Neuropathic Research Paper

Analgesic effect of perineural local anesthetics, steroids, and conventional medical management for trauma and compression-related peripheral neuropathic pain: a retrospective cohort study

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Abstract

Introduction: Trauma and compression are common causes of peripheral neuropathic pain (NP) refractory to conventional medical management (CMM). The role of perineural interventions in relieving this type of pain is unclear.

Objectives: The objectives of this retrospective study were to determine the analgesic benefits of adding a combination of perineural local anesthetic and steroids (LA-S) to CMM compared with CMM alone in patients who had moderate-to-severe refractory NP after trauma to the ankle and the foot.

Methods: Health care records of 60 patients in exposed (3 injections of perineural LA-S at weekly intervals with CMM) and 60 in unexposed (CMM) cohorts were reviewed. Data on patient characteristics, pain, and mental and physical function were extracted at baseline and at the postintervention follow-up. Data were analyzed to evaluate analgesic benefit from the study interventions and the impact of baseline characteristics.

Results: Perineural LA-S with CMM cohort had lower pain numerical rating scale scores at 1 to 3 months after the intervention as compared to the CMM alone cohort (5.50 [interquartile range 4.00–7.00] and 7.00 [interquartile range 5.00–8.00], respectively; \(P < 0.01\)). However, multivariable analysis did not show an independent beneficial analgesic effect with the addition of perineural LA-S to CMM compared with CMM alone. A greater severity of preintervention catastrophizing (each unit increase in pain catastrophizing score increased pain score at follow-up by 0.04, 95% confidence interval: 0.01–0.07) was associated with reduction in the analgesic benefit.

Conclusion: Perineural local anesthetic and steroid injections do not confer an analgesic benefit for trauma- or compression-related peripheral NP.

Keywords: Trauma, Compression, Peripheral neuropathic pain, Perineural local anesthetics and steroids

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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1. Introduction

Peripheral neuropathic pain (NP) is defined as pain caused by a lesion or disease affecting the peripheral somatosensory nervous system. Peripheral NP has a prevalence of 2.5% to 4% in the general population. Neuropathic pain is often severely debilitating, it is largely resistant to pharmacological treatment, and its management and sequelae are a significant burden on health care resources. Peripheral NP has multiple etiologies but trauma leading to entrapment or compression of the nerves is an important cause. Nerve fibers in lower limbs are often involved in trauma to the ankle and the foot (e.g., crush injury, fractures, ligament tears or sprains, and surgery) and this can result in chronic pain of moderate-to-severe intensity that often has predominantly neuropathic characteristics and is associated with functional limitations.

Injured or damaged sensory neurons in the injured limbs of patients with peripheral NP display enhanced or aberrant activity. When applied directly to injured nerve fibers, a combination of local anesthetics (LA) and steroids (LA-S) can suppress the secretion of inflammatory mediators and decrease ectopic discharge from the injured nerve, thereby alleviating edema and providing analgesia. Perineural injection of LA-S was reported for treatment of posttraumatic or compression-related neuropathies in a case series. A systematic review and meta-analysis of 5 randomized controlled trials (RCT) in patients with peripheral NP after compression or trauma by our group revealed a small effect size in favor of perineural LA-S as compared to injection of only LA or conventional medical management (CMM). The studies in this review had clinical heterogeneity in terms of etiologies of peripheral NP and analgesic interventions, and considerable variation in analgesic benefit was also observed across the studies. An adequately powered RCT for patients with trauma- or compression-related peripheral NP would provide high-quality evidence on efficacy and adverse effects of perineural LA-S added to conventional management compared with conventional management alone. An additional challenge for health care providers when considering perineural LA-S for trauma- or compression-associated peripheral NP is the selection of patients most likely to benefit from its use. However, evaluating existing data to estimate the effect size and to explore the feasibility of a trial can be useful in planning an RCT.

We conducted an observational retrospective cohort study to evaluate analgesic benefits of adding perineural LA-S to conventional management compared with conventional management alone in patients who had sustained primary (direct injury) or secondary (surgical intervention for bony or ligamentous injuries) neural trauma to their ankle and foot. The objectives of this study were to evaluate analgesic outcomes and adverse effects in the 2 cohorts at 1 to 3 months after the interventions. We also evaluated the association between pretreatment variables including patient characteristics, mental and physical function at baseline, and the observed analgesic benefit. Analgesic outcomes were evaluated in terms of the absolute numerical rating scale (NRS) scores for pain and the proportion of patients achieving a clinically meaningful reduction of 30% or greater in the pain NRS score after the interventions.

