enrollment of participants and inclusion of a comparative group using the current surgical standard of care. Despite these study limitations, this pilot phase of REPOSE showed an overall improvement in outcomes following neuroma excision and subsequent repair with the nerve cap.

Conclusions

This study showed universal improvements in pain, quality of life metrics, and a reduction of opioid use for enrolled participants. These findings are consistent with what is expected with a reduction of painful neuroma symptoms. While this study used a Morton's neuroma model, preventing neuroma reformation after neurectomy is critical for treatment of all painful neuromas and the neurectomy procedure used here is the same as neurectomy procedures used for neuromas all over the body. Therefore, these results are likely generalizable to other neuromas treated with neurectomy. Results from the literature indicate that residual pain after neurectomy can occur in up to 37% of patients,[10] while in the present study no recurrence was observed. The reduction in pain recurrence seen in this study is likely due to a reduction in new symptomatic neuroma formation at the nerve stump due to use of the nerve cap. This may be due to the unique attributes of the nerve cap. The nerve cap is derived from porcine SIS and contains internal architecture that is meant to provide an avenue for axonal growth while blocking external growth signals so that the growth will eventually exhaust, thereby reducing the risk of recurrent neuroma. The nerve cap also aids to protect the nerve stump from painful mechanical stimulation. Overall, the observed results indicate that the nerve cap is safe, effective and reproducible for the management of painful neuroma.

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Financial Disclosure

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Declaration of competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. Garrett, Dr. Martin and Dr. Frania have no disclosures.
Dr. Pereira and Dr. Thomajan serve as consultants for Axogen Corporation.
Dr. Thomajan, Dr. Van Gils, and Dr. Dauphinee have received research funding from Axogen Corporation.

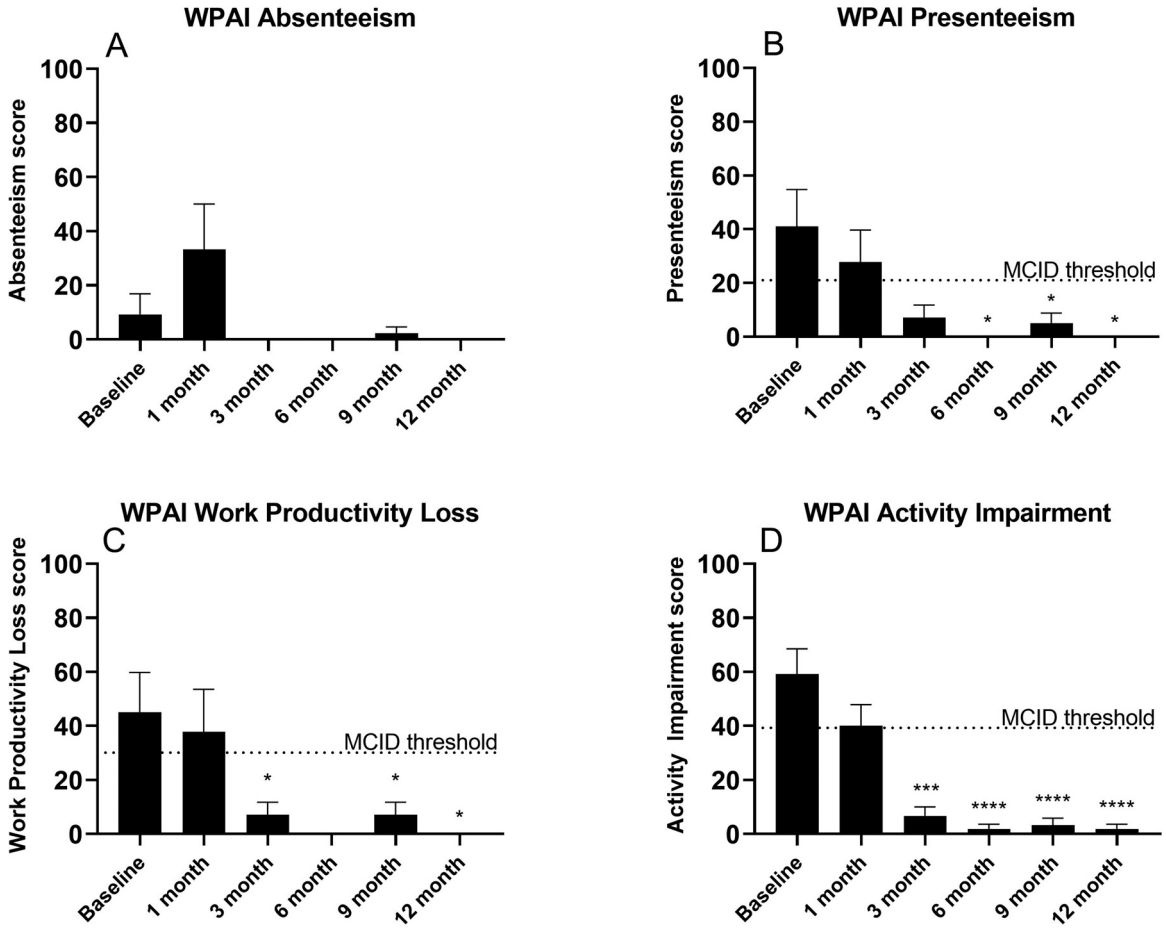

Fig. 5. WPAI Absenteeism (A), Presenteeism (B), Word Productivity Loss (C), and Activity Impairment (D) scores all showed reductions over time with most reaching statistical significance. Scores below the MCID threshold are considered clinically meaningful. Data are represented as mean + SEM; *p<0.05, ***p<0.001, ****p<0.0001.

Informed patient consent

Complete informed consent was obtained from the patient for the publication of this study and accompanying images.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.fastrc.2022.100179.

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