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Multicenter, Randomized, Placebo-controlled Crossover Trial Evaluating Topical Lidocaine for Mechanical Cervical Pain

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Neck pain, which commonly involves a myofascial source, has a lifetime prevalence near 50%
- Delivery of lidocaine *via* skin patches is an increasingly utilized non-opioid analgesic with a relatively favorable safety profile and has shown some efficacy in several pain conditions

What This Article Tells Us That Is New

- In this multisite, double-blind, crossover randomized clinical trial in civilian, active-duty military, and veteran patients with non-neuropathic mechanical neck pain, a 4-week lidocaine patch treatment was not associated with greater reduction in group-level average neck pain (–1 point) than placebo (–0.5 point)
- Exploratory analysis revealed that the lidocaine was associated with decreased pain sensitivity upon standardized mechanical pain testing, with higher pressure pain thresholds observed after lidocaine treatment than after placebo
- Larger studies investigating specific phenotypic patient- or disease-level characteristics associated with greater response are needed in the future

ABSTRACT

Background: There are few efficacious treatments for mechanical neck pain, with controlled trials suggesting efficacy for muscle relaxants and topical nonsteroidal anti-inflammatory drugs. Although studies evaluating topical lidocaine for back pain have been disappointing, the more superficial location of the cervical musculature suggests a possible role for topical local anesthetics.

Methods: This study was a randomized, double-blind, placebo-controlled crossover trial performed at four U.S. military, Veterans Administration, academic, and private practice sites, in which 76 patients were randomized to receive either placebo followed by lidocaine patch for 4-week intervals (group 1) or a lidocaine-then-placebo patch sequence. The primary outcome measure was mean reduction in average neck pain, with a positive categorical outcome designated as a reduction of at least 2 points in average neck pain coupled with at least a 5-point score of 7 points on the Patient Global Impression of Change scale at the 4-week endpoint.

Results: For the primary outcome, the median reduction in average neck pain score was –1.0 (interquartile range, –2.0, 0.0) for the lidocaine phase *versus* –0.5 (interquartile range, –2.0, 0.0) for placebo treatment ($P = 0.17$). During lidocaine treatment, 27.7% of patients experienced a positive outcome *versus* 14.9% during the placebo phase ($P = 0.073$). There were no significant differences between treatments for secondary outcomes, although a carryover effect on pain pressure threshold was observed for the lidocaine phase ($P = 0.015$). A total of 27.5% of patients in the lidocaine group and 20.5% in the placebo group experienced minor reactions, the most common of which was pruritis ($P = 0.36$).

Conclusions: The differences favoring lidocaine were small and nonsignificant, but the trend toward superiority of lidocaine suggests more aggressive phenotyping and applying formulations with greater penetrance may provide clinically meaningful benefit.

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In the 2015 Global Burden of Disease Study, low back and neck pain ranked as the leading worldwide cause of years lost to disability at 820 per 100,000, with neck pain

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separately accounting for 44% of cases.[1] According to a systematic analysis of the Global Burden of Diseases Study using data between 1990 and 2017, the point prevalence of neck pain was 3.6%, and annual incidence was 8.1%.[2] In another systematic review, the lifetime prevalence of neck pain was estimated to be 48.5%.[3] There are currently no approved medical treatments for neck pain.

Compared to the low back, the neck is responsible for less loadbearing but greater motion, which places greater stress on musculature and facet joints than on discs. In a prospective study performed at a military hospital in 100 individuals with neck pain, 43% had nociceptive pain, and 50% had possible neuropathic or mixed pain.[4] In another study performed in 152 patients seen in a neurosurgery clinic, 37.5% had predominantly non-neuropathic pain.[5] The evidence that soft tissues play a prominent role in neck pain is supported by the observations that the only medications shown to be beneficial in placebo-controlled trials are topical nonsteroidal anti-inflammatory drugs and muscle relaxants[6] and that most studies evaluating trigger point injections were conducted in the neck.[7,8]

Unlike for back pain, in which placebo-controlled trials have failed to demonstrate efficacy,[9] studies evaluating topical lidocaine for cervical pain have been more auspicious. A placebo-controlled trial by Lin *et al.*[10] in 60 patients with myofascial neck pain found that a 7-day application of topical lidocaine significantly reduced pain and disability at 14 days but not at 7 or 28 days. Another randomized study that compared two trigger point injections to 4 days of lidocaine or placebo patches in 60 patients with myofascial back or neck pain found greater pain relief in the injection and lidocaine patch groups than the placebo group through 9 days.[11] Collectively, these findings suggest that topical lidocaine may provide relief for mechanical neck pain (a subset of nociceptive pain, often exacerbated by movement, that results from injury to spinal structures and surrounding soft tissues) more than back pain given the preponderance of patients with a myofascial component and the more superficial depth of the cervical musculature in relation to the penetration of topical lidocaine, which is approximately 1 cm without penetrants.[12]

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The global market for topical medications is projected to increase from $4.8 billion/yr in 2021 to $7.3 billion in 2031, with anti-inflammatory drugs and lidocaine comprising the bulk of sales.[13] The use of topical medications to treat neck pain is appealing in populations such as the elderly (muscle atrophy) and service members and athletes (overuse injuries), for whom the use of oral medications is limited by side effects, drug interactions, and cognitive and psychomotor impairment.[14–16] Recently, a new formulation of lidocaine patch was approved for the treatment of postherpetic neuralgia in the United States that has improved adherence, penetration, and bioavailability compared to previously studied formulations.[17,18] We hypothesized that this patch would be efficacious for mechanical neck pain. The objectives of this study were to determine the efficacy of topical lidocaine in individuals with chronic (more than 3 months in duration) neck pain and to identify a subset of responders.

Materials and Methods

Permission to conduct this randomized, placebo-controlled study was separately granted by the institutional review boards (IRBs) of Johns Hopkins Medical Institutions, which served as the IRB of record for Walter Reed National Military Medical Center, the District of Columbia Veterans Administration Medical Center, and the New England Institutional Review Board on behalf of the Pain Management Institute. The study was registered on May 4, 2020, at clinicaltrials.gov (NCT04378959) by the Principal Investigator (S.P.C.). The first subject was treated on February 25, 2021, while the remaining participants were treated between September 7, 2021, and June 1, 2023, due to a COVID-19 pandemic–related supply chain delay.