2. Methods

2.1. Study design

This was a retrospective, double (sequential) cohort study of analgesic efficacy of perineural LA-S for chronic posttraumatic or compression-related, moderate-to-severe chronic NP in the ankle and the foot. Approval for this study was obtained from the Institutional Research Ethics Board (# 13–6862-AE).

2.2. Data source

Data for this study were obtained from medical records of patients treated at our tertiary, academic, multidisciplinary pain centre at the University Health Network, Toronto, Canada, between August 2009 and July 2013. This pain centre is staffed by pain physicians, neurologists, surgeons, physical therapists, psychologists, and pharmacists with expertise in diagnosing and treating NP. The cohort of patients for this study included patients with chronic peripheral NP of moderate-to-severe intensity after injury to the ankle and/or the foot and who were either not considered surgical candidates or who had persistent pain despite surgery and had failed at least 6 weeks of management with anti-inflammatory medications and physical therapy (PT) (desensitization, range of motion, and strengthening exercises). Patients were assessed by pain physicians and those deemed to have NP on history and examination (descriptors of NP, presence of allodynia and hyperalgesia) were given conventional management, i.e., pharmacotherapy as per guidelines for treating NP. Patients who responded to this conventional management (i.e., pain NRS ≤3/10) were discharged from the pain centre after one follow-up. Patients who continued to report moderate-to-severe pain (pain NRS ≥4/10) with peripheral NP features (as diagnosed by clinical assessment) despite optimization with 12 weeks of conventional management were seen for multiple follow-ups until their discharge. Data on pain and related outcomes were recorded in the database for 3 months because their health care insurer (Workplace Safety Insurance Board, Ontario, Canada) funded care for this duration and patients were subsequently discharged to pain clinics in the community. The data on patients accrued from August 2009 to August 2011 comprised the conventional management cohort in this observational study. Perineural LA-S injections were offered to patients with peripheral NP refractory to 6 weeks of conventional management starting in August 2011 and these patients also continued to receive conventional management during the 6 weeks when the injections were administered, similar to the August 2009 to July 2011 cohort that received conventional management for a total of 12 weeks. In summary, the study sample consisted of patients who received conventional management alone from August 2009 to July 2011 and of patients who received perineural LA-S and conventional management from August 2011 to June 2013 (Fig. 1).

2.3. Participants: inclusion and exclusion criteria

The inclusion criteria included an etiology of trauma (soft tissue or bone fracture) to the ankle and the foot in patients 18 to 80 years of age, peripheral NP as per clinical assessment (history of trauma, sensitivity to touch and/or coexisting numbness, and findings of allodynia, hyperalgesia, or hypohesthesia on examination in the sensory distribution of nerves innervating the foot and the ankle), pain NRS score of 4/10 or more persisting for more than 3 months, and at least one follow-up visit between 1 and 3 months after the study interventions. Exclusion criteria included uncontrolled diabetes mellitus, preexisting neuropathy due to a systemic cause, previous perineural injection of LA or steroids in the ankle and the foot, repeat trauma to foot, or history of similar episode of pain in the past.
2.4. Cohorts

2.4.1. Exposed (local anesthetic and steroids with conventional management) group

The ankle and the foot are supplied by 5 nerves (tibial, superficial peroneal, deep peroneal, sural, and saphenous) that are associated with specific anatomic territories. These patterns of distribution of pain were used to identify the target nerves for 3 ultrasound-guided perineural LA-S injections at weekly intervals (as per the prevailing practice) within 7 to 12 weeks of initiating conventional management in the “exposed” cohort. The injectate consisted of 4 mg of methylprednisolone (steroid) per milliliters (mL) of 0.25% bupivacaine (LA). The volume of the perineural injectate varied from 2 to 6 mL per nerve with a maximum of 20 mL injected per session (ie, 8–24 mg of methylprednisolone per nerve with a maximum of 80 mg per session and 240 mg over 3 sessions, a dose consistent with that administered for peripheral nerves in the published literature). Injections were performed under ultrasound guidance to ensure circumferential perineural spread at weekly intervals over 3 weeks to provide analgesic benefit to the patient from the sensory neural blocking effect of LA, thereby facilitating PT to the ankle and the foot.

2.4.2. Unexposed (conventional management alone) group

Patients in this group received only conventional management for 12 weeks. The conventional management consisted of recommended pharmacotherapy for treating NP. Pharmacotherapy for NP (as part of conventional management) included gabapentinoids (gabapentin or pregabalin) with addition of a tricyclic antidepressant (eg, amitriptyline and nortriptyline) after 3 weeks if the gabapentinoids were not tolerated or ineffective. Doses for these medications were based on a balance between benefits and adverse effects as reported by the patients with the dose range for gabapentin varying from 900 to 3600 mg daily (or pregabalin 75–600 mg daily) and the dose range for tricyclic antidepressants was from 25 to 75 mg daily.

2.5. Data extraction

Details of data extraction are provided in Appendix 1 (available as supplemental digital content at http://links.lww.com/PR9/A114).

2.6. Analysis plan

Continuous variables were summarized as mean values and SD (or, if nonnormally distributed, median values with 25th and 75th centiles), and categorical variables were presented as frequencies or proportions. Continuous data were compared using parametric and nonparametric methods. Categorical data were compared using the $\chi^2$ test or Fisher exact test. Pain intensity at 1 to 3 months after the interventions as measured by the NRS was compared using the Mann–Whitney $U$ test. Multivariable linear regression, adjusting for statistically and clinically meaningful differences in baseline characteristics of the 2 cohorts, was then conducted to evaluate whether the intervention was independently associated with pain intensity scores after treatments. Mean change in pain intensity (postintervention minus baseline) for the groups was also compared using the Mann–Whitney $U$ test. The proportion achieving a 30% or greater decrease in postintervention NRS score from baseline was calculated and compared using a $\chi^2$ test or Fisher exact test when more than 20% of the cells had expected frequencies less than 5.
adverse effects were reported as counts for each type of event. Univariable analysis was conducted to compare the opioid doses, incidences (counts) of return to work, and of tolerating PT between the conventional management with perineural LA-S and only conventional management groups at 1 to 3 months after the interventions. Predictors or variables likely to influence response to study treatments as determined from clinical sensibility and published literature and those with \( P < 0.1 \) from the univariable analyses were included in the multivariable linear and logistic regression analyses (details in Appendix 2, available as supplemental digital content at http://links.lww.com/PR9/A114). The outcome of interest for the linear regression was the pain NRS score at posttreatment follow-up. For the logistic regression, presence of a 30% or greater reduction in NRS pain scores after study treatments as compared to baseline was the outcome of interest. All analyses were conducted using SAS v 9.3 (SAS Institute, Cary, North Carolina). A two-sided \( P \)-value of \( <0.05 \) was considered statistically significant. Details of feasibility and power calculation for this study are also provided in Appendix 2 (available as supplemental digital content at http://links.lww.com/PR9/A114).

3. Results

3.1. Data extraction

Data from 60 patients in each cohort who met the inclusion criteria were extracted and included for analysis. The reasons for excluding patients’ data were missing data for interventions and/or primary objective, incomplete interventions in the exposed group (less than 3 injections in the exposed group), and surgical treatment between the study interventions and assessment of primary outcome. Imputation was not used for missing data because there were no missing data for the key outcomes of interest.

3.2. Baseline and demographic data

Patient characteristics were similar in both groups (Table 1). All the patients were within the age range for a working population (18–70 years). Approximately two-thirds of the patients in both groups were males, and the majority of patients were engaged in physically demanding occupations (construction, manufacturing, and domestic or clinical personal care). Most patients in both groups were not working at the time of their assessment. The prevalence of other preexisting chronic non–injury-related pain syndromes in addition to ankle and foot pain was low in both groups.

3.3. Pain-related data

3.3.1. Intensity and quality of pain and opioid use

Baseline pain-related characteristics were compared between the 2 groups (Table 2). The distribution of NRS pain scores was skewed in both groups with the baseline (preintervention) median pain score of 7 (interquartile range [IQR] 6–8) in both groups. The median (IQR) duration of pain before intervention was longer in the exposed cohort as compared to the unexposed cohort (14 [IQR 9–20.5] and 9 [IQR 6–15] months, respectively; \( P < 0.01 \)). Approximately 1 in 3 (19/60) patients in the exposed group and 2 in 3 (36/60) patients in the conventional management group were taking opioids on a regular basis for pain. The baseline daily opioid dose in oral morphine equivalents was lower in the exposed cohort as compared to the unexposed cohort (0 [IQR 0–12.5] and 15 [IQR 0–30] mg, respectively; \( P = 0.01 \)).

3.3.2. Psychological and physical status

The median pain catastrophizing scale (PCS) score (range is 0–52) was lower in the exposed cohort as compared to the unexposed cohort (26 [IQR 15–35] and 34.5 [IQR 16–44], respectively; \( P < 0.01 \)) with a higher incidence of severe catastrophizing (PCS ≥ 38) in the unexposed cohort (50% in unexposed cohort vs 22% in exposed cohort; \( P = 0.02 \)). There was no difference in the severity of depression (PHQ-9 scores) between the 2 groups. The Lower Extremity Functional Scale scores indicated that majority of patients in both cohorts had moderate-to-severe functional limitations.