Participants and Settings

Participating institutions include an inner-city tertiary care teaching hospital (Johns Hopkins), an urban military treatment facility (Walter Reed), an urban Veterans Administration hospital, and a two-site urban private practice. Inclusion criteria were age between 18 and 90 yr, axial (localized, without radiation or neurologic deficits) neck pain more than 3 months in duration, average neck pain score of at least 4 points of 10 for the week before enrollment, a stable analgesic regimen for more than 2 weeks, and tenderness to palpation (pain elicited when an average 4-kg force in a 70-kg individual is applied) in the affected areas bounded by the upper trapezius muscles, mastoid processes, and shoulders. Exclusion criteria included radiculopathy, greater than 30 oral morphine equivalents per day of opioids, structural defect presumed to be the primary pain generator, previous cervical spine surgery, serious psychiatric or medical comorbidities (*e.g.*, elevated liver function tests) that might interfere with participation or response, diffuse pain phenotype, secondary gain, painDETECT score

greater than 18 suggesting non-nociceptive pain, allergy to lidocaine, pregnancy, and skin defect over the painful area(s).

Design, Randomization, and Interventions

In this randomized, placebo-controlled crossover trial, patients were randomized in a 1:1 ratio *via* computer-generated randomization tables in blocks ranging between 8 and 16 depending on enrollment estimates at each institution into one of two groups: placebo patch for 4 weeks followed by lidocaine patch after a 1-week washout period estimated based on the short half-life (2 h) and expected duration of action (24 h) of the medication (group 1)[19]; or lidocaine patch followed by placebo patch after the same washout (group 2). All investigators except for the research pharmacist, who released 4 weeks of medications for dispensation, were blinded to treatment allocation. Participants were enrolled by investigators, who entered blinded orders for treatment and used blinded note templates. The 1.8% lidocaine patches are 10 cm × 14 cm × 0.08 cm in size and contain 36 mg of active substance that provides 40 to 50% bioavailability *versus* less than 10% in most other commercial products, greater than 90% adherence in 75% of individuals *versus* less than 60% for other commercial products at 12 h, and increased penetrance (more than 1 cm *vs.* 5 to 10 mm; ZT Lido, Scilex, USA).[17,18] The placebo patches were identical in dimensions, texture, and smell.

Participants could receive one to three patches depending on the extent of their pain, applied in a 12-h on–off fashion: they were instructed to keep the patches on during the day if their pain was activity-dependent or at night if it was worse during sleep. During the study course, no therapeutic interventions in addition to structured (*e.g.*, physical therapy) or nonstructured exercise were permitted.

Data Collection, Outcome Measures, and Follow-Up

Baseline data were collected within 24 h before phase 1 and 2 medication dispensation and included age, sex, race and ethnicity, pain duration, laterality and number of patches, military status, inciting events, chronic pain and psychiatric comorbidities, social variables including smoking and disability status, analgesic medications, average and worst arm and neck pain score on a 0 to 10 numerical rating scale over the past week, function measured by the Neck Disability Index, sleep quality measured by the Athens Insomnia Scale, neuropathic and nociplastic contributions to pain burden estimated by painDETECT, and pressure pain threshold (PPT) (newton/mm^2) estimated by the mean threshold measured at the three most affected areas.[20–22]

At the 4-week phase 1 and 2 follow-ups (window, 24 to 42 days), a blinded, disinterested investigator not involved in treatment recorded outcomes. These outcomes included average and worst pain scores measured through daily pain diaries; function; sleep quality; mean PPT; adverse effects *via* set (skin reactions) and open-ended questions; compliance (less than 75% of prescribed patches)[23]; the binary variable "medication reduction," predefined as cessation of a nonopioid analgesic or more than 20% reduction in opioid consumption; Patient Global Impression of Change measured on a 1 to 7 Likert scale, in which 1 indicates no change or worse, 3 indicates slightly better, 5 indicates moderately better, and 7 indicates definitely better; and a binary categorical outcome of success, which was predesignated as a 2-point or greater reduction in average neck pain coupled with a score of at least 5 points on the Patient Global Impression of Change scale.[24–26] The primary outcome measure was mean reduction in average neck numerical rating scale pain score calculated over the past week.

Statistical Methods and Study Adjustments Due to COVID-19

This crossover study was powered to detect a minimal difference between lidocaine patch and a placebo patch using STATA 14.2 (USA). The study was conservatively powered to detect the difference between the two treatment groups based on the following assumptions[10,26,27]:

- Baseline pain score: 6.0 (SD 1.8)
- Lidocaine treatment: a 2.3-point reduction in numeric pain rating score (SD 2.2)
- Placebo treatment: 1.2-point reduction in numerical pain score (SD 2.0)
- Dropout rate: 16%
- Statistical power: 90%, α: 0.05

Based on these assumptions, we estimated that 37 patients in each treatment arm (lidocaine–placebo, placebo–lidocaine) were needed to achieve 90% power to detect a clinically meaningful difference of 1.1 points between the treatments. For 80% power, we estimated that 65 patients needed to be randomized. To account for an anticipated 15% dropout rate, we planned to enroll 84 total patients.

Because this study began during the pandemic caused by the severe acute respiratory syndrome coronavirus 2 (COVID-19), a 6-month hiatus occurred between the first and subsequent patients enrolled while we addressed issues regarding in-person visits, the supply chain, and IRB administrative requirements. The IRBs requested that telehealth visits be permitted in lieu of some in-person visits before restarting the study, which prevented collection of PPT data on those participants. The study was halted after 76 patients were randomized because of expiration of the placebo and lidocaine patches.

Outcomes were assessed by treatment type and analyzed *via* intention-to-treat without missing data imputation. Nonparametric tests were applied for variables as indicated based on the results from the Shapiro–Wilk test, frequency histograms, and examination of Q-Q plots. Continuous variables were analyzed with the Wilcoxon rank sum test. For the binary categorical outcome of success *versus* failure, Pearson's chi-squared test was utilized. Odds ratios and 95% CIs were

calculated to measure the association of age, sex, and duration of pain with the binary outcome. Backward stepwise logistic regression was performed to calculate adjusted odds ratios for the association of the aforementioned explanatory variables with the binary outcome of success using variables found to be associated ($P < 0.25$) with lidocaine patch treatment outcome in univariable analysis and those postulated *a priori* to have an effect on treatment outcome (*e.g.*, age, sex, duration of pain, and the most predictive measure of disease burden, Neck Disability Index).