3.4. Details of study interventions

3.4.1. Conventional management

The pharmacotherapy medications used by patients included gabapentinoids (gabapentin at daily dose 900–2700 mg or pregabalin at daily dose 150–600 mg) with or without with a tricyclic antidepressant (eg, amitriptyline or nortriptyline at daily dose 25–100 mg) and/or a serotonin–norepinephrine reuptake inhibitor (eg, duloxetine at daily dose 60–90 mg). By the end of 12 weeks of the study period, 20 patients in the conventional management alone cohort (33% of the cohort) and 21 patients in the LA-S with conventional management cohorts (35% of the cohort) were taking one or more medications for NP. Lack of analgesic benefit and/or adverse effects (as reported in Incidence of adverse effects below) were the 2 main reasons for discontinuing these medications.

3.4.2. Perineural injections

The median number (IQR) of nerves targeted in the ankle and the foot per patient per session was 4 (IQR 2.5–4) in the exposed cohort.

3.5. Outcomes at follow-up

3.5.1. Intensity of pain

The data for pain and related outcomes are provided in Table 3. The median NRS pain scores at 1 to 3 months after conventional management without (unexposed) or with (exposed) perineural LA-S injections were lower in the exposed cohort as compared to the unexposed cohort (5.50 [IQR 4.00–7.00] and 7.00 [IQR 5.00–8.00], respectively; \( P < 0.01 \)) at the time of follow-up. The median pain NRS score at postintervention follow-up decreased from the baseline value in the exposed group (1.00 points; IQR −2.75 to 0.00; \( P < 0.01 \)) but no change was observed in the unexposed group. Approximately 1 in 3 patients in the exposed group (19/60) but only 1 in 7 patients in the unexposed cohort (9/60) reported 30% or greater reduction in NRS pain scores (\( P = 0.03 \)). The NRS pain scores at follow-up were assessed earlier in the exposed group after the treatment (49.50 days; IQR: 35.00–82.50 days) than in the unexposed group (69.50 days; IQR: 49.00–100.50 days) (\( P = 0.03 \)).

Multivariable linear regression was performed to address imbalances between the cohorts that may have had an impact on the NRS scores for pain at the follow-up at 1 to 3 months. Covariates that were selected based on clinical sensibility and statistical evidence included NRS score for pain at baseline, work status, PCS scores, daily opioid dose and duration of pain at the time of first presentation, and the time interval between study interventions and the postintervention follow-up. The omnibus F-
test for the analysis was significant ($P = 0.01$) with baseline pain NRS ($P = 0.01$) and PCS ($0.02$) scores having a strong influence on the postintervention analgesic outcomes. With consideration for these covariates, no difference between a combination of conventional management with perineural injection of LA-S and only conventional management was found with respect to the NRS pain scores at follow-up (Table 4). The assumptions for multivariable linear regression were also verified including normal distribution of residuals, no influential outlier values, and no multicollinearity among the independent variables.

A total of 28 patients in the study population (19 in the exposed cohort and 9 in the unexposed cohort) had 30% or greater reduction from baseline in pain NRS score for pain at 1 to 3 months after the intervention. A comparison of covariate differences between those who did and did not experience a 30% or greater reduction in pain NRS score at posttreatment follow-up are presented in Appendix 3 (available as supplemental digital content at http://links.lww.com/PR9/A114). The preintervention PCS scores were lower in patients who reported an analgesic response ($P = 0.02$).

### 3.5.2. Association of pretreatment (baseline) and treatment variables with analgesic response

Multivariable logistic regression was performed to assess the impact of pretreatment variables on predicting the presence (30% or greater reduction in NRS for pain) or absence of analgesic response at follow-up after the study interventions. Based on clinical sensitivity and statistical evidence, 4 covariates were considered in the logistical regression model: exposure to perineural LA-S and conventional management or no exposure, PCS score at baseline, duration of pain in months at the time of study treatments, and the time interval in days between the end of study treatments and assessment of NRS pain scores. The baseline PCS score but not exposure to perineural LA-S with conventional management was independently associated with the likelihood of analgesic response at follow-up (Table 5). Given this, the impact of baseline PCS score on analgesic response was evaluated by treatment group. For the exposed cohort (conventional management with steroid and LA) group, the mean PCS score for responders (20.81 ± 13.38) was lower than the score for nonresponders (29.26 ± 13.52; $P = 0.04$). For the unexposed cohort (conventional management only) group, the mean PCS was 28.50 ± 15.66 for responders and 36.48 ± 14.69 for nonresponders with no statistically significant difference between responders and nonresponders ($P = 0.25$).

There was no significant difference between the 2 groups in the daily dose of opioids at the time of follow-up to treat pain (Table 6). Eighteen patients in the exposed group were taking opioids at the first follow-up as compared to 19 at baseline. In the unexposed group, 12 patients were taking opioids at the first follow-up as compared to 38 at baseline, although there had been no significant reduction in NRS pain scores. Data on 2 other surrogate markers for pain relief—return to work and tolerance of PT—were also evaluated. These data are provided in Table 6.

### 3.5.3. Incidence of adverse effects

The reported adverse effects in both groups included mild cognitive impairment: 15 patients in exposed cohort (25%) and 17 patients in unexposed cohort (28%) with no difference between the 2 cohorts ($P = 0.3$). These effects could be attributed to medications used by patients including gabapentinoids, antidepressants, and opioids. No patient in the exposed group reported known local adverse effects of perineural steroids and LA (eg, infections, skin discoloration, and necrosis). However, presence or absence of systemic adverse effects of perineural steroids and LA could not be ascertained because of the lack of data on these adverse effects (ie, a definitive yes or no) in the health records.

### 4. Discussion

This retrospective study is the first investigation to evaluate the impact of adding image-guided perineural LA and steroids to conventional management in 120 patients with trauma- and compression-related moderate-to-severe NP in the ankle and the foot. The results of this study indicate that patients in the exposed
Pain-related characteristics in the exposed (perineural local anesthetics and steroids with conventional medical management [CMM + LA-S]) and unexposed (conventional medical management [CMM]) groups.

| Variable | CMM + LA-S (n = 60) “exposed” | CMM (n = 60) “unexposed” | P    |
|----------|-------------------------------|--------------------------|------|
| Baseline NRS pain score (median [25th–75th centile]) | 7.00 (6.00–8.00) | 7.00 (6.00–8.00) | 0.71 |
| Patients with baseline DN4 score ≥4/10 | | | 0.11 |
| No | 9 (15.00%) | 16 (27.00%) | 0.11 |
| Yes | 51 (85.00%) | 44 (73.00%) | |
| Duration of pain (mo) (median [25th–75th centile]) | 14.00 (8.00–20.50) | 9.00 (6.00–15.00) | 0.001 |
| Baseline oral opioid dose* (morphine equivalents mg per day) (median [25th–75th centile]) | 0.00 (0.00–12.50) | 15.00 (0.00–30.00) | 0.01 |
| Mechanism of injury | | | 0.42 |
| Blunt soft-tissue trauma | 19 (31.67%) | 23 (38.33%) | |
| Closed fracture of one or more bones | 15 (25.00%) | 18 (30.00%) | |
| Penetrating trauma/ORIF | 26 (43.33%) | 19 (31.67%) | |
| Operative intervention | | | 0.73 |
| Before presentation | 25 (41.67%) | 15 (24.09%) | |
| After presentation | 1 (1.67%) | 1 (2.27%) | |
| None | 34 (66.67%) | 28 (63.64%) | |
| EMG and NCV studies | | | 0.92 |
| Normal | 10 (21.57%) | 22 (61.11%) | |
| Abnormal | 6 (37.50%) | 14 (38.89%) | |
| Baseline PCS score (median [25th–75th centile]) | 26.00 (15.00–35.00) | 34.50 (16.00–44.00) | 0.009 |
| Severity of catastrophizing (PCS grade) | | | 0.02 |
| <16/52 (mild) | 14 (27.45%) | 6 (16.67%) | |
| 16–37/52 (moderate) | 26 (50.98%) | 12 (33.33%) | |
| ≥38/52 (severe) | 11 (21.57%) | 18 (50.00%) | |
| Baseline depression (PHQ9 score) [means ± SD] | 11.91 ± 7.26 | 13.56 ± 8.77 | 0.43 |
| Baseline physical disability (LEFS score) [means ± SD] | 24.33 ± 13.03 | 20.90 ± 13.17 | 0.21 |
| LEFS grade | | | 0.36 |
| <20: severe loss of function | 21 (38.89%) | 21 (63.85%) | |
| 20–39: moderate loss of function | 28 (51.85%) | 15 (48.46%) | |
| ≥40: mild loss of function | 5 (9.26%) | 3 (7.69%) | |

Data are means ± SD, medians (25th–75th centile) or numbers (percentages). DN4, Douleur Neuropathique—4 (score 0–10; score ≥4 indicates neuropathic pain)—applied retrospectively; EMG, electromyogram; LA, local anesthetics; LEFS, Lower Extremity Functional Scale (score 0–80 with a lower score indicating greater disability); NCV, nerve conduction velocity; NRS, Numerical Rating Scale; PCS, Pain Catastrophizing Scale (score 0–52); PHQ9, Patient Health Questionnaire—9 items (score 0–27).