Role of the Funding Sources

The Department of Defense paid for personnel at Walter Reed and Johns Hopkins, the D.C. Veterans Administration Hospital paid for personnel costs at their hospital, while Scilex paid for personnel at Johns Hopkins and IRB fees for the Pain Management Institute. The funding sources played no role in study design, data collection and analysis, or manuscript preparation.

Results

Baseline Data

A total of 76 people were enrolled and randomized between February 2021 and June 2023. A total of 60 patients completed both phases, receiving both lidocaine and placebo treatment, while 12 patients only completed a single phase (7 placebo patch and 5 lidocaine patch). Five patients were noncompliant (less than 75% utilization), all in phase 1. There were no significant differences in demographics or baseline outcome measures between the treatment groups (fig. 1; table 1).

The baseline differences between phases 1 and 2 stratified by group allocation are shown in supplemental table 1 (https://links.lww.com/ALN/D395). Phase difference in baseline average neck pain was not significantly different ($P = 0.84$) between group 1 (median [interquartile range], 0.0 [−2.0, 0.0]) and group 2 (0.75 [−1.0, 0.0]). Phase difference in baseline worst neck pain was also not significantly different between groups ($P = 0.80$). There was a significant difference in the difference of mean PPT between phase 1 and 2 when comparing group 1 (−2.0 [−5.0, 0.2]) with group 2 (4.0 [0.0, 10.0]; $P = 0.015$; n = 30), suggesting a small carryover effect for lidocaine (supplemental table 1, https://links.lww.com/ALN/D395; fig. 2).

Primary Outcome Measure

There was no difference in the primary outcome measure, reduction in average neck pain score, between lidocaine (−1.0 [−2.0, 0.0]) and placebo (−0.5 [−2.0, 0.0]) patches ($P = 0.17$). Average neck pain score at the end of treatment was also not significant between lidocaine (4.0 [2.0, 6.0]) and placebo (5.0 [3.0, 7.0]) treatments ($P = 0.26$). A successful outcome was observed in 27.7% of patients during lidocaine treatment *versus* 14.9% during the placebo phase ($P = 0.073$; table 2).

Secondary Outcome Measures

The secondary outcomes are presented in table 2. The reduction in worst neck pain score with lidocaine treatment (−1.0 [−2.0, 0.0]) was again twice as high as with placebo (−0.5 [−2.0, 0.0]) treatment, but neither this difference ($P = 0.38$) nor the difference in median worst neck pain (7.0 [5.0, 8.0] for lidocaine *vs.* 7.0 [5.0, 9.0] for placebo; $P = 0.43$) was statistically significant. The change in the Neck Disability Index was higher after the placebo phase (−3.0 [−10.0, 2.0]) than after lidocaine treatment (0.0 [−6.0, 5.0]; $P = 0.16$). Individuals reported a slightly higher Patient Global Impression of Change score after the lidocaine phase than after placebo treatment (3.0 [1.0, 5.0], corresponding to "slightly better" *vs.* 2.0 [1.0, 3.5] corresponding to "almost the same"), but again this difference fell shy of statistical significance ($P = 0.24$). There were no other trends or significant differences between treatment groups for other secondary outcome measures.

Factors Associated with Positive Outcome

Factors associated with successful treatment outcome in the lidocaine phase are shown in table 3. In subgroup analyses, those with a shorter duration of neck pain were more likely to experience a positive outcome (odds ratio, 0.91; 95% CI, 0.82 to 0.98; $P = 0.033$) as were those with a lower baseline Neck Disability Index (odds ratio, 0.97; 95% CI, 0.94 to 1.00; $P = 0.037$). However, when adjusted for multiple comparisons, shorter duration of neck pain and Neck Disability Index failed to reach significance. Individuals who were nonadherent experienced only marginally less pain relief (odds ratio, 1.36; 95% CI, 0.21 to 26.71; $P = 0.78$) compared to compliant patients. Neither PPT (odds ratio, 0.98; 95% CI, 0.94 to 1.02; $P = 0.34$), anxiety (odds ratio, 0.60; 95% CI, 0.22 to 1.50; $P = 0.30$) or depression history (odds ratio, 0.58; 95% CI, 0.21 to 1.43; $P = 0.26$), age (odds ratio, 1.02; 95% CI, 0.99 to 1.05; $P = 0.11$), or sex (odds ratio, 1.44; 95% CI, 0.59 to 3.76; $P = 0.43$) was associated with lidocaine outcome at the 4-week endpoint. In the placebo phase, older age exhibited the strongest association with positive outcome but did not reach statistical significance (odds ratio, 1.05; 95% CI, 1.00 to 1.11; $P = 0.08$). When analyses were conducted using difference of difference (lidocaine–placebo) scores, the results did not significantly change (table 3).

Adverse Events

Of all patients, 27.5% reported adverse effects in the lidocaine phase compared to 20.5% of patients in the placebo treatment phase ($P = 0.36$). The most common complication in both phases was pruritus, which 9.0% of placebo