* 19 patients in CMM + steroids-LA group and 38 patients in CMM group were taking opioids.

The analgesic benefit of adding steroids to LA for treating compression- and trauma-related peripheral NP is more challenging to treat as compared to its nociceptive counterpart.17,23,36 Medications recommended for treatment of NP have low success rates with, at best, only 1 in 6 patients reporting pain relief.17

In the conventional management cohort in this study reported minimal improvement in NRS scores for pain despite over 12 weeks of trials with first-line medications for NP. These low success rates with medications and the severity of NP, also reported extensively in literature,17,36 have prompted a search for more efficacious analgesic strategies. Perineural injections of LA and steroids around injured nerves are one of these commonly used strategies to treat refractory peripheral NP. Patients in the conventional management with LA-S cohort in this study reported lower pain scores at postintervention follow-up, and perineural LA-S for peripheral compression- and traumarelated NP.

Injuries to the extremities are common in the working age population with an annual population incidence of around 5%.2,13,37 Furthermore, many painful conditions that are associated with degenerative conditions, trauma, and/or compression and that have been traditionally regarded as “nociceptive” are now recognized to have a prominent neuropathic character with 15% to 45% patients displaying such features.21,24 Neuropathic pain is more challenging to treat as compared to its nociceptive counterpart.17,23,36 Medications recommended for treatment of NP have low success rates with, at best, only 1 in 6 patients reporting pain relief.17

Perineural LA and steroids are often used for treating compression- and trauma-related peripheral NP but this practice is based mostly on practitioners’ preference and anecdotal experience rather than unequivocal evidence. The published literature on this topic consists of small RCTs that are often underpowered and lack blinding of investigators and participants. The analgesic benefit of adding steroids to LA for treating compression- and trauma-related pain remains unclear,19,40 while concomitant catastrophizing and depression can decrease the likelihood and magnitude of pain relief.30 Injection of steroids into perineural compartments can also be associated with adverse effects that can be local (eg, infection) or systemic (eg, osteoporosis and myopathy).20,22 This retrospective study adds to the limited body of knowledge on the analgesic benefit with perineural LA-S.
approximately 1 in 3 patients had a clinically meaningful reduction of NRS pain scores by over 30% as compared to 1 in 7 patients in the conventional management only cohort attaining this outcome. Consistent with the findings of this study, nonpharmacologic modalities used for treatment of ankle and foot ligamentous injuries (immobilization, PT, or surgery) have been reported to have relatively poor efficacy in treating pain with 10% to 30% patients reporting long-term pain on weight-bearing.29 Finally, NP is often associated with significant allodynia and dysesthesias—these phenomena make it difficult for patients to tolerate PT for rehabilitation. Image-guided perineural LA-S should be investigated as an adjunct to conventional management to accelerate rehabilitation and return to work but providers and patients should be aware of the unclear evidence for benefit.

The results of this study diverge from reports of clinical investigations attributing significant analgesic benefit with perineural steroids in 30% to 40% of patients with Morton neuroma, a nontraumatic NP condition in the foot.34,43 A possible reason for this difference may be Morton neuroma is a truer NP condition compared with trauma- or compression-related pain that may have elements of both neuropathic and nociceptive pain.

Negative psychological phenomena in patients with chronic pain such as catastrophizing and depression are associated with a higher reported intensity and chronicity of pain as well as a decrease in response to analgesic interventions.11,14,27,30,31 The severity of pain-related catastrophizing, as measured by the PCS, was lower in the combination of conventional management with perineural LA-S group as compared to the

| Table 3 |
| --- |
| Outcomes at 1 to 3 months after conventional medical management (CMM) with or without injections of perineural local anesthetics (LA) and steroids. |
| Variable | CMM + steroids—LA (n = 60) | CMM (n = 60) | P |
| --- | --- | --- | --- |
| Baseline NRS pain scores | 7.00 (6.00–8.00) | 7.00 (6.00–8.00) | 0.71 |
| Interval in days between start of treatment and follow-up | 49.50 (35.00–82.50) | 69.50 (49.00–100.50) | 0.03 |
| NRS pain scores at follow-up | 5.50 (4.00–7.00) | 7.00 (5.00–8.00) | 0.001 |
| Change in pain NRS scores (within group) | 1.00 (–2.75 to 0.00) | 0.00 (–1.00 to 0.00) | 0.001 |
| Change in pain NRS scores from baseline <30% | 20 (33.33%) | 40 (66.67%) | 0.001 |
| Improvement <30% | 22 (36.67%) | 12 (20.00%) | 0.12 |
| Improvement 30%–50% | 8 (13.33%) | 6 (10.00%) | 0.30 |
| Improvement >50% | 10 (16.67%) | 2 (3.33%) | 0.30 |
| Oral opioid dose at follow-up* (in morphine equivalents in mg per day) | 0.00 (0.00–2.50) | 0.00 (0.00–0.00) | 0.37 |
| Resumed work after pain treatment | 0.00 (0.00–2.50) | 0.00 (0.00–0.00) | 0.37 |
| Able to tolerate physiotherapy better than before treatment | 0.00 (0.00–2.50) | 0.00 (0.00–0.00) | 0.37 |

Data are means ± SD, medians (25th–75th centile) or numbers (percentages).

* 18 patients in CMM + steroids-LA group and 12 patients in CMM group were taking opioids at posttreatment follow-up.

CMM, conventional medical management; LA, local anesthetics; LEFS, Lower Extremity Functional Scale; NRS, Numerical Rating Scale.

| Table 4 |
| --- |
| Multivariable linear regression model for the entire database (exposed and unexposed) with NRS pain scores at follow-up after the study treatments as the outcome variable (R² for the model: 0.34). |
| Predictor variable | Unstandardized beta coefficient (95% CI) | Test statistic | P |
| Omnibus F-test (ndf, ddf) | — | 5.26 (1, 71) | 0.01 |
| Baseline pain NRS score | 0.43 (0.13 to 0.73) | 0.01 |
| Work status (not working vs working) | −0.07 (−0.95 to 0.83) | 0.88 |
| PCS score | 0.04 (0.01 to 0.07) | 0.02 |
| Opioid dose at baseline (in MME per day) | 0.01 (−0.01 to 0.03) | 0.11 |
| Perineural LA-S (“exposed”) | −0.71 (−1.60 to 0.20) | 0.12 |
| Interval in days between start of treatment and follow-up | −0.01 (−0.03 to 0.01) | 0.09 |
| Duration of pain in months before start of treatment | −0.01 (−0.03 to 0.01) | 0.44 |

LA-S, local anesthetics-steroids; CI, confidence interval; MME, morphine milligram equivalents; NRS, Numerical Rating Scale; PCS, Pain Catastrophizing Scale; PHQ-9, Patient Health Questionnaire—9-item for depression.
Conventional management only group in our study cohort. It can be speculated that patients with less catastrophizing were more likely to agree receive perineural interventions. The research on patient-reported pain with procedures involving injections shows an association between the degree of catastrophizing and the reported intensity of procedural pain. A comparison of baseline PCS scores between analgesic responders and nonresponders in this study indicated lower PCS scores in patients with analgesic response (Appendix 3, available as supplemental digital content at http://links.lww.com/PR9/A114), while a greater severity of catastrophizing was found to be associated with a lower probability of analgesic response in the entire cohort (Table 5). A comparison of baseline PCS scores between analgesic responders and nonresponders in the 2 study cohorts also showed that the PCS score was lower in responders in the exposed but not the unexposed cohort (Appendix 3, available as supplemental digital content at http://links.lww.com/PR9/A114). Multivariable logistic regression analysis showed that pain catastrophizing, but not the type of treatment (conventional management only vs combination of conventional management with perineural LA-S), impacted on the likelihood of achieving 30% or greater reduction in the intensity of pain. Further analysis found that, within the exposed cohort, the severity of pain catastrophizing was lower for responders than for nonresponders. The results of this study indicate that the presence of catastrophizing should be identified through clinical assessment and validated instruments (eg, PCS) before offering interventional treatments. Appropriate cognitive behavioral treatments should be provided to patients with a high degree of pain catastrophizing before interventions. Coexisting depression should also be addressed because it can impact the response to interventional treatments for pain.

Chronicity of pain has been associated with worsening of outcomes. There is also evidence to support use of interventional procedures early after onset of pain in patients with NP syndromes, and analgesic benefit after perineural LA and steroids in patients with compression-related neuropathies can attenuate with time. The primary outcome of the study, NRS scores for pain, was measured later in the conventional management alone cohort as compared to the LA-S with conventional management cohort (median of 49.5 vs 69.5 days, respectively, \( P = 0.03 \); Appendix 3, available as supplemental digital content at http://links.lww.com/PR9/A114), and this may have contributed to the higher pain scores in the conventional management alone cohort. Although patients in the conventional management alone cohort had a shorter duration of pain at presentation to the pain clinic (median of 9 months vs 14 months, \( P = 0.001 \); Table 2), this variable did not impact on post-intervention pain scores when it was examined in a multivariable linear regression model (Table 4).