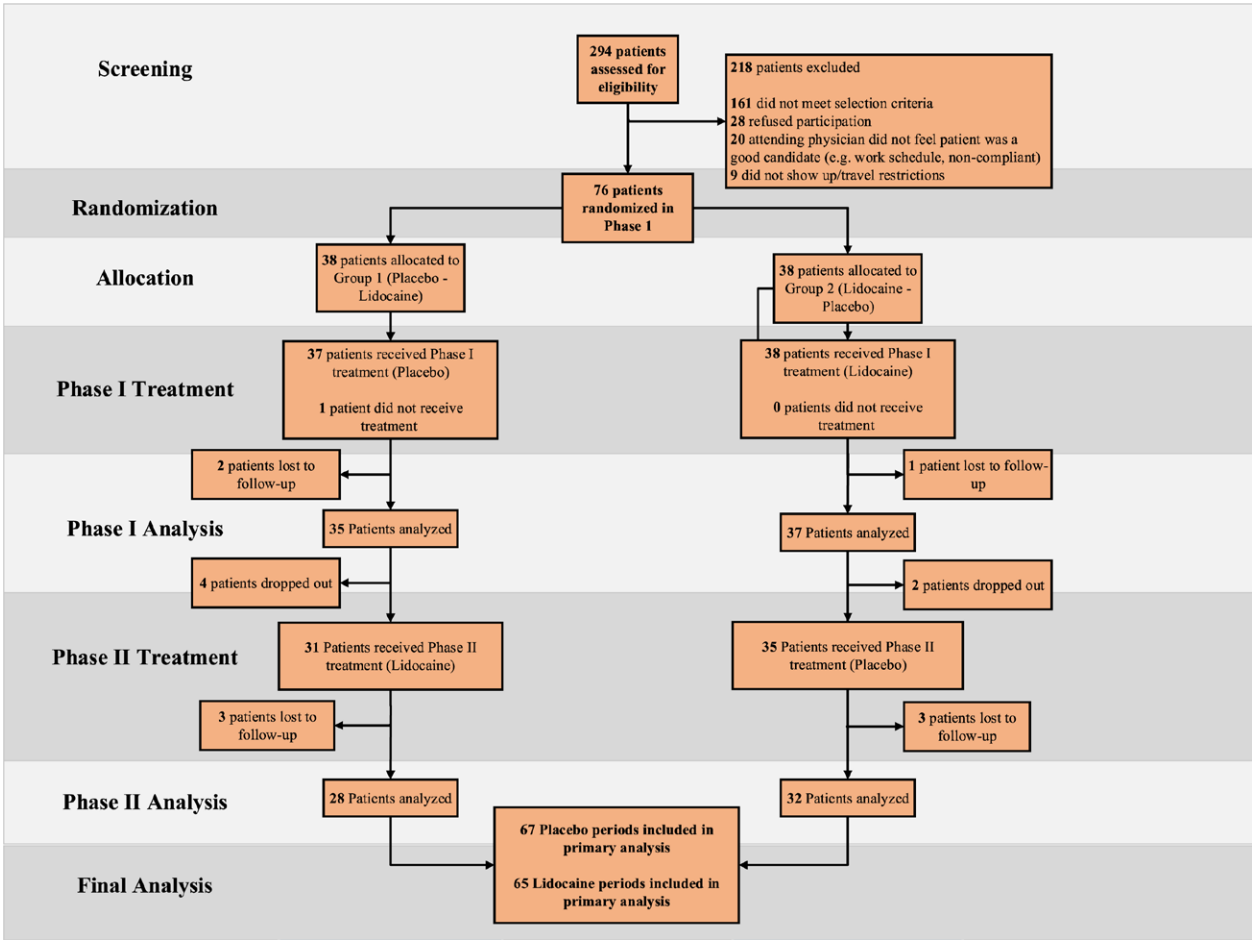

Fig. 1. Flow chart demonstrating study progression.

phase patients and 9.2% of lidocaine phase patients experienced. Rash localized to the sites of patch administration occurred in three patients each with lidocaine and placebo. Mild erythema was reported in three patients during the placebo phase and one patient in the lidocaine phase. In the lidocaine phase, other complaints included trapped sweat (n = 1), worsening pain (n = 1), nausea (n = 1), and neck numbness (n = 1). In the placebo phase, one patient complained of difficulty removing the patches, and one patient complained of difficulty putting on patches. Side effects necessitated aborting the treatment in only two patients, with one each in group 1 and group 2 not proceeding to phase 2 because of a rash.

Effectiveness of Blinding

A total of 58.3% of patients correctly guessed the sequence of their treatment. Three patients (4.17%) guessed that they received the same treatment in both phases. Among the remaining patients, the James Blinding Index was 0.77 (95% CI, 0.68 to 0.86), indicating effectiveness of blinding.

Discussion

Main Findings and Literature Comparison

The main findings in this study were that no significant differences were observed between the lidocaine and placebo patches, with the increased pain relief associated with lidocaine patches translating to higher, albeit still low, success rates. Our findings were comparable to the placebo-controlled trials of Lin *et al.*,[10] who found a small difference (mean, 0.44) after 2 weeks of application but not earlier or at 3 weeks (mean difference, 0.22), but less propitious than those of Affaitati *et al.*,[11] who found an enormous effect at 9 days (mean difference, 61.85 mm on a 100-mm visual analog scale), 4 days after cessation of a 4-day treatment protocol. Differences between our selection criteria and these studies were that Lin *et al.*[10] required a taut band of muscle that elicited a local twitch response (trigger point) and used only clinical findings to rule out neurologic disease, while Affaitati *et al.*[11] enrolled only those with acute myofascial pain.