There were some limitations of this study in addition to unrecognized confounders and biases that are inherent drawbacks of retrospective studies. Furthermore, although retrospective cohort study designs help us to understand associations, they do not allow casual inferences. Our analysis may have been affected by selection bias because data from only those patients who had received the interventions of interest in their entirety and had followed up at our center were included. Data on the doses of antineuropathic medications taken by patients were not extracted for our study because it was incompletely reported in

### Table 5

| Variable | Odds ratio | 95% confidence intervals | \( P \) |
|----------|------------|-------------------------|-------|
| Wald’s statistic | — | — | 0.19 |
| Perineural LA-S | 1.34 | 0.42–4.31 | 0.63 |
| PCS | 0.96 | 0.92–0.99 | 0.03 |
| Duration of pain (mo) | 1.01 | 0.99–1.04 | 0.40 |
| Interval between treatment and follow-up (d) | 1.01 | 0.99–1.02 | 0.28 |

The c-statistic for the model was 0.70.

LA-S, local anesthetics and steroids; PCS, Pain Catastrophizing Scale.

### Table 6

| Variable | CMM + LA-S (n = 60) “exposed” | CMM (n = 60) “unexposed” | \( P \) |
|----------|-------------------------------|-------------------------|-------|
| Oral opioid dose at follow-up* (in morphine equivalents in mg per day) | 0.00 (0.00–2.50) | 0.00 (0.00–0.00) | 0.37 |
| Resumed work after pain treatment | 11 (18.33%) | 31 (51.67%) | 0.001 |
| Yes | 9 (15.00%) | 1 (1.67%) | |
| Unknown | 31 (51.67%) | 18 (30.00%) | |
| Never stopped | 9 (15.00%) | 10 (16.67%) | |
| Able to tolerate physiotherapy better than before treatment | 11 (18.33%) | 6 (10.00%) | 0.04 |
| Yes | 11 (18.33%) | 3 (5.00%) | |
| Unknown | 46 (76.67%) | 46 (76.67%) | |

Data are medians (25th–75th centile) or numbers (percentages). Mann–Whitney \( U \) test was used to compare medians, and the \( \chi^2 \) (or Fisher exact, depending on cell sizes) test was used to compare counts.

* 18 patients in CMM + steroids-LA group and 12 patients in CMM group were taking opioids at posttreatment follow-up.

LA-S, local anesthetics and steroids.
most of the case records. There was also some variation in the dose of steroid injected around each nerve with a range of 8 to 24 mg of methylprednisolone per perineural injection. The adverse effects of study interventions were reported based on chart documentation and there was no standardized protocol for evaluating and reporting these effects. Therefore, absence of data on adverse effects in patients’ records cannot confirm lack of adverse effects in the patients. The presence of anxiety, a psychological state likely to impact on the pain experience, was also not assessed using a validated measure. Furthermore, the analgesic effect of perineural steroids may have been due to their systemic absorption and effects on the central nervous system. The treatment evaluated in this study (perineural injections of LA and steroid) were not found to be associated with the known local or systemic adverse effects of perineural injection or of injected steroids. However, this may partly be due to the lack of documentation of adverse effects in patients’ records. Future studies on perineural LA and steroids should clearly define AE of interest and the process for evaluating these effects. It should also be noted this study was not designed for multivariable linear regression with 6 covariates. Significant differences between the 2 groups at baseline were not expected a priori and we did not anticipate using multivariable linear regression as a major analysis technique in this study. It is therefore possible this study was underpowered (ie, inadequate sample size) to detect small and medium treatment differences between the 2 groups. Last, although this retrospective study did not show analgesic benefits with perineural interventions, a lack of placebo and an absence of blinding in studies evaluating invasive analgesic interventions can overestimate treatment effects. Several factors including the information offered in relation to the treatments, patients’ expectations, and the therapeutic setting can exacerbate the placebo effects and these factors need to be addressed in studies that evaluate analgesic interventions. In conclusion, although this study revealed that patients with trauma- or compression-related chronic peripheral refractory NP in the ankle and the foot treated with perineural LA-S injections and conventional management compared with conventional management alone had more pain relief at 1 to 3 months after the intervention, this effect was not found when baseline imbalances in the cohorts were considered. This study also found that a higher degree of catastrophizing reduces the probability of analgesic benefit with treatments for NP. The results of this study indicate the need for an RCT that compares the impact of perineural steroids and LA when combined with conventional management against LA with conventional management and conventional management alone in patients with chronic peripheral refractory NP.

Disclosures

The authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A114.

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