Table 1. Baseline Characteristics for Study Participants

Variable	Entire Cohort (N = 75)*	Placebo–Lidocaine (N = 37)*	Lidocaine–Placebo (N = 38)*	*P* Value†
Age, median (interquartile range)	54.00 (41.50, 63.50)	56.00 (42.00, 67.00)	53.50 (41.25, 62.00)	0.36
Sex, female (%)	48 (64)	23 (62)	25 (66)	0.75
Obesity	25 (33)	9 (24)	16 (42)	0.11
Smoking	6 (8.0)	5 (14)	1 (2.6)	0.11
Disability/worker's compensation/military medical board	29 (39)	14 (39)	15 (39)	0.96
Duration, median (interquartile range)	5.00 (1.8, 10.00)	5.00 (2.00, 8.50)	5.00 (1.81, 11.75)	0.48
Opioid use	10 (13)	5 (14)	5 (13)	0.96
Active duty	3 (4.0)	1 (2.7)	2 (5.3)	1
Laterality				0.87
Unilateral	25 (33)	12 (32)	13 (34)	
Bilateral	50 (67)	25 (68)	25 (66)	
Number of patches, median (interquartile range)	2.00 (1.00, 3.00)	2.00 (1.00, 2.00)	2.00 (1.25, 3.00)	0.35
painDETECT, median (interquartile range)	7.00 (4.00, 11.00)	8.00 (4.00, 11.00)	7.00 (4.00, 11.00)	0.54
Inciting event				0.35
None	49 (65)	22 (59)	27 (71)	
Fall	7 (9)	5 (14)	2 (5.3)	
Motor vehicle collision	14 (19)	9 (24)	5 (13)	
Sports/training	3 (4)	1 (2.7)	2 (5.3)	
Other	3 (4)	1 (2.7)	2 (5.3)	
Concomitant pain conditions				
Back pain	39 (52)	17 (46)	22 (58)	0.31
Arthralgia	19 (25)	10 (27)	9 (24)	0.74
Headache	18 (24)	9 (24)	9 (24)	0.95
Neuropathic pain	4 (5.3)	1 (2.7)	3 (7.9)	0.61
Fibromyalgia/widespread pain	3 (4.0)	2 (5.4)	1 (2.6)	0.61
Other	9 (12)	4 (11)	5 (13)	1
Multiple	25 (33)	9 (24)	16 (42)	0.11
None	19 (25)	9 (24)	10 (26)	0.84
Coexisting psychiatric conditions				
Depression	26 (35)	20 (54)	6 (16)	< 0.001
Anxiety	26 (35)	17 (46)	9 (24)	0.042
Posttraumatic stress disorder	6 (8)	5 (14)	1 (2.6)	0.11
Substance abuse	3 (4)	2 (5.4)	1 (2.6)	0.61
Other	3 (4)	2 (5.4)	1 (2.6)	0.61
Multiple	20 (27)	16 (43)	4 (11)	< 0.001
None	35 (47)	10 (27)	25 (66)	< 0.001
Outcome measures at baseline, median (interquartile range)				
Average neck pain	5.50 (4.00, 7.00)	5.00 (4.00, 7.00)	5.75 (4.12, 7.00)	0.78
Worst neck pain	8.00 (7.00, 9.00)	8.00 (7.00, 9.00)	8.00 (7.00, 10.00)	0.71
Neck Disability Index	42.00 (27.00, 50.00)	42.00 (28.00, 54.00)	40.00 (26.00, 48.00)	0.41
Athens Insomnia Scale	10.00 (7.00, 13.00)	9.00 (7.00, 12.00)	11.00 (6.25, 13.00)	0.69
Pressure pain threshold	26.00 (21.25, 32.00)	24.00 (21.00, 28.00)	22.67 (20.00, 28.70)	0.61

Pain scores were measured on a 0 to 10 numerical rating scale. The Neck Disability Index scores from 0 to 100%, with higher numbers indicating greater disability. The Athens Insomnia Scale scores from 0 to 24 with higher scores indicating greater sleep dysfunction.

*n (%); median (interquartile range). †Pearson's chi-square test, Fisher's exact test, and Wilcoxon rank sum test.

Explanation of Findings

Although our study was negative and indicates that this topical lidocaine preparation is unlikely to produce clinically important benefits in a general population, the small, nonsignificant effects favoring lidocaine suggest the possibility that an enriched population, refined by measurable characteristics, might experience clinically meaningful benefit. Skin and muscles are the two largest organ systems in the body, with both capable of being pain generators. One reason why topical local anesthetic patches have previously failed to elicit benefit is poor penetrance and adherence, which is why newer formulations with greater adherence and penetrance may theoretically improve outcomes.[26] The distance from skin to the deep intrinsic lumbar spinal muscles ranges from 4 to 6 cm, which may help explain the negative studies for back pain.[9,28] The musculature in the neck generally extends between 6 and 12 mm under the skin, which is slightly greater than the penetrance of traditional topical patches but comparable to those of the product we studied.[17,18,29] However,

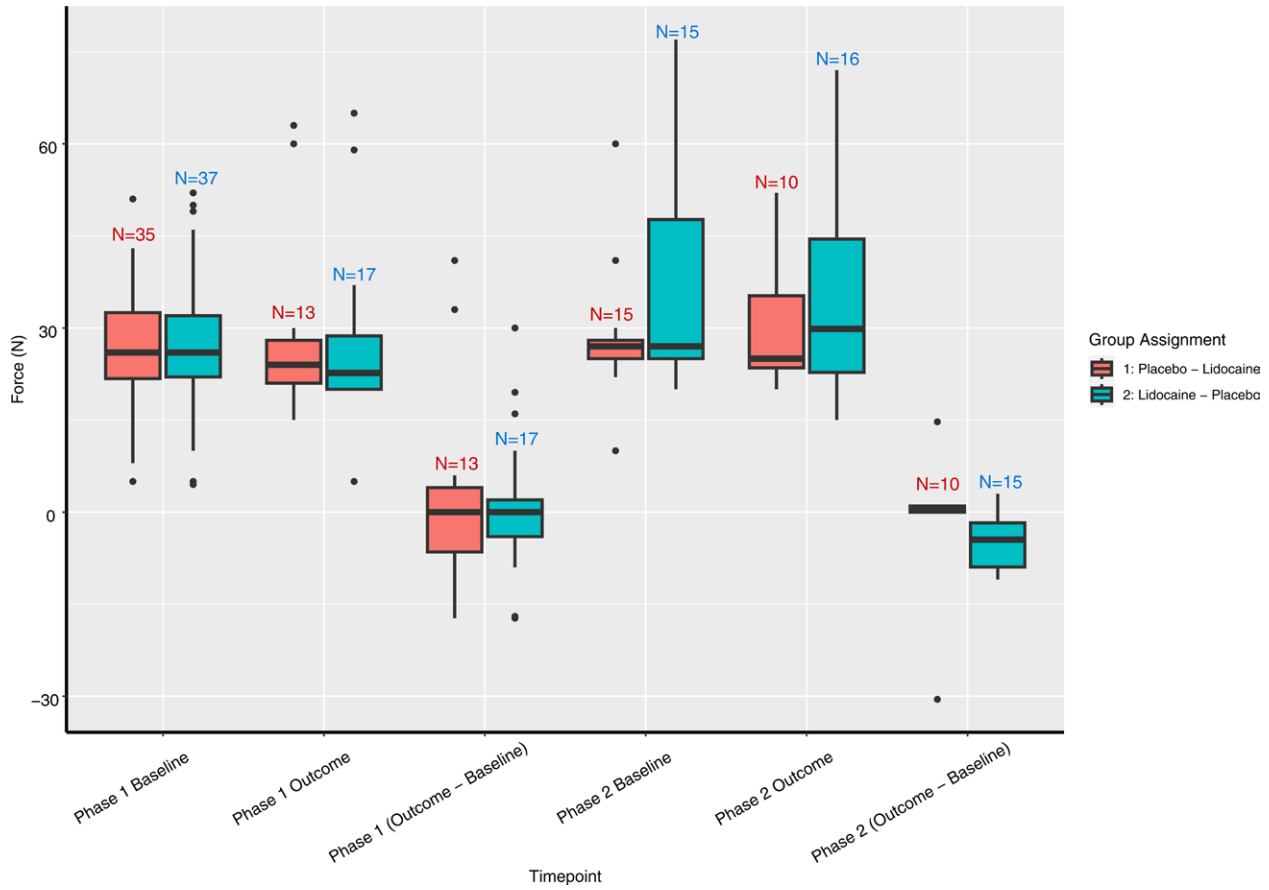

Fig. 2. Box plot demonstrating differences in pain pressure thresholds stratified by study group.

myofascial pain frequently co-occurs with spine pathology that does not respond to topical therapies,[6] and one study that examined neck pain patients with normal imaging failed to find correlations between myofascial pathology and pain, suggesting the possibility of nociplastic pain (*i.e.*, nonspecific neck pain).[30,31] Although we attempted to rule out non-nociceptive causes of pain by screening with painDETECT, this instrument is not designed to identify central sensitization as a mechanism. Individuals with central sensitization have been shown in numerous studies to be more likely to fail interventional and pharmacologic treatments, including for neck pain.[32,33]

Clinical Phenotyping

In multivariable analysis, greater duration of pain and higher Neck Disability Index scores were negatively correlated to treatment outcome. This is consistent with other studies demonstrating an inverse relationship between disease burden (including duration of pain and disability) and treatment effect for neck and back pain.[34,35] The recent emphasis on personalized medicine and phenotyping has led to attempts to identify likely responders, which may improve the cost-effectiveness and risk:benefit ratios. Studies performed in diabetic neuropathy suggest an "irritable nociceptor" phenotype may be more likely to respond to both topical and intravenous lidocaine, but whether higher baseline pain thresholds predispose to failure for mechanical pain is unknown.[36,37] An irritable nociceptor phenotype that might respond to topical lidocaine could present with lower mechanical pain thresholds in the neck but not diffusely, with preserved small fiber function. These individuals would lack evidence of pronounced central sensitization in the form of temporal summation or impaired conditioned pain modulation on quantitative sensory testing or abnormal scores on instruments such as the Central Sensitization Inventory.[38] In contrast, those with central sensitization may have lower pain thresholds in both painful and nonpainful areas. We found no significant effect for baseline PPT, but reasons other than sensitized nociceptors can cause low PPTs, including nonorganic pathology, nociplastic pain, and secondary gain, all of which are associated with treatment failure.[31,34,35] The trend toward younger age being associated with a positive lidocaine treatment outcome may be attributed to the higher contribution of myofascial pain (greater muscle mass) in younger individuals compared

Table 2. Outcomes at 4 Weeks Stratified by Treatment

Variable	Lidocaine Patch (N = 65)	Placebo Patch (N = 67)	*P* Value*
Average neck pain	4.0 (2.0, 6.0)	5.0 (3.0, 7.0)	0.26
Change in average neck pain	−1.0 (−2.0, 0.0)	−0.5 (−2.0, 1.0)	0.17
Worst neck pain	7.0 (5.0, 8.0)	7.0 (5.0, 9.0)	0.43
Change in worst neck pain	−1.0 (−2.0, 0.0)	−0.5 (−2.0, 0.0)	0.38
Neck Disability Index	34.0 (22.0, 46.0)	36.0 (24.0, 45.0)	0.99
Change in Neck Disability Index	0.0 (−6.0, 5.0)	−3.0 (−10.0, 2.0)	0.16
Athens Insomnia Score	9.0 (6.0, 12.0)	10.0 (6.0, 13.0)	0.61
Change in Athens Insomnia Score	0.0 (−2.0, 1.0)	0.0 (−2.0, 1.0)	0.64
Pressure pain threshold, median (N; interquartile range)	24.0 (28; 20.8, 29.9)	26.0 (29; 22.0, 41.0)	0.35
Change in pressure pain threshold, median (N; interquartile range)	0.0 (28; −4.0, 1.5)	−3.0 (29; −8.6, 2.0)	0.50
Patient global impression of change	3.0 (1.0, 5.0)	2.0 (1.0, 3.5)	0.24
Medication reduction, N (%)	13 of 52 (25)	11 of 55 (20)	0.68
Successful outcome, N (%)†	18 of 65 (28)	10 of 67 (15)	0.073

The values are noted as the median (interquartile range), unless otherwise noted.

*Wilcoxon rank sum test and Pearson's chi-square test. †Defined as 2-point or greater reduction in average neck pain coupled with a score or at least 5 of 7 points on the patient global impression of change scale.

Table 3. Factors Associated with Positive Lidocaine Treatment Outcome

	Unadjusted Odds Ratio		Adjusted Odds Ratio, Full Model	
Variable	Odds Ratio (95% CI)*	*P* Value*	Odds Ratio (95% CI)*	*P* Value*
Age, yr	1.02 (0.99–1.05)	0.11	1.01 (0.99–1.04)	0.28
Duration of pain, yr	0.91 (0.82–0.98)	0.033	0.93 (0.84–1.01)	0.12
Sex, female	1.44 (0.59–3.76)	0.43	1.55 (0.59–4.42)	0.38
Neck Disability Index	0.97 (0.94–0.997)	0.037	0.98 (0.95–1.00)	0.11
Compliant, yes	1.36 (0.21–26.71)	0.78	1.76 (0.25–35.94)	0.63

*Backward, stepwise logistic regression (N = 132).

to the degenerative processes such as facetogenic and discogenic neck pain that predominate in the elderly.[6]

Responder Analysis

The IMMPACT guidelines assert that either greater than 2 points or greater than 30% reduction in pain represents the minimal clinically important difference for an individual patient, and in our protocol, we predesignated the former.[25] When reanalyzed using the latter, 15% of placebo period (N = 10 of 67) and 23% of lidocaine period (N = 15 of 65) attained a positive outcome ($P = 0.22$), which did not alter the analysis. Studies in chronic pain have yielded mixed results on the linearity of pain scales, which would suggest that in some scenarios, utilizing a percentage cutoff would be more sensitive to identifying responders.[39,40]

Implications and Future Research

Our results indicate that when applied to a general population of individuals with mechanical neck pain, the benefits afforded by a high bioavailability lidocaine patch are small and questionably meaningful. However, the risk:benefit and cost:effectiveness ratios may be more favorable in a clinically refined or enriched population consisting perhaps of younger, thinner, or more muscular individuals; those with evidence of irritable nociceptors (*e.g.*, low thermal pain thresholds without evidence of central sensitization)[38,41]; and those at high risk of pharmacologic side effects. Given the strong signal for clinically meaningful efficacy, determining whether formulations that contain higher doses or greater penetrance increase the effect size is an avenue for future investigation.

Limitations

There are several limitations in this study that warrant consideration. First, although the sample size is extremely large for a placebo-controlled crossover study,[42] we enrolled slightly fewer patients than our maximum allotment owing to an IRB-mandated pandemic hiatus, during which we had to implement risk-mitigation strategies and owing to the patches expiring; hence, the study may have been underpowered to detect a small difference. One of the risk-mitigation

measures applied was permitting telehealth appointments, which resulted in many visits being conducted over the phone or *via* video, which decreased the number of patients in whom PPTs were recorded. This may have also resulted in lower overall success rates, as most telephone visits were performed by a nurse rather than physician, with some studies reporting lower pain scores when visits are conducted by a doctor.[43] Second, although we tried to eliminate individuals with significant central sensitization, this was accomplished *via* history and physical exam and painDETECT rather than a validated instrument such as the Central Sensitization Inventory.[44] Third, it is possible that measuring pain at different time points (*e.g.*, at multiple points, or at a distal point to exploit the unforeseen possible carryover effect) rather than only at the end of treatment may have increased the effect size. Whereas a 1-week washout period is consistent with other crossover trials evaluating topical lidocaine, evidence for this includes the carryover effect in the lidocaine group observed in our study, as well as the finding by Lin *et al.*[10] finding no difference at treatment end between lidocaine and placebo patches for neck pain but a significant treatment effect 1-week after treatment cessation.[10,17,45] Last, accounting for a possible small carryover effect in a crossover trial creates statistical implications with no consensus on analysis, with some statisticians believing that only the first period should be analyzed when a clear carryover effect exists.[46] In our study, analyzing data only for the first period would have changed our primary outcome from a trend to statistical significance.

Conclusions

In summary, although most important measures showed trends for greater improvement with lidocaine, the differences were small and not significant. This suggests a need for additional studies evaluating products with greater dosing and penetrance, applied with more stringent selection criteria based on phenotyping, to determine whether topical lidocaine may provide meaningful benefit in a subset of patients with chronic neck pain.

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Competing Interests

Dr. Cohen is a consultant for Avanos (Alpharetta, Georgia), SPR Therapeutics (Cleveland, Ohio), Scilex (Palo Alto, California), Persica Pharmaceuticals (Canterbury, Kent, UK), and Sword Health (Draper, Utah; active) and previously was a consultant for Releviate Therapeutics (San Diego, California) and Clearing (New York, New York; ended within the past 3 yr). Dr. Cohen also conducted institutionally funded research by Avanos and Scilex. The other authors declare no competing interests.

Reproducible Science

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Supplemental Digital Content

Supplemental Table 1. Difference in Phase Baseline Stratified by Treatment, https://links.lww.com/ALN/D395

References

1. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators: Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388:1545–602
2. Safiri S, Kolahi AA, Hoy D, et al.: Global, regional, and national burden of neck pain in the general population, 1990–2017: Systematic analysis of the Global Burden of Disease Study 2017. BMJ 2020; 368:m791
3. Fejer R, Kyvik KO, Hartvigsen J: The prevalence of neck pain in the world population: A systematic critical review of the literature. Eur Spine J 2006; 15:834–48

4. Liu R, Kurihara C, Tsai HT, Sylvestri PJ, Bennett MI, Cohen SP: Classification and treatment of chronic neck pain: A longitudinal cohort study. Reg Anesth Pain Med 2017; 42:52–61
5. Tampin B, Briffa NK, Goucke R, Slater H: Identification of neuropathic pain in patients with neck/upper limb pain: Application of a grading system and screening tools. Pain 2013; 154:2813–22
6. Cohen SP, Hooten W: Neck pain: Advances in the diagnosis and management of neck pain. BMJ 2017; 358:j3221
7. Scott NA, Guo B, Barton PM, Gerwin RD: Trigger point injections for chronic non-malignant musculoskeletal pain: A systematic review. Pain Med 2009; 10:54–69
8. Navarro-Santana MJ, Sanchez-Infante J, Gómez-Chiguano GF, et al.: Dry needling versus trigger point injection for neck pain symptoms associated with myofascial trigger points: A systematic review and meta-analysis. Pain Med 2022; 23:515–25
9. Santana JA, Klass S, Felix ER: The efficacy, effectiveness and safety of 5% transdermal lidocaine patch for chronic low back pain: A narrative review. PM R 2020; 12:1260–7
10. Lin YC, Kuan TS, Hsieh PC, Yen WJ, Chang WC, Chen SM: Therapeutic effects of lidocaine patch on myofascial pain syndrome of the upper trapezius: A randomized, double-blind, placebo-controlled study. Am J Phys Med Rehabil 2012; 91:871–82
11. Affaitati G, Fabrizio A, Savini A, et al.: A randomized, controlled study comparing a lidocaine patch, a placebo patch, and anesthetic injection for treatment of trigger points in patients with myofascial pain syndrome: Evaluation of pain and somatic pain thresholds. Clin Ther 2009; 31:705–20
12. Singh P, Roberts MS: Dermal and underlying tissue pharmacokinetics of lidocaine after topical application. J Pharm Sci 1994; 83:774–82
13. Allied Market Research: Pain patch market by product type (non-opioid patches, opioid patches), by type (prescription medicines, OTC medicines), by distribution channel (hospital pharmacies, drug Stores and retail pharmacies, online providers): Global oppportunity analysis and industry forecast, 2021–2031. 2023. Available at: https://www.alliedmarketresearch.com/pain-patches-market-A12676. Accessed December 29, 2023.
14. Kazeminasab S, Nejadghaderi SA, Amiri P, et al.: Neck pain: Global epidemiology, trends and risk factors. BMC Musculoskelet Disord 2022; 23:26
15. Cohen SP, Gallagher RM, Davis S, Griffith SR, Carragee EJ: Spine area pain in military personnel: A review of epidemiology, etiology, diagnosis and treatment. Spine J 2012; 12:833–42
16. Hogg-Johnson S, van der Velde G, Carroll LJ, et al.; Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders: The burden and determinants of neck pain in the general population: Results of the Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders. Spine (Phila Pa 1976) 2008; 33:S39–51
17. Gudin J, Argoff C, Fudin J, et al.: A randomized, open-label, bioequivalence study of lidocaine topical system 1.8% and lidocaine patch 5% in healthy subjects. J Pain Res 2020; 13:1485–96
18. Greuber E, Vought K, Patel K, et al.: Biorelevant in vitro skin permeation testing and in vivo pharmacokinetic characterization of lidocaine from a nonaqueous drug-in-matrix topical system. AAPS PharmSciTech 2021; 22:215
19. List T, Mojir K, Svensson P, Pigg M: A new protocol to evaluate the effect of topical anesthesia. Anesth Prog 2014; 61:135–44
20. Soldatos CR, Dikeos DG, Paparrigopoulos TJ: Athens Insomnia Scale: Validation of an instrument based on ICD-10 criteria. J Psychosom Res 2000; 48:555–60
21. Vernon H, Mior S: The neck disability index: A study of reliability and validity. J Manipulative Physiol Ther 1991; 14:409–15
22. Freynhagen R, Baron R, Gockel U, Tölle TR: painDETECT: A new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006; 22:1911–20
23. Reading SR, Black MH, Singer DE, et al.; ATRIA-CVRN Investigators: Risk factors for medication non-adherence among atrial fibrillation patients. BMC Cardiovasc Disord 2019; 19:38
24. Scott W, McCracken LM: Patients' impression of change following treatment for chronic pain: Global, specific, a single dimension, or many? J Pain 2015; 16:518–26
25. Dworkin RH, Turk DC, Wyrwich KW, et al.: Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008; 9:105–21
26. Brutcher RE, Kurihara C, Bicket MC, et al.: Compounded topical pain creams to treat localized chronic pain: A randomized controlled trial. Ann Intern Med 2019; 170:309–18
27. Cohen SP, Strassels SA, Kurihara C, et al.: Randomized study evaluating the accuracy of 025 ml and 05 ml cervical facet joint nerve (medial branch) blocks. Anesthesiology 2010; 112:144–52
28. Harrison GR, Clowes NW: The depth of the lumbar epidural space from the skin. Anaesthesia 1985; 40:685–7
29. Cha YD, Lee MH, Yoon YH, et al.: Depth by ultrasound from skin surface to the C6 transverse process while applying pressure. Pain Med 2011; 12:1026–31
30. Ezzati K, Ravarian B, Saberi A, et al.: Prevalence of cervical myofascial pain syndrome and its correlation

with the severity of pain and disability in patients with chronic non-specific neck pain. Arch Bone Jt Surg 2021; 9:230–4
31. Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Häuser W: Chronic primary musculoskeletal pain: A new concept of nonstructural regional pain. Pain Rep 2022; 7:e1024
32. Ablin JN, Berman M, Aloush V, et al.: Effect of fibromyalgia symptoms on outcome of spinal surgery. Pain Med 2017; 18:773–80
33. Morffi D, Larach DB, Moser SE, Goesling J, Hassett AL, Brummett CM: Medial branch radiofrequency ablation outcomes in patients with centralized pain. Reg Anesth Pain Med 2019: rapm-2018-100275
34. Cohen SP, Doshi TL, Kurihara C, et al.: Multicenter study evaluating factors associated with treatment outcome for low back pain injections. Reg Anesth Pain Med 2022; 47:89–99
35. Cohen SP, Doshi TL, Dolomisiewicz E, et al.: Nonorganic (behavioral) signs and their association with epidural corticosteroid injection treatment outcomes and psychiatric comorbidity in cervical radiculopathy: A multicenter study. Mayo Clin Proc 2023; 98:868–82
36. Demant DT, Lund K, Finnerup NB, et al.: Pain relief with lidocaine 5% patch in localized peripheral neuropathic pain in relation to pain phenotype: A randomised, double-blind, and placebo-controlled, phenotype panel study. Pain 2015; 156:2234–44
37. Wilkinson ID, Teh K, Heiberg-Gibbons F, et al.: Determinants of treatment response in painful diabetic peripheral neuropathy: A combined deep sensory phenotyping and multimodal brain MRI study. Diabetes 2020; 69:1804–14
38. Themistocleous AC, Ramirez JD, Shillo PR, et al.: The Pain in Neuropathy Study (PiNS): A cross-sectional observational study determining the somatosensory phenotype of painful and painless diabetic neuropathy. Pain 2016; 157:1132–45
39. Wang B-K, Liu T-H, Xie F, Liu Y-Q: Pain vision system for evaluating chronic pain: A comparison with VAS scoring. Pain Res Manag 2020:6312581. Available at: https://doi.org/10.1155/2020/6312581. Accessed December 29, 2023.
40. Kersten P, White PJ, Tennant A: Is the pain visual analogue scale linear and responsive to change? An exploration using Rasch analysis. PloS One 2014; 9:e99485
41. Baron R, Maier C, Attal N, et al.; German Neuropathic Pain Research Network (DFNS), and the EUROPAIN, and NEUROPAIN Consortia: Peripheral neuropathic pain: A mechanism-related organizing principle based on sensory profiles. Pain 2017; 158:261–72
42. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A: Meta-analyses involving cross-over trials: Methodological issues. Int J Epidemiol 2002; 31:140–9
43. Martin KD, Van Buren JP, Wake J, Dawson L: Comparison of visual analog pain score reported to physician vs. nurse. Foot Ankle Int 2018; 39:300–3
44. Neblett R, Cohen H, Choi Y, et al.: The Central Sensitization Inventory (CSI): Establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. J Pain 2013; 14:438–45
45. Hasuo H, Sakuma H, Uchitani K, Ohue K, Fukunaga M: Short-term effects of 10% lidocaine ointment on allodynia in cancer pain: A randomized, double-blind, placebo-controlled crossover study. J Palliat Med 2019; 22:1364–9
46. Li T, Yu T, Hawkins BS, Dickersin K: Design, analysis, and reporting of crossover trials for inclusion in a meta-analysis. PLoS One 2015; 10:e0133